Effect of Exercise on the Pharmacokinetics of Paracetamol in Normal Healthy Volunteers

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Master of Science Thesis in Pharmacology

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Thesis Title	Effect of Exercise on the Pharmacokinetics of Paracetamol in Normal Healthy Volunteers
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ชื่อวิทยานิพนธ์	ผลของการออกกำลังกายต่อเภสัชจลนศาสตร์ของยาพาราเซตามอลในอาสาสมัครสุขภาพปกติ
ผู้เขียน	นางสาว อุไรรัตน์ แผ่นทอง
สาขาวิชา	เภสัชวิทยา
ปีการศึกษา	2544

บทคัดย่อ

พาราเซตามอล (อะเซตามิโนเฟน) เป็นยาแก้ปวด-ลดไข้ที่ใช้กันอย่างแพร่หลาย ส่วนการออกกำลังกายก็ได้รับความนิยมเพิ่มขึ้นเนื่องจากก่อให้เกิดผลดีต่อสุขภาพ แต่อย่างไรก็ตามบุคคลที่ออกกำลังกายอาจมีไข้หรือปวดศีรษะ และจำเป็นต้องใช้ยาพาราเซตามอลเพื่อบรรเทาอาการปวดและลดไข้ดังกล่าว การออกกำลังกายมีผลต่อการเปลี่ยนแปลงการไหลเวียนของเลือด อุณหภูมิ และการทำงานของทางเดินอาหารซึ่งอาจมีผลต่อเภสัชจลนศาสตร์ของยาหลายชนิด ดังนั้นการศึกษาครั้งนี้จึงมีวัตถุประสงค์เพื่อศึกษาถึงผลของการออกกำลังกายต่อเภสัชจลนศาสตร์ของยาพาราเซตามอล ในกรณีที่ได้รับยาพาราเซตามอลอย่างเดียว เปรียบเทียบกับในกรณีที่มีการออกกำลังกายในระดับปานกลางโดยการวิ่งบนลู่วิ่งด้วยความเร็ว 5 กม./ชม.เป็นเวลา 30 นาทีภายหลังรับประทานยาพาราเซตามอลในอาสาสมัครชายไทยสุขภาพปกติจำนวน 14 คน ค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาพาราเซตามอลได้จากค่าความเข้มข้นของยาในพลาสมา ณ เวลาต่างๆในช่วงเวลา 8 ชั่วโมงหลังรับประทานยาครั้งเดียวในขนาด 1,000 มก.ซึ่งวัดโดย high performance liquid chromatography (HPLC) และนำข้อมูลมาทดสอบทางสถิติโดยใช้ Student's paired t-test พบว่า ในอาสามัครที่มีการออกกำลังกายภายหลังได้รับยาพาราเซตามอลมีค่าคงที่ของอัตราการดูดซึมยา (Ka) เพิ่มขึ้น 1.95 เท่า

(4.90 ± 1.52 ต่อชม. เทียบกับ 2.51 ± 1.02 ต่อชม., $P < 0.01$) ความเข้มข้นสูงสุดของยาในพลาสมา (C_{max}) เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (18.64 ± 0.70 มคก./มล. เทียบกับ 17.24 ± 1.06 มคก./มล., $P < 0.01$) ในขณะที่เวลาที่ยามีความเข้มข้นสูงสุดในพลาสมา (T_{max}) ลดลง 0.68 เท่า (0.85 ± 0.11 ชม. เทียบกับ 1.25 ± 0.11 ชม., $P < 0.01$) และ ค่าครึ่งชีวิตการดูดซึมยา ($t_{1/2}$ (abs)) ลดลง 0.50 เท่า (0.15 ± 0.05 ชม. เทียบกับ 0.31 ± 0.09 ชม., $P < 0.01$) ส่วนค่าพื้นที่ใต้กราฟความสัมพันธ์ระหว่างระดับยาพาราเซตามอลกับเวลา (AUC), ค่าคงที่อัตราการกำจัดยา (Ke), ค่าครึ่งชีวิตการกำจัดยา ($t_{1/2}$), ค่าปริมาตรการกระจายของยา (Vd/f), ค่าอัตราการชำระยา (Cl/f) และเวลาก่อนที่ยาจะถูกดูดซึม พบว่า ไม่มีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติ (66.10 ± 3.37 มก./ลิตร.ชม. เทียบกับ 64.83 ± 2.88 มก./ลิตร.ชม., 0.39 ± 0.05 ต่อชม. เทียบกับ 0.38 ± 0.04 ต่อชม., 1.99 ± 0.17 ชม. เทียบกับ 2.02 ± 0.09 ชม., 0.71 ± 0.05 ลิตร/กก. เทียบกับ 0.67 ± 0.08 ลิตร/กก., 0.25 ± 0.02 ลิตร/ชม./กก. เทียบกับ 0.25 ± 0.02 ลิตร/ชม./กก. และ 0.24 ± 0.05 ชม. เทียบกับ 0.31 ± 0.08 ชม. ตามลำดับ) ผลจากการศึกษาครั้งนี้แสดงให้เห็นว่า การออกกำลังกายในระดับปานกลางเพิ่มอัตราการดูดซึมยาพาราเซตามอลโดยคาดว่าเป็นผลจากการเพิ่มอัตราการว่างของกระเพาะอาหาร

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ABSTRACT

Paracetamol (acetaminophen) is widely used as an analgesic-antipyretic drug while exercise is getting more popular among people since it has a positive impact on health. However, these population may have fever or headache, and may need paracetamol to relieve their pain and fever. Exercise can influence a number of physiological factors such as haemodynamics, body temperature and gastrointestinal function that may affect the pharmacokinetics of various drugs. The objective of this study was to investigate the effect of exercise on the pharmacokinetics of paracetamol in fourteen healthy Thai male volunteers receiving paracetamol alone compared to moderate exercise by treadmill-running 5 km/hr for 30 minutes after paracetamol ingestion. The pharmacokinetics parameters were determined from plasma paracetamol concentration change during a 8-hour period after subjects receiving a single oral dose of 1,000 mg paracetamol by using high performance liquid chromatography (HPLC). Statistical analysis by using Student's paired t-test indicated that when subjects exercise after paracetamol treatment, the absorption rate constant (Ka) increased by about 1.95-fold ($4.90 \pm 1.52\ hr^{-1}$ vs $2.51 \pm 1.02\ hr^{-1}$, $P < 0.01$), the maximal

concentration (C_{max}) increased significantly (18.64 ± 0.70 μg/ml vs 17.24 ± 1.06 μg/ml, $P < 0.01$) whereas the time to reach the maximal concentration (T_{max}) decreased by about 0.68-fold (0.85 ± 0.11 hr vs 1.25 ± 0.11 hr, $P < 0.01$) and the absorption half-life ($t_{1/2}$(abs)) decreased by about 0.50-fold (0.15 ± 0.05 hr vs 0.31 ± 0.09 hr, $P < 0.01$). In contrast, the area under the concentration-time curve (AUC), elimination rate constant (Ke), elimination half-life ($t_{1/2}$), apparent volume of distribution (Vd/f), apparent oral clearance (Cl/f) and the lag times were not significantly different (66.10 ± 3.37 mg/l.hr vs 64.83 ± 2.88 mg/l.hr, 0.39 ± 0.05 hr^{-1} vs 0.38 ± 0.04 hr^{-1}, 1.99 ± 0.17 hr vs 2.02 ± 0.09 hr, 0.71 ± 0.05 l/kg vs 0.67 ± 0.08 l/kg, 0.25 ± 0.02 l/hr/kg vs 0.25 ± 0.02 l/hr/kg and 0.24 ± 0.05 hr vs 0.31 ± 0.08 hr, respectively). Therefore, the present results could suggest that moderate exercise increased the rate of paracetamol absorption supposed to be through the increase in the gastric emptying rate.

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LIST OF ABBREVIATIONS

a.m. = ante meridiem

AUC = area under the concentration-time curve

BUN = blood urea nitrogen

°C = degree celcius

Cl/f = apparent oral clearance

cm = centimeter

C_{max} = maximal plasma concentration

e.g. = exampli gratia

F.S. = full scale

g = gram

µg = microgram

Hb = hemoglobin

Hct = hematocrit

hr = hour

HR_{max} = maximal heart rate

^{125}I = iodine 125

I.D. = internal diameter

i.e. = id est

i.p. = intraperitoneal

I.U. = international unit

i.v. = intravenous

Ka = absorption rate constant

LIST OF ABBREVIATIONS (Continued)

Ke	=	elimination rate constant
kg	=	kilogram
km	=	kilometer
kpm	=	kilometer per minute
l	=	litre
µl	=	microlitre
M	=	molar
µm	=	micrometer
mg	=	milligram
min	=	minute
ml	=	millilitre
mm	=	millimeter
m/min	=	meter per minute
mmol	=	millimole
µmol	=	micromole
mph	=	mile per hour
m/s	=	meter per second
mV	=	millivolt
ng	=	nanogram
nm	=	nanometer
P	=	P value
p.m.	=	post meridiem

LIST OF ABBREVIATIONS (Continued)

PMN	=	polymorphonuclear neutrophils
r	=	correlation coefficient
®	=	trade name
rpm	=	round per minute
S.D.	=	standard deviation
SGOT	=	serum glutamic oxaloacetic transaminase
SGPT	=	serum glutamic pyruvic transaminase
$t_{1/2}$	=	elimination half-life
$t_{1/2}$ (abs)	=	absorption half-life
T_{max}	=	time to maximal plasma concentration
uv	=	ultraviolet
Vd/f	=	apparent volume of distribution
$\dot{V}O_{2max}$	=	maximal oxygen uptake
vs	=	versus
v/v	=	volume by volume
WBC	=	white blood cell
wk	=	week
W_{max}	=	maximal aerobic power
w/v	=	weight by volume
yr	=	year
%	=	percent

CHAPTER 1

INTRODUCTION

Paracetamol (Acetaminophen, N-acetyl-p-aminophenol, 4′-hydroxy acetanilide) was first used in medicine by Von Mering in 1893. However, it has been gained popularity since 1949, after it was recognized as the major active metabolite of both acetanilide and phenacetin which proved to be excessively toxic.

Paracetamol is an effective analgesic-antipyretic drug which has a week anti-inflammatory action. It is only a week inhibitor of prostaglandin biosynthesis. Some evidence suggest that it may be more effective against enzymes in the central nervous system than those in the periphery perhaps because of the high concentrations of peroxides that are found in inflammatory lesion (Marshall, 1987).

Single or repeated therapeutic doses of paracetamol have no effect on neither cardiovascular nor respiratory systems. Acid-base changes do not occur. Paracetamol does not produce gastric irritation, erosion, or bleeding as occur after administration of salicylates. Moreover, it has no effect on platelets, bleeding time or excretion of uric acid.

Paracetamol is well tolerated and produces fewer side effects than aspirin. It is available as over the counter drug. Therefore, it has earned a prominent place as a common household analgesic. However, acute overdosage (usually doses greater than 10 to 15 g) can cause hepatotoxicity (Barker *et al.*, 1977;

Bonkowsky *et al.*, 1978; Clissold, 1986; Hamlyn *et al.*, 1978; Paul, 1991). Because the excessive amount of paracetamol causes saturation of glucuronidation and sulphation, large proportions of paracetamol undergo cytochrome P-450 mediated N-hydroxylation to form N-acetyl-benzo-quinoneimine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione. However, after a large dose of paracetamol, the metabolite is formed in large amount and can cause depletion of the hepatic glutathione; under these circumstances, reaction with sulfhydryl groups in hepatic proteins is increased and hepatic necrosis can be resulted from paracetamol overdosage.

As paracetamol pharmacokinetics seem to be predominantly dependent on various factors, e.g., food (Holt *et al.*, 1979a; Houston and Levy, 1975, 1976; Pantuck *et al.*, 1984; Prescott *et al.*, 1993), gastric emptying time (Clements *et al.*, 1978; Holt *et al.*, 1979a), posture (Nimmo and Prescott, 1978), obesity (Abernethy *et al.*, 1982), drugs (Dordoni *et al.*, 1973; Iqbal *et al.*, 1995; Nimmo *et al.*, 1973; Rashid and Bateman, 1990) and diseases (El-Azab *et al.*, 1996; Forfar *et al.*, 1980; Forrest *et al.*, 1979; Ismail *et al.*, 1995). Factors that alter the plasma paracetamol concentration will influence the paracetamol toxicity or efficacy.

On theoretical backgrounds, exercise may affect the pharmacokinetics of certain drugs. During exercise, profound haemodynamic changes occur: cardiac output is increased and blood flow redistributed, away from the splanchnic area and the kidneys, towards the active skeletal muscle and skin. Exercise may reduce tissue, blood and urinary pH; urine flow may be decreased;

gastrointestinal function may be affected. Body temperature, skin temperature and sweat rate may be increased. These and other factors may affect the pharmacokinetics of some drugs. Indeed, changes have been occured after exercise (Henry *et al.*, 1981; Hurwitz *et al.*, 1983; Mason *et al.*, 1980; Powis and Snow, 1978; Sweeney, 1981; Weber *et al.*, 1987; Ylitalo and Hinkka, 1985; Ylitalo *et al.*, 1977).

Mason *et al.* (1980) found that the renal clearance of atenolol was reduced by approximately 8% during exercise. The authors suggested that decrease in the renal clearance of the drug was probably due to decreased renal blood flow during exercise.

Exercise is getting more popular among people since it has a positive impact on health. However, these population may have fever or headache, and may need paracetamol to relieve their pain and fever. Exercise may affect the pharmacokinetics of paracetamol. Therefore, the present study was undertaken to determine the effect of exercise on the pharmacokinetics of paracetamol in normal healthy volunteers.

CHAPTER 2

LITERATURE REVIEW

Paracetamol

Paracetamol (Acetaminophen, N-acetyl-p-aminophenol, 4′-hydroxy acetanilide, p-acetamidophenol, N-(4-hydroxyphenyl) acetamide, p-hydroxyacetanilide, p-acetaminophenol, p-acetylaminophenol) is a derivative of acetanilide, an aniline-like compound. In 1886, acetanilide was introduced into medical practice by Cahn and Hepp and it was soon found to have unacceptable side effects, the most alarming one is cyanosis due to methaemoglobinemia. Paracetamol was first used in medicine by Von Mering in 1893. However, it has been gained popularity since 1949, after it was recognized as the major active metabolite of both acetanilide and phenacetin which proved to be excessively toxic.

The molecular weight of paracetamol is 151.2. It is a moderately water and lipid-soluble, weak organic acid with a pK_a of 9.5, and is thus largely unionized over the physiological range of pH.

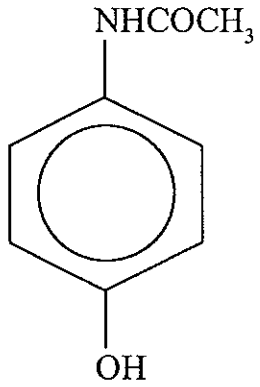

Figure 1 Molecular structure of paracetamol

Pharmacological effects and mechanism of action

Paracetamol has antipyretic and analgesic actions, it has only a weak anti-inflammatory action, because it is a weak prostaglandin inhibitor and possesses no significant anti-inflammatory effects (Clissold, 1986). Single or repeated therapeutic dose of paracetamol does not affect the cardiovascular nor respiratory systems. Acid-base balance does not change and the drug does not produce gastric irritation, erosion, or bleeding as that may occur after administration of salicylates. It has no effect on platelets aggregation, bleeding time, nor excretion of uric acid (Mycek *et al.*, 1997).

Paracetamol has analgesic and antipyretic properties, because it is more effective against enzymes for prostaglandins biosynthesis in the central nervous system than those in the periphery. The explanation of this property is that there might be high concentrations of peroxides which can stimulate the activity of the enzymes for prostaglandins biosynthesis, in inflammatory lesion (Clissold, 1986; Marshall *et al.*, 1987; Mycek *et al.*, 1997).

1. Pharmacokinetic properties

1.1 absorption

Paracetamol absorption appears to be negligible from stomach but very rapid from small intestine. The mean absorption rates of paracetamol were similar in proximal and distal parts of small intestine (Gramatte and Richter, 1993). In rats, absorption does occur slowly from stomach and colon, and is most rapid from small intestine, with 70% of the drug being absorbed within 30 minutes (Bagnall *et al.*, 1979). Absorption is by passive transport with first-order kinetics. The gastric emptying is the rate-limiting step in the absorption of paracetamol (Clements *et al.*, 1978).

Although paracetamol is rapidly absorbed from gastrointestinal tract, it is incompletely available to systemic circulation after oral administration, a variable proportion being lost through first-pass metabolism (Hirate *et al.*, 1990; Perucca and Richens, 1979; Rawlins *et al.*, 1977). Some metabolism may occur during absorption. Josting *et al.* (1976), for example, noted that 8% of the drug was metabolised by the perfused rat intestinal loop during a 30-minute period. The proportion of the dose reaching the systemic circulation appears to depend upon the amount administered, decreasing from 90% after 1 to 2 g to 68% after 0.5 g (Rawlins *et al.*, 1977). The concentration reaches a peak in 30 to 60 minutes and the plasma half-life is about 2 hours after therapeutic doses (Paul, 1991). The usual therapeutic doses produce plasma concentration of 5 to 20 μg/ml. After 8 hours, only small amount of unchanged paracetamol is detectable in plasma (Clissold, 1986).

Mean time to maximal plasma paracetamol concentration in fasting healthy

subjects have been noted at 22 minutes after ingestion of paracetamol in solution (Nimmo *et al.*, 1975a), and at 60 minutes (Dordoni *et al.*, 1973) after ingestion of paracetamol tablets.

As paracetamol absorption seems to be predominantly dependent on the rate of gastric emptying, any drug, disease, or other condition which alters the rate of gastric emptying may influence the rate of paracetamol absorption.

1.1.1 Effect of Weight and Sex

Abernethy *et al.* (1982) investigated the effect of obesity and sex on paracetamol disposition in 21 obese (14 women; 7 men) and 21 normal (11 women; 10 men) drug-free and age-matched subjects. The subjects were given single 650 mg intravenous doses of paracetamol. Mean total body weights (TBW) for the groups were as follow: obese men, 134.9 kg; control men 70.6 kg; obese women, 87.9 kg; and control women, 55.0 kg. Paracetamol half-life ($t_{1/2}$ beta) did not differ among the groups. Absolute volume of distribution (Vd) was greater in obese than in control men (109 and 771, $P < 0.05$) and greater in control men than in control women (77 and 521, $P < 0.05$), but Vd corrected for TBW was smaller in obese than in control men (0.81 and 1.09 l/kg TBW, $P < 0.05$) and smaller in obese than control women (0.71 and 0.95 l/kg TBW, $P < 0.05$). Absolute metabolic clearance was greater in obese than in control men (484 and 323 ml/min, $P < 0.05$), in obese than in control women (312 and 227 ml/min, $P < 0.05$), and in control men than women (323 and 227 ml/min, $P < 0.05$).

After oral administration, the maximal plasma paracetamol concentrations were found to be significantly higher in women than in men, in both the luteal

(66%) and follicular phase (48%) of their ovulatory cycles. The mean AUC for paracetamol in the blood of female subjects was significantly increased by 51% and 39%, respectively, taking into account the follicular and luteal phase, in comparison with the AUC of male volunteers (Wojcicki *et al.*, 1979).

1.1.2 Effect of Food

Holt *et al.* (1979a) showed that gastric emptying rate and paracetamol absorption rate were slower after gel fibre (guar gum and pectin mixed solution) but the total absorption was not significantly reduced. They suggested that viscosity is an important property of dietary fiber to alter gastric emptying rate. Prescott *et al.* (1993) found that absorption rate of paracetamol was significantly impaired in the vegetarians compared with the non-vegetarians as shown by a lower mean maximal plasma paracetamol concentration (11.7 ± 1.4 vs 15.6 ± 1.6 mg/l; $P \leq 0.05$), increased time to reach maximal plasma concentration (0.75-3 hr vs 0.25-2 hr).

1.1.3 Effect of Posture

Nimmo and Prescott (1978) found that paracetamol absorption rate were markedly reduced when subjects lay on their left side compared with when ambulant, after paracetamol ingestion the plasma concentration were 0.18 and 2.8 μg/ml at 15 minutes and 7.8 and 20.8 μg/ml at 30 minutes, respectively. The authors suggested that the alteration of paracetamol absorption were caused by changing in gastric emptying time.

1.1.4 Effect of Drugs

In healthy volunteers, propantheline 30 mg administered intravenously delayed the mean time to reach peak plasma paracetamol concentration from 70

to 160 minutes while the mean maximum concentration was reduced from 26.3 to 17.5 μg/ml. After intravenous administration of metoclopromide 10 mg, the mean time to reach the maximum plasma concentration was reduced from 120 to 48 minutes, while the mean maximum concentration increased from 12.5 to 20.5 μg/ml (Nimmo *et al.*, 1973).

Nimmo *et al.* (1975b) observed that there was marked delayed in the rate of gastric emptying and paracetamol absorption in patients during labour after receiving pethidine, diacetylmorphine (heroin), or pentazocine. In healthy volunteers, intramuscularly administered pethidine (150 mg) and diacetylmorphine 10 mg markedly delayed the absorption of paracetamol. The mean peak plasma concentration 20 μg/ml in the control, 13.8 μg/ml after pethidine and only 5.2 μg/ml after diacetylmorphine, while the mean time taken to achieve peak plasma concentrations were 22, 114 and 142 minutes, respectively (Nimmo *et al.*, 1975a).

Activated charcoal (10 g) taken at the same time as paracetamol caused a more than 4-fold reduction in the mean maximum paracetamol concentration, and average reduction of 63% in the area under the concentration-time curve for the period 0 to 120 minutes. There was a concomitant increase in the time taken to reach the mean peak plasma concentration, from 60 to 120 minutes. When activated charcoal was taken 60 minutes after paracetamol, the mean reduction in absorption was only 23% (Dordoni *et al.*, 1973). Similar findings have been reported by Levy and Houston (1976), who noted that following the administration of 1 g of paracetamol the total amount absorbed were reduced by 68% and 50% after 10 g and 5 g of activated charcoal, respectively.

Cholestyramine (12 g) taken with paracetamol caused a similar reduction in the peak plasma paracetamol concentrations, with a mean reduction in absorption of 62%. This reduction was less marked (only 16%) when the drug was given 60 minutes after the paracetamol (Dordoni *et al.*, 1973).

Rashid and Bateman (1990) showed that both the rate and the extent of paracetamol absorption were significantly decreased by various doses of atropine in young and elderly volunteers. The authors suggested that atropine produces its inhibitory effect on gastric motility by its well-known muscarinic cholinergic blocking effect. The young did not demonstrate any significant dose effect on any parameter (C_{max}, t_{max} and AUC_{0-6}) of paracetamol absorption. In contrast, the elderly showed a significant dose effect in all the above parameters. The authors suggested that in the elderly subjects, atropine may have a different dose-response effect from the young. This may indicate an age-related change in cholinergic function of the stomach.

Iqbal *et al.* (1995) studied the influence of caffeine (60 mg) on the pharmacokinetic characteristics of paracetamol (500 mg single dose) in ten healthy male human. Caffeine caused a highly significant ($P < 0.01$) increased in AUC, a significant ($P < 0.05$) increase in C_{max}, an a significant ($P < 0.05$) decrease in clearance (Cl/f) of paracetamol. The authors concluded that caffeine taken in dose commonly available commercially or in a cup of coffee can significantly potentiate the therapeutic potential of paracetamol in man.

1.1.5 Effect of Disease

1.1.5.1 Gastrointestinal disease

Gastrointestinal diseases may slow gastric emptying and delay the complete

absorption of paracetamol such as graft-versus-host-disease (GVHD) of the gut, Behcet's syndrome and scleroderma involving the gastrointestinal tract may directly reduced paracetamol absorption (Gubbins and Bertch, 1991).

Holt *et al.* (1979b) found that the paracetamol absorption was slower in the Coeliac and Crohn's disease patients, as indicated by later and reduced peak plasma paracetamol concentration but total absorption was not different.

Ueno *et al.* (1995) found that the paracetamol absorption was faster in patients with total gastrectomy. The authors suggested that an early maximum serum drug concentration in patients with total gastrectomy was presumably a result of the absence of a delaying effect on absorption from the intestine of gastric emptying. In short bowel syndrome patients, the extent of absorption of paracetamol appeared to be decreased compared with absorption in healthy subjects, emphasising the role of the jejunum as an absorption site.

1.1.5.2 Thyroid disease

In untreated thyrotoxicosis, absorption is significantly faster than when the patients are euthyroid. The peak paracetamol concentration, however, was lower in thyrotoxic patients due to an apparent increase in the total body clearance and a shorter plasma half-life. Both absorption and elimination rates were reduced in hypothyroid patients, but were not significantly different from the euthyroid results (Forfar *et al.*, 1980).

1.1.5.3 Malnutrition

Bolme *et al.* (1982) compared the paracetamol absorption between the Swedish children and Ethiopian children. The Ethiopian children were divided into three groups: normal children with adequate nourishment, children with

Marasmus (moderate malnutrition) and those with Kwashiochor (severe malnutrition). The absorption half-life ($t_{1/2}$(abs)) (means ± S.D.) was similar among the 3 groups (19.6 ± 0.8 min, 11.0 ± 0.4 min, and 13.4 ± 5.5 min, respectively) but the fraction of absorption was reduced in all 3 groups (67.9%, 51.3%, and 34.2%, respectively) of the Ethiopian children which was related to nutritional status.

1.1.5.4 Pregnancy

Galinsky and Levy (1984) showed that the oral dose of paracetamol was absorbed much more slowly and incompletely on the last day of pregnancy than 38 days postpartum. The authors suggested that the slowly and incompletely paracetamol absorption was due to decreasing gastric emptying rate in late human pregnancy.

Simpson *et al.* (1988) showed that plasma paracetamol concentrations were significantly lower at 30, 40 ($P < 0.05$), 60 ($P < 0.01$) and 75 ($P < 0.05$) min in patients who were 12-14 weeks pregnant compared to control subjects. The 12-14 weeks pregnant group had lower peak paracetamol concentrations, and showed a delay in the time taken to reach a peak compared with controls ($P < 0.05$). The area under the plasma paracetamol concentration-time curve (AUC) at 1 and 2 hr were less in 12-14 weeks pregnant patients compared to controls ($P < 0.05$). The authors suggested that the reduction in mean plasma paracetamol concentrations in the 12-14 weeks pregnant patients, in the study, represented a delay in gastric emptying. The smaller area under the plasma paracetamol conentration-time curve in these patients reflected a reduction in paracetamol absorption.

1.1.5.5 Liver disease

El- Azab *et al.* (1996) showed that in elderly patients (45-65 years old) with liver cirrhosis from schistosomal infection, plasma paracetamol concentration in early state, before the time to reach maximal plasma concentrations, was significantly higher than younger patients and healthy subjects. The authors suggested that in these patients with higher initial plasma concentration, it is probably due to the development of collateral circulation and reduce the first-pass metabolism of paracetamol in the liver.

1.1.5.6 Renal disease

Prescott *et al.* (1989) showed that paracetamol was rapidly absorbed in the healthy volunteers and renal failure patients with mean peak plasma concentrations of 20.0 mg/l and 17.9 mg/l occuring on average at 0.35 hr and 0.5 hr respectively after administration. The mean plasma half-life from 2 hr to 8 hr was similar in the healthy volunteers, patients with moderate renal failure and dialysis patients (2.2 ± 0.3 hr, 2.3 ± 0.5 hr and 2.1 ± 0.4 hr). However, after 8 hr there were significant differences between the groups. Paracetamol continued to disappear rapidly from 8 to 24 hr in the healthy volunteers with a mean half-life of 4.9 ± 2.1 hr while low levels persisted in the renal failure patients and the corresponding half-life in both renal groups were 11.7 ± 5.2 hr. As a result, the total AUC for paracetamol was greater in the renal failure patients than in the healthy volunteers. The authors suggested that the late elimination phase was greatly extended in the patients with renal disease and possible rate-limiting mechanisms included slow transfer of residual drug from peripheral tissues back to the circulation and augmented enterohepatic circulation of paracetamol

conjugates with regeneration of the parent drug. The latter is more likely since similar unexpected impairment of elimination of paracetamol.

1.2 Distribution

Paracetamol distributes throughout most tissues and fluids, reaching a tissue: plasma concentration ratio of about unity in all tissues except fat and cerebrospinal fluid. With normal therapeutic doses, paracetamol is slightly bound to plasma proteins (Donald, 1992), only 20 to 50% may be bound at the concentrations encountered during acute intoxication (Paul, 1991). Generally, the apparent volume of distribution of paracetamol is about 1 l/kg. The distribution volume is similar in healthy subjects, in patients with epilepsy (Perucca and Richens, 1979), Gilbert's syndrome (Douglas *et al.*, 1978b) and in anephric patients (Lowenthal *et al.*, 1976). In patients with thyrotoxicosis, hypothyroid or euthyroid, there were no significant differances among these groups with regard to rate constants or apparent volume of distribution in the peripheral compartment, although the overall apparent volume of distribution tended to be largest in the thyrotoxic group and smallest in the hypothyroid group (Forfar *et al.*, 1980).

Divoll *et al.* (1982) demonstrated that the volume of distribution of paracetamol (corrected for weight) was larger in men than in woman (0.99 and 0.86 l/kg) and declined with age in both sexs. The authors explained that the reduction in volume of distribution of paracetamol in women and elderly might be due to increasing fat per kilogram body weight and incomplete distribution of nonlipophilic property of paracetamol into body fat.

Beaulac-Baillargeon and Rocheleau (1994) found an inverse correlation ($r = 0.85$) between maximal plasma paracetamol concentration and the weight of the pregnant women ($P < 0.01$) but not with the weight of the control women. The authors suggested that weight gain in pregnant women due to the expansion of total body water caused by an increase in the plasma volume, extracellular fluid and amniotic fluid. So that increasing in volume of distribution of paracetamol relates to lower in maximal plasma paracetamol concentration.

1.3 Metabolism

Paracetamol is extensively metabolised predominantly in the liver. It is metabolised to a minor extent in gut (Josting *et al.*, 1976) and kidney (Jones *et al.*, 1979; Mitchell *et al.*, 1977). At therapeutic dosage, it normally undergoes glucuronidation and sulphation to the corresponding conjugates, which together comprise 95% of the total excreted metabolites. The alternative cytochrome P-450-dependent glutathione (GSH) conjugation pathway accounts for the remaining 5%. When paracetamol intake far exceeds therapeutic doses, the glucuronidation and sulphation pathways are saturated, and the cytochrome P-450-dependent pathway becomes increasingly important. Little or no hepatotoxicity results as long as glutathione is available for conjugation. However, with time, hepatic glutathione is depleted faster than it can be regenerated, accumulation of a reactive and toxic metabolite occurs. In the absence of intracellular nucleophiles such as glutathione, this reactive metabolite [thought to be an N-hydroxylated product or an N-acetyl-p-benzoquinoneimine (NAPQI)] reacts with nucleophilic groups present on cellular macromolecules

such as protein, resulting in hepatotoxicity (Maria and Neal Castagnoli, 1984) (Figure 2).

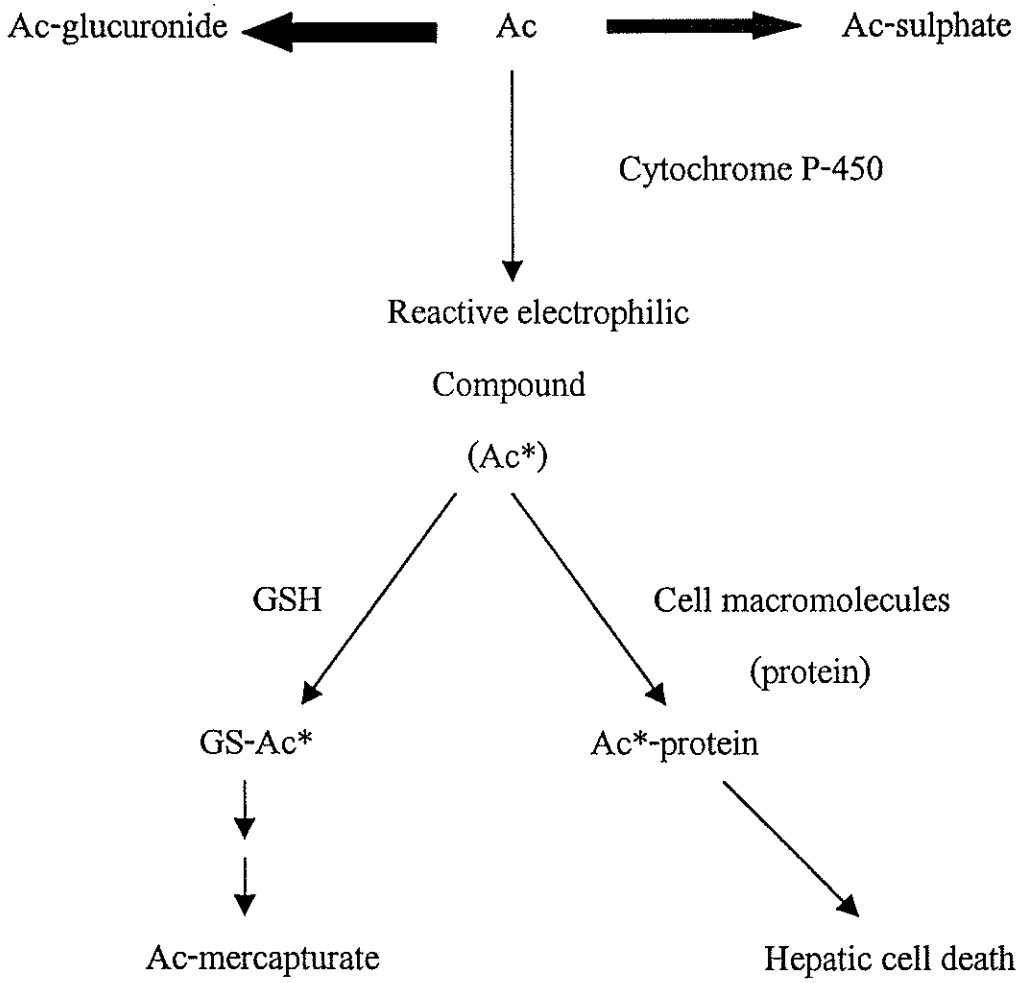

Figure 2 Pathways of paracetamol (Ac) metabolism.

(GSH = glutathione; GS = glutathione moiety;

Ac* = reactive intermediate)

(Source : Maria, A.C. and Neal Castagnoli, J.R. 1984. Pharmacokinetics: Drug biotransformation. In B.G. Katzung (ed.), *Basic and Clinical Pharmacology* (2^{nd} ed), pp. 42. Sanfrancisco: Lang Medical Publications).

1.4 Elimination

In young healthy subjects approximately 85-95% of therapeutic dose is excreted in urine within 24 hours, with about 4%, 55%, 30%, 4% and 4% appearing as unchanged paracetamol, glucuronide, sulphate, cysteine and mercapturic acid conjugates, respectively (Forrest *et al.*, 1979; Prescott, 1980). In neonates and children under 9 years old approximately 68% of therapeutic dose is excreted in urine, with about 4%, 18% and 50% appearing as unchanged paracetamol, glucuronide, sulphate conjugates, respectively. The results of this study suggested that the limited ability of neonates to conjugate phenolic drugs with glucuronic acid is compensated to a degree by a well-developed capability for sulphate conjugation (Levy *et al.*, 1975; Miller *et al.*, 1976). The kinetics of unchanged paracetamol can be determined from samples of breast milk (Notarianni *et al.*, 1987) and saliva (Kamali *et al.*, 1987; Lowenthal *et al.*, 1976), since levels (in saliva) are similar to those in plasma (Lowenthal *et al.*, 1976). The paracetamol concentrations were consistently lower in breast milk, with a mean milk/plasma AUC ratio of 0.76. As less than 0.1% of the maternal dose would be present in 100 ml milk (Bitzen *et al.*, 1981). Paracetamol crosses the placenta (Naga Rani *et al.*, 1989; Wang *et al.*, 1986; Weigand *et al.*, 1984).

Other minor metabolites have been described, each accounting for 1% or less of a therapeutic dose. These include sulphate and glucuronide conjugates of 3-methoxy-paracetamol, 3-hydroxy-paracetamol (Andrews *et al.*, 1976) and 3-methyl-thioparacetamol (Klutch *et al.*, 1978).

As a moderately lipid-soluble weak organic acid, paracetamol is filtered by glomerulus with subsequent extensive tubular reabsorption. Excretion of

paracetamol is independent of urinary pH but appears to be weakly correlated with urine flow rate (Morris and Levy, 1984; Prescott, 1980). The highly polar sulphate and glucuronide conjugates of paracetamol are apparently active secreted by the tubules (Morris and Levy, 1984). There are many reports shown various factors that affect to paracetamol elimination.

1.4.1 Effect of Age

Neonates and children aged 3 to 10 years excreted significantly less glucuronide and more sulphate conjugate than children aged 12 years and adults (Alam *et al.*, 1977; Levy *et al.*, 1975; Miller *et al.*, 1976; Peterson and Rumack, 1978). And the elimination half-life was significantly prolong in neonates. The authors suggested that the limited ability of neonates to conjugate paracetamol with glucuronic acid is compensated to a degree by a well-developed capability for sulphate conjugation.

Divoll *et al.* (1982) showed that paracetamol clearance tended to decline with age in men and women, but difference were of borderline significant.

The plasma paracetamol half-life has been noted to be significantly prolonged in geriatric subjects compared with younger subjects: 2.17 hours *versus* 1.75 hours (Triggs *et al.*, 1975). The plasma half-life in the geriatric subjects, however, are in the same range as those reported by other workers for healthy young subjects (Forrest *et al.*, 1979; Prescott *et al.*, 1971; Rawlins *et al.*, 1977).

Barbara *et al.* (1991) studied the effect of age on glucuronidation and sulphation of paracetamol *in vitro* in human liver samples from 22 subjects aged 40-89 years. The results shown that glucuronidation and sulphation

of paracetamol by liver fractions *in vitro* do not fall significantly with normal aging. The authors suggested that any age-related decrease in paracetamol clearance is likely to reflect reduced liver volume and liver blood flow.

1.4.2 Effects of Sex, Environmental or Genetic Factors

Miners *et al.* (1983) found that paracetamol clearance was 22% greater in males compared to (normal) females. This differance was entirely due to increased activity of the glucuronidation pathway in males. The paracetamol half-life was found to be slightly, although not significantly, longer in women in the follicular phase and in the luteal phase of their ovulatory cycles, than in men (Wojcicki *et al.*, 1979).

Shively and Vessel (1975) showed that paracetamol elimination half-life in healthy males at 6 a.m. was significantly longer (15%) than at 2 p.m., the plasma clearance was not significantly different at these time. The mean apparent volume of distribution of paracetamol decreased by approximately 13% from 6 a.m. to 2 p.m. The authors suggested that the difference was presumably due to a change in volume of distribution.

Mucklow *et al.* (1980) found that the elimination half-life of paracetamol was significantly longer (18%) and the clearance significantly slower (21%) in Asians in London compared with Caucasian subjects. Thus, available evidence suggested that the paracetamol disposition affected by race, but the later study found that the disposition of paracetamol was not different between the healthy young adult male Caucasians and Chinese (Osborne *et al.*, 1991).

Critchley *et al.* (1986) studied the 24 hr urinary excretion of paracetamol and its metabolites following a single oral dose of 1.5 g in 111 Caucasians

(Scotland), 67 West Africans (Ghana) and 20 East Africans (Kenya). The fraction recovery of the mercapturic acid and cysteine conjugates of paracetamol was 9.3% in the Caucasians compared with only 5.2% and 4.4% in the Ghanaians and Kenyans, respectively ($P < 0.0005$). This probably indicates markedly reduced metabolic activation of paracetamol in the Africans. There were no ethnic differences in the sulphate conjugation of paracetamol, but the mean fraction recovery of the glucuronide conjugate in Caucasians (54%) was significantly less than in the Africans (58%). The sulphate conjugation of paracetamol was increased and glucuronide conjugation reduced in Caucasians females compared with males. A similar trend was seen in the Ghanaians but there were no other significant sex differences. The authors suggested that these ethnic differences in paracetamol metabolism may be related to genetic or environmental factors including differences in diet and protein intake. The later study have been reported by Sommers *et al.* (1987), no significant differences were found between the data for total Venda, rural Venda, Westernized Venda and Caucasian students for the calculated metabolite parameters. The environmental effects showed no apparent influence on the sulphate and glucuronide conjugation of paracetamol, and no hereditary effect was evident between the Venda and Caucasians.

1.4.3 Effect of Disease

1.4.3.1 Thyroid disease

In patients with untreated thyrotoxicosis, the mean plasma half-life was shorter, and the total body clearance of the drug was increased, compared with value obtained when the patients were subsequently euthyroid. In hypothyroid

subjects there was only a slight reduction in the elimination rate (Forfar *et al.*, 1980).

Sonne *et al.* (1990) studied the effect of severe hypothyroidism on the pharmacokinetics of paracetamol 750 mg given intravenously (n = 8) before and after treatment with levothyroxine. The median (rang) clearance of paracetamol under hypothyroid conditions was 3.12 ml/min/kg (1.64-4.40 ml/min/kg) and 4.70 ml/min/kg (3.18-5.70 ml/min/kg) following replacement therapy ($P < 0.01$). The authors suggested that the increase in paracetamol clearance following replacement therapy with levothyroxine was substantial, and could be related almost entirely to the increase in partial clearance of the glucuronide (1.86 ml/min/kg to 2.70 ml/min/kg).

1.4.3.2 Liver disease

The plasma paracetamol clearance was found to be significantly lower in patients with Gilbert's syndrome than in healthy subjects (255 ± 23 ml/min vs 352 ± 40 ml/min). The result suggest that paracetamol elimination impaired in Gilbert's syndrome could be attributed to a decrease in hepatic glucuronyl transferase activity (Douglas *et al.*, 1978b).

The elimination of paracetamol from the plasma in patients with chronic liver disease has been studied by a number of workers (Andreasen and Hutters, 1979; Arnman and Olsson, 1978; Forrest *et al.*, 1977; Forrest *et al.*, 1979). These studies have shown that in patients with cirrhosis who have a normal plasma albumin concentration and prothrombin time, the plasma paracetamol half-life or clearance is similar to that seen in healthy subjects. However, in patients with cirrhosis who have a low plasma albumin and an increased prothrombin time

ratio elimination is grossly abnormal. Accordingly, Forrest *et al.* (1979) the mean plasma half-lives were 2.43 ± 0.19 hours in healthy subjects, 2.16 ± 0.54 hours in patients with chronic liver disease and a normal plasma albumin and/or prothrombin time ratio, and 4.25 ± 1.15 hours in patients in whom both these indices were abnormal.

Forrest *et al.* (1979) showed that a greatly prolonged plasma paracetamol half-life with very high concentrations of unchanged paracetamol and low concentrations of the glucuronide and sulphate conjugates was noted in a patient with a porto-systemic shunt; this finding is consistent with shunting and greatly reduced first-pass metabolism.

Benson (1983) evaluated the safety of paracetamol in therapeutic dose in subjects with stable chronic liver disease. Six subjects with chronic liver disease were given paracetamol 4.0 g daily for 5 days. The elimination half-life of paracetamol was prolonged to a mean of 3.42 hr (2.13-5.77 hr), which is 70% higher than in normal subjects (2.04 hr). However, there was no evidence of drug accumulation or hepatotoxicity after receiving paracetamol 4.0 g daily for 5 days. There is, therefore, no contraindication to the use of paracetamol in the therapeutic doses in the presence of stable chronic liver disease.

Al-Obaidy *et al.* (1996) demonstrated that the rate constant of glucuronide formation was higher in the children with liver disease (age 7 months to 12 years) compared to the value reported in healthy children of similar age, while the rate constant of the formation of paracetamol sulphate was not different from that in normal children. The plasma half-life of paracetamol was positively related to prothrombin time, and negatively to the serum albumin. The authors

suggested that there is no cause for concern in the use of single standard therapeutic dose of paracetamol in children with chronic liver disease.

El-Azab *et al.* (1996) showed that elimination of paracetamol was significantly prolonged in liver cirrhotic patients suffering from schistosomal infection both younger (9-25 years old) and elderly (45-65 years old) groups compared to the normal group. Plasma concentration of paracetamol-glucuronide formation was greatly decreased in both patient groups, whereas no significant different in the plasma concentration of paracetamol-sulphate formation compared to those in corresponding healthy subjects. The authors suggested that this may be due to the different stage of post-schistosomal infection, since the increase of the sulfotransferase activity is observed at 10 weeks post infection with *S. mansoni* and the return to the control level 14 weeks after the infection. The decrease of urinary excretion of paracetamol-sulphate in elderly patient group could be explained by the renal insufficiency.

Jorup-Ronstrom *et al.* (1986) studied the single-dose pharmacokinetic of paracetamol in patients with viral hepatitis during the acute and the convalescent phase. Plasma clearance was significantly decreased during the acute phase compared to convalescence, while plasma peak concentrations were unaffected. The highly significant difference (50%) in clearance between the acute and convalescence phase of hepatitis shows depressed metabolism during the acute phase. The data suggest normal single dosage for paracetamol in acute viral hepatitis, and dose modification only in severe cases.

1.4.3.3 Renal disease

Lee *et al.* (1996) demonstrated that the plasma paracetamol, sulphate and

glucuronide concentrations were significantly ($P < 0.05$) reduced in haemodialysis patients during haemodialysis when compared with the same patients on a non-haemodialysis day and to the chronic ambulatory peritoneal dialysis group except for plasma glucuronide. This indicates the effective removal of paracetamol and metabolites by haemodialysis. In contrast, chronic ambulatory peritoneal dialysis seemed to remove glucuronide only. More work needs to be done in chronic ambulatory peritoneal dialysis patients to determine the clinical significance of this reduced elimination of paracetamol and its sulphate metabolite especially during chronic dosing.

Prescott *et al.* (1989) showed that in the patients with moderate renal failure the renal clearance of paracetamol glucuronide and sulphate were greatly reduced and correlated with the plasma creatinine concentration. The authors suggested that the polar glucuronide and sulphate conjugates are excreted primarily by active tubular secretion but the renal clearance of paracetamol depends on glumerular filtration with extensive passive tubular reabsorption. The strikingly disproportionate decrease in the clearance of the conjugates implies much greater reduction in the capacity for active tubular transport than for passive reabsorption. It is also possible that competition or saturation of tubular transport by retained endogenous anions contributes to the very low clearance of the conjugates in patients with renal failure.

Chan *et al.* (1997) showed that the absorption and elimination of paracetamol were unaffected in 38 Chinese patients with non-insulin-dependent diabetes mellitus (NIDDM) who had either normal renal function or varying degrees of renal impairment. However, the area under the plasma concentration

time curve and the elimination half-life of paracetamol metabolites increased significantly with worsening renal insufficiency. Mean renal clearances of paracetamol and its conjugates were significantly reduced in these subjects. There was no evidence of altered metabolic activation with renal impairment. The results demonstrate that paracetamol disposition in minimally affected by diabetic nephropathy; however, extensive accumulation of conjugates may occur.

Martin *et al.* (1991) compared the disposition of oral paracetamol (1 g 3 times daily for 10 days) in 6 healthy volunteers and 6 conservatively-managed patients with chronic renal failure (mean plasma creatinine 451 μmol/l). The plasma concentrations of paracetamol were higher in the renal failure p..ients than in the healthy volunteers. The mean values over the 10 days of treatment of 3.1 ± 0.6 mg/l and 1.1 ± 0.3 mg/l, respectively ($P < 0.01$). The mechanisms are unknown, but it has been suggested that biliary excretion of paracetamol conjugates may become more important when their urinary excretion is reduced in renal failure. In such circumstances the enterohepatic circulation of glucuronide and sulphate metabolites may be increased and paracetamol may be regenerated by hydrolysis of the conjugates by gastrointestinal flora, with subsequent reabsorption of the parent drug. The mean daily plasma concentrations of the sulphate and glucuronide conjugates of paracetamol were markedly higher in the renal failure group. The authors suggested that in patients with renal failure the ability of the kidney to eliminate polar metabolites is limited, and during repeated dosing significant accumulation of paracetamol conjugates was expected.

Martin *et al.* (1993) showed that the plasma concentrations of glucuronide

and sulphate conjugates of paracetamol are decreased in 6 patients with end-stage renal failure (creatinine clearance < 5 ml/min) maintained on haemodialysis 2 or 3 times per week. The authors suggested that in patients with renal failure, there is retention of sulphate derived from dietary sources as a consequence of its decreased renal excretion. Another explanation for the lower plasma concentrations of the glucuronide conjugate in the haemodialysis patients might be increased biliary excretion of the retained metabolites. Enterohepatic cycling may become more important in renal failure and increased biliary excretion of the glucuronide and sulphate conjugates may have compensated for the reduced renal clearance in these patients.

1.4.3.4 Diabetes Mellitus

Kamali *et al.* (1993) showed that the partial clearance to paracetamol glucuronide were not significantly different, but the partial clearance to paracetamol sulphate was significantly reduced (62 ± 18 ml/hr/kg vs 86 ± 17 ml/hr/kg) and the renal clearance of paracetamol was significantly increased (56 ± 20 ml/hr/kg vs 22 ± 6 ml/hr/kg) in the non-insulin dependent diabetic patients, compared with the control group. The authors suggested that the significantly lower clearance of paracetamol by sulphation in the non-insulin dependent diabetic patients, could be explained either by a reduction in sulphotransferase activity, or by a decrease in the supply of 3′-phosphoadenosine-5′-phosphosulphate (PAPS). The latter could be as a result of the dietary restrictions in the patients, although sulphation has been shown to be less sensitive to change in nutritional status than glucuronidation. The reason for the higher renal clearance of paracetamol in non-insulin dependent diabetic patients

is not clear.

1.4.3.5 Pregnancy

Beaulac-Baillargeon and Rocheleau (1994) showed that the mean paracetamol half-life was significantly lower and oral clearance was significantly higher in the first trimester of human pregnancy (8-12weeks) compared to the normal women (1.62 ± 0.06 hr vs 2.02 ±0.08 hr, 7.14 ± 0.72 l/hr/kg vs 5.22 ±0.46 l/hr/kg, respectively).

1.4.3.6 Cystic fibrosis

Hutabarat *et al.* (1991) studied the disposition of paracetamol after oral administration in adults with cystic fibrosis (n = 5) and in age-matched healthy control subjects (n = 5). The total plasma clearance of paracetamol was found to be greater ($P < 0.025$) in subjects with cystic fibrosis (0.326 ± 0.081 l/hr/kg) than in control subjects (0.247 ± 0.022 l/hr/kg). This difference in clearance was found to be primarily attributable to a greater metabolic clearance of paracetamol to paracetamol sulphate (0.080 ± 0.023 l/hr/kg for subjects with cystic fibrosis and 0.045 ± 0.008 l/hr/kg for control subjects; $P < 0.05$) and to a greater metabolic clearance of paracetamol to paracetamol glucuronide (0.189 ± 0.051 l/hr/kg for subjects with cystic fibrosis and 0.114 ± 0.017 l/hr/kg for control subjects; $P < 0.05$) in person with cystic fibrosis. The authors suggested that the mechanisms that may be responsible for these differences, the most likely is enhanced activity (in subjects with cystic fibrosis) of the transferases that mediate the metabolism of paracetamol to paracetamol sulphate and paracetamol glucuronide, respectively.

1.4.3.7 Malnutrition

Jung (1984) studied the influence of dietary protein deficiency on the pharmacokinetics of paracetamol in male Sprague-Dawley rats fed for 4 weeks on 23% (control) or a 5% (low) protein diet. The total plasma clearance per kilogram of body weight and elimination rate constant were both decreased by approximately 36% when compared to rats on normal protein diet. Rats on a low protein diet excreted a larger percentage of the administered dose as the glucuronide conjugate (34.6 ± 4.4% *vs* 12.3 ± 1.4%) and a smaller percentage paracetamol sulphate (41.0 ± 2.7% *vs* 70.1 ± 2.4%). In addition, there was reduction in the partial metabolic clearance to paracetamol sulphate and a concomitant 2-fold increase in the partial metabolic clearance to paracetamol glucuronide. The author suggested that the availability of sulphate ions, usually derived from dietary proteins, may still be lower than normal in the protein-deficient rats. Thus, the pool of inorganic sulphate may be depleted when high doses of substrates of sulfotransferase are administered or when one is on a low protein diet. A reduction in the inorganic sulphate concentration in the blood will lead to a decrease in the rate of synthesis of adenosine 3′-phosphat-5′-phosphosulfate, the cosubstrate for sulphate conjugation and, ultimately, the *in vivo* rate of sulphation. In addition, the increase in the proportion of the dose excreted as the glucuronide conjugate as well as the higher plasma concentration of paracetamol glucuronide in the protein-deficient rates is consistent with the observation that a diet low in sulfur-containing amino acids, such as methionine and cysteine, induces an increase in UDP-glucuronyl transferase activity. In as much as glucuronic acid is derived from carbohydrate metabolism, the increased

excretion of the glucuronide conjugate could be due to the fact that the low protein diet was also a high carbohydrate diet.

1.4.3.8 Congestive heart failure

Ochs *et al.* (1983) studied the pharmacokinetics of paracetamol in twelve patients, 30-66 years of age, with stable class III or IV congestive heart failure (CHF) and 12 healthy controls matched for age, sex, and weight received single 650 mg intravenous doses of paracetamol. Compared with controls, mean total clearance of paracetamol was reduced in CHF patients (3.56 vs 4.59 ml/min/kg, $P < 0.025$), indicating reduced biotransformation capacity in these disease. Volume of distribution was also significantly reduced in CHF patients (0.85 vs 1.02 l/kg, $P < 0.05$). Since elimination half-life depends on both volume of distribution and clearance (both of which were reduced), the half-life was similar between groups (2.87 vs 2.34 hr). Thus, hepatic conjugation of paracetamol is impaired in CHF patients.

1.4.3.9 Other disease

Ismail *et al.* (1995) showed that neither during nor after treatment of falciparum malaria affected to paracetamol disposition in Thai patients [oral clearance (malaria 3.6 ml/min/kg, convalescence 3.9 ml/min/kg), the elimination half-life (malaria 3.8 hr, convalescence 3.7 hr) and apparent volume of distribution (malaria 1.2 l/kg, convalescence 1.2 l/kg)]. In addition, the urinary excretion of paracetamol and its major phase II metabolites and their formation clearances from paracetamol were not significantly different between the two study phases.

1.4.3.10 Alcoholism

Girre *et al.* (1993) showed that the elimination half-life of paracetamol was significantly shorter in the alcoholic patients than in the controls (1.70 ± 0.55 vs 2.84 ± 0.30 hr, $P < 0.001$). Similarly, total plasma paracetamol clearance was significantly higher in the patients than in the controls (29.19 ± 13.37 vs 24.45 ± 11.10 l/hr, $P < 0.05$). These results suggest that its potential liver toxicity might be enhanced in chronically alcoholic patients.

1.4.4 Effect of Other Drugs

1.4.4.1 Oral Contraceptive steroids

Ochs *et al.* (1984) showed that paracetamol clearance in subjects receiving oral contraceptive steroids was greater (5.2 ml/min/kg vs 6.1 ml/min/kg) and $t_{1/2}$ shorter (2.2 hr vs 1.9 hr) compared to control subjects.

Miners *et al.* (1983) found that paracetamol clearance in females using oral contraceptive steroids was 49% greater than in the control females. Glucuronide and oxidation metabolism were both induced in the oral contraceptive steroids users but sulphation was not altered.

Mitchell *et al.* (1983) examined the effect of low-dose estrogen oral contraceptive steroids on paracetamol metabolism and elimination. Plasma paracetamol clearance rose from 287 ± 13 ml/min to 470 ± 51 ml/min in women taking oral contraceptive steroids, whereas the elimination half-life decrease from 2.40 ± 0.14 hr to 1.67 ± 0.16 hr. The fraction clearance and rate of elimination of paracetamol by glucuronidation increase in women taking oral contraceptive steroids, but the clearance and elimination by sulphation did not differ significantly from values in control subjects. Fractional clearance of the

cysteine adduct also increased significantly, but clearance of paracetamol mercapturic acid did not change. The authors suggested that the increased clearance of paracetamol from plasma in women taking oral contraceptive steroids results from increased glucuronidation of the drug, although the mechanism is not know.

Scavone *et al.* (1990) evaluated the effect of chronic conjugated estrogen use on paracetamol pharmacokinetics in thirty healthy female volunteers. In this study, conjugated estrogen use did not alter paracetamol pharmacokinetics, although low-dose estrogen-containing oral contraceptives has been reported to enhance the metabolic clearance of paracetamol. The authors suggested that difference between the effect of oral contraceptives and conjugated estrogens on the disposition of paracetamol which undergo glucuronide and sulphate conjugation may be attributable to the influence of progestins, or to the combination of progestins and estrogens in oral contraceptive preparations.

1.4.4.2 Sulfinpyrazone

Miners *et al.* (1984) demonstrated that pretreatment with 800 mg per day of sulfinpyrazone for 1 wk increased paracetamol clearance by 23% (from 5.70 ± 0.21 ml/min/kg to 7.00 ±0.39 ml/min/kg). The increase in paracetamol clearance was a result of induction of paracetamol glucuronidation and oxidation; clearance of glucuronic acid conjugate was 26% greater and clearance of glutathione-derived conjugates, reflecting the activity of oxidative pathway, was 43% greater than the values in control group.

1.4.4.3 Anticonvulsant

Miners *et al.* (1984) showed that paracetamol clearance was increased

in patients receiving anticonvulsant drugs, phenytoin or carbamazepine, by 46% (8.32 ± 0.45 ml/min/kg and 5.70 ± 0.21 ml/min/kg) and paracetamol half-life was correspondingly decreased. The reduction was a result of an approximately 60% increase in clearance of glucuronic acid conjugate and glutathione-derived conjugates, with clearance of sulphate conjugate unaltered. The increase in paracetamol clearance was a result of induction of paracetamol glucuronidation and oxidation.

1.4.4.4 Propranolol

Baraka *et al.* (1990) demonstrated that pretreatment with 60 mg per day of propranolol HCl for 4 days increased the paracetamol half-life by 25 ± 12% and lower its clearance by 14 ± 3%. Fractional clearance of paracetamol as glucuronide, cysteine and mercapturate conjugates were significantly reduced (27 ± 6%, 16 ± 3% and 32 ± 7%, respectively) but not as sulphate. The authors suggested that propranolol inhibits paracetamol metabolism predominantly through inhibition of the oxidation and glucuronidation pathways.

1.4.4.5 Isoniazid

Epstein *et al.* (1991) investigated the inhibition of the metabolism of paracetamol by isoniazid. Pretreatment with isoniazid 300 mg daily for 7 days markedly inhibited the clearance of the glutathione metabolites by 69.7%. Total paracetamol clearance was lower by 15.2%. There was no effect of isoniazid on the non-oxidative pathways of paracetamol elimination. Two days after isoniazid was discontinued, paracetamol metabolism had returned to pre-isoniazid values. The result showed that isoniazid is a potent reversible inhibitor of the oxidative metabolism of paracetamol. This small effect of isoniazid on

paracetamol clearance represents a clinically inconsequential drug interaction. If, however, isoniazid were ingested at the same time as an acute or chronic paracetamol overdose, a clinically useful drug interaction, the inhibition of formation of the toxic intermediate and prevention of hepatotoxicity, might occur. The effect of paracetamol on the risk of isoniazid hepatotoxicity is presently unknown. This study suggests that concomitant administration of isoniazid and paracetamol is not associated with an increased formation of the toxic metabolite of paracetamol; in fact the reverse was shown.

1.4.4.6 Probenecid

Kamali (1993) investigated the influence of probenecid on the pharmacokinetics of paracetamol in healthy volunteers. Pretreatment with probenecid caused a significant decrease in paracetamol clearance by 54.9% (6.23 ml/min/kg to 3.42 ml/min/kg). The urinary excretion of paracetamol sulphate (243 mg to 193 mg) and glucuronide (348 mg to 74.5 mg) were significantly reduced, whereas that of paracetamol was unchanged. The authors suggested that probenecid inhibits the activity of the hepatic enzyme, uridine diphosphate glucuronyl transferase (UDPG-transferase) and competes with the active renal excretion of paracetamol sulphate.

1.4.4.7 Cimetidine

Slattery *et al.* (1989) investigated effect of cimetidine on paracetamol disposition in humans. Pretreatment with cimetidine 300 mg every 6 hours for 50 hours and continuing for 22 hours after paracetamol, the result showed that cimetidine has no effect on the clearance of any paracetamol metabolite. Studies in microsomes indicated that cimetidine (1.5 mmol/l) inhibited

paracetamol reactive metabolite formation (approximately 80%). Though this effect did not occur at 0.02 mmol/l cimetidine, which is a concentration 5 to 10 times the concentration required for 50% inhibition of acid secretion in human (0.002 to 0.005 mmol/l). The authors concluded that cimetidine, at least in therapeutic doses, will not protect against paracetamol-induced hepatotoxicity in normal human but a substantially higher dose which is effective in rats and mice may be effective in human.

1.4.4.8 Mestranol

Drozdzik *et al.* (1994) investigated the effect of mestranol on the pharmacokinetics of paracetamol. The study was carried out on 20 female rabbits. The study revealed an increase in AUC and paracetamol half-life as well as decrease in the total body clearance. The authors concluded that there is an interaction between mestranol and paracetamol leading to a decrease in total body paracetamol clearance.

1.4.4.9 Sodium salicylate

Douidar *et al.* (1985) studied the effect of sodium salicylate (SS) pretreatment on paracetamol (APAP) metabolism and hepatotoxicity in mice. Mice were given a single oral dose of SS (100 mg/kg) 1 hr before graded doses of APAP (150-500 mg/kg). At 500 mg of APAP per kg, mortality rate was 38% in SS+APAP group; no mortality was seen among animal treated with APAP alone. Incidence of hepatic necrosis and mean lesion grades at 300- and 500-mg/kg doses increased in mice pretreated with SS. Mice that received SS+APAP had significantly higher levels of serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase and isocitric dehydrogenase

at a doses compared to mice treated with APAP alone. APAP glucuronide and sulphate conjugates decreased and APAP mercapturate conjugate increased in urine of mice receiving SS+APAP treatment. The authors suggested that SS pretreatment alters APAP biotransformation profile and potentiates the hepatotoxic effect of APAP in mice. Since mercapturic acid conjugate (N-acetylcysteine-APAP conjugate) is a urinary degradation product of APAP-S-glutathione conjugate formed in the liver. Glutathione acts as a detoxifying agent for the toxic reactive metabolite of APAP formed by hepatic cytochrome P-450 mixed-function oxidase system. The increase in mercapturic acid conjugate excreted in urine reflects the increase in APAP glutathione conjugate that results from the increase in formation of APAP toxic metabolite. The decrease in APAP sulphate excretion is not completely understood. The APAP glucuronide conjugate decreased in urine of mice receiving SS+APAP group suggested that salicylates may interfere with APAP for the glucuronidation process in the liver. This interference, whether competitive or noncompetitive, thus altering the metabolism profile of APAP in mice.

1.4.5 Effect of Food

Houston and Levy (1975, 1976) showed that large doses of vitamin C (3 g) can reduce sulphate conjugation of paracetamol by competing for available sulphate in the body.

Pantuck *et al.* (1984) showed that the glucuronidation and metabolic clearance of paracetamol are increased during consumption of cabbage and Brussels sprouts, as evidenced by a 17% increase in mean metabolic clearance rate. These changes indicate that this diet stimulates the metabolism of

paracetamol. When the subjects were fed the Brussels sprouts-and cabbage-containing diet there was an increase in plasma in the ratio of paracetamol glucuronide to paracetamol, indicating that the increase in paracetamol metabolism was due, at least in part, to enhanced glucuronide formation. Further support for a stimulatory effect of the Brussels sprouts-and cabbage-containing diet on paracetamol glucuronidation is provided by the finding that when the subjects were fed this diet, the proportion of paracetamol excreted in urine in 24 hr as glucuronide conjugate increased. There were, however, no comparable increases in ratio in plasma of paracetamol sulphate to paracetamol or in proportion of paracetamol excreted in urine in 24 hr as sulphate conjugate when the subjects ate the Brussels sprouts-and cabbage-containing diet, indicating that this diet did not stimulate sulphate conjugation.

Indications

Although equivalent to aspirin as an effective analgesic and antipyretic agent, paracetamol differs by its lack of anti-inflammatory property. It does not affect uric acid level and lacks platelet inhibiting property. The drug is useful in mild to moderate pain such as headache, myalgia, postpartum pain, and other circumstances in which aspirin is an effective analgesic. Paracetamol alone is inadequate therapy for inflammatory conditions such as rheumatoid arthritis, although it may be used as an analgesic adjunct to anti-inflammatory therapy. For mild analgesia, paracetamol is the preferred drug in patients allergic to aspirin or when salicylates are poorly tolerated. It is preferable to aspirin in patients with hemophilia or a history of peptic ulcer and in those in whom

bronchospasm is precipitated by aspirin. Unlike aspirin, paracetamol does not antagonize the effects of uricosuric agents; it may be used concomitantly with probenecid in the treatment of gout. Concomitant use with aspirin may increase blood levels of the latter drug.

Adverse Effects

With normal therapeutic doses, paracetamol is virtually free of any significant adverse effects. Skin rash and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial, but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions (Clissold, 1986; David and Edward, 1994; Mycek *et al.*, 1997). Patients who show hypersensitivity reactions to the salicylates only rarely exhibit sensitivity to paracetamol and related drugs (Stevenson and Lewis, 1987). There may be minor alterations in leukocyte count, but these are generally transient (Mycek *et al.*, 1997). In a few isolated cases, the use of paracetamol has been associated with agranulocytosis, neutropenia, thrombocytopenia, and pancytopenia (Paul, 1991).

Toxic Effects

The toxic metabolite of paracetamol is N-acetyl-p-benzoquinone imine (NAPQI) (James and Raphael, 1990; Mycek *et al.*, 1997; Paul, 1991). NAPQI is formed by the cytochrome P450s CYP 2E1, 1A2, and 3A4. The quantitatively most significant of these is CYP 2E1 (Raucy *et al.*, 1989). This reactive metabolite reacts with nucleophilic groups present on cellular

macromolecules such as protein, resulting in hepatotoxicity. In large toxic doses paracetamol causes acute centrilobular hepatic necrosis in animals (Lim *et al.*, 1994) and humans (Golden *et al.*, 1981; McJunkin *et al.*, 1976). There are considerable species differences in susceptibility and acute hepatotoxic doses in hamsters, mice, and rats are about 150 mg/kg, 300mg/kg, and 3,000 mg/kg, respectively. In adults hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (150 to 250 mg/kg) of paracetamol (Barker *et al.*, 1977; Bonkowsky *et al.*, 1978; Clissold, 1986; Hamlyn *et al.*, 1978; Paul, 1991); doses of 20 to 25 g or more are potentially fatal, death being caused by severe hepatotoxicity with central lobular necrosis, sometimes associated with acute renal tubular necrosis. Symptoms during the first 2 days of acute poisoning by paracetamol may not reflect the potential seriousness of the intoxication. Nausea vomiting, anorexia, and abdominal pain occur during the initial 24 hours and may persist for a week or more. Clinical indication of hepatic damage become manifest within 2 to 4 days of ingestion of toxic doses. Initially, plasma transaminases are elevated (sometimes markedly so), and the concentration of bilirubin in plasma may be increased; in addition, the prothrombin time is prolonged. Perhaps 10% of poisoned patients who do not receive specific treatment develop severe liver damage; of these, 10 to 20% eventually die of hepatic failure. Acute renal failure also occurs in some patients.

Severe liver damage (with levels of aspartate aminotransferase activity in excess of 1,000 I.U. per liter of plasma) occurs in 90% of patients with plasma concentrations of paracetamol greater than 300 μg/ml at 4 hours or 45 μ

g/ml at 15 hours after the ingestion of the drug (Paul, 1991; Prescott *et al.*, 1979). Minimal hepatic damage can be anticipated when the drug concentration is less than 120 μg/ml at 4 hours or 30 μg/ml at 12 hours after ingestion (Paul, 1991). The potential severity of hepatic necrosis can also be predicted from the half-life of paracetamol observed in the patient; values greater than 4 hours imply that necrosis will occur, while values greater than 12 hours suggest that hepatic coma is likely (Gazzard *et al.*, 1977; Prescott *et al.*, 1971). In patients with severe liver damage there may be a progressive increase in the plasma half-life. This impaired paracetamol metabolism seems to reflect almost immediate interference with hepatocyte function rather than concentration-dependent saturation of glucuronide conjugation. Prolongation of the plasma paracetamol half-life is associated with a marked increase in the ratio of the plasma concentrations of unchanged to conjugated drug, and in patients with fatal hepatic necrosis the conjugation of paracetamol may virtually cease.

In children, risk is defined as doses > 150 mg/kg. Maximum liver damage occurs 2-4 days after ingestion, and elevated levels of bilirubin in serum and jaundice may appear 2-6 days after ingestion. Symptoms include vomiting, anorexia, and epigastric pain. Hepatic encephalopathy may develop, even in relatively mild cases. Paracetamol levels in serum associated with hepatotoxicity are usually > 300 μg/ml at 4 hr postingestion or > 50 μg/ml at 12 hr. Hepatotoxicity is usually not seen at levels < 120 or < 50 μg/ml at 4 hr and 12 hr, respectively (Adamson, 1988; Clissold, 1986; Miners *et al.*, 1988).

Paracetamol causes methaemoglobinemia and oxidative hemolysis in dogs, pigs and cats but not normally in humans, even after over dosage (Henne-Bruns

et al., 1988). In chronic toxicity studies, paracetamol has less potential for nephrotoxicity (renal papillary necrosis) than aspirin and the non-steroidal anti-inflammatory analgesics (Golden *et al.*, 1981). Strain-dependent cataract formation and other ocular abnormalities have been described in induced mice (Zhao and Shichi, 1998) and in one study, paracetamol produced a high incidence of liver cell tumors in 1F mice (Flaks, 1983). High doses of paracetamol given chronically to animals may cause testicular atrophy and inhibition of spermatogenesis (Wiger *et al.*, 1995).

Treatment

Early diagnosis is vital in the treatment of overdosage with paracetamol, and methods are available for the rapid determination of concentrations of the drug in plasma. However, therapy should not be delayed while awaiting laboratory results if the history suggests a significant overdosage. Vigorous supportive therapy is essential when intoxication is severe. Gastric lavage should be performed in most cases, preferably within 4 hours of the ingestion. Activated charcoal is usually not administered because it can absorb the antidote, N-acetylcysteine, and reduce its efficacy (Paul, 1991).

Liver damage following paracetamol overdosage can be prevented by early treatment (within 8-10 hours of the overdosage) with sulfhydryl compounds like N-acetylcysteine and methionine (Crome *et al.*, 1976; McJunkin *et al.*, 1976; Prescott *et al.*, 1979; Vale *et al.*, 1981), which probably act, in part, by replenishing hepatic stores of glutathione. N-acetylcysteine is particularly effective when given orally. The drug is recommended if less than 24 hours has

elapsed since ingestion of paracetamol, although treatment with N-acetylcysteine is more effective when given less than 10 hours after ingestion. An oral loading of 140 mg/kg is given, followed by the administration of 70 mg/kg every 4 hours for 17 doses. Treatment should being immediately upon suspecting a significant paracetamol overdosage, and it is terminated if assays of paracetamol in plasma indicate that the risk of hepatotoxicity is low (Paul, 1991).

Preparations, Routes of Paracetamol, and Dosage

1. Oral forms

Paracetamol is marketed under many trade names (e.g. TEMPRA, TYLENOL). Oral dosage forms available include tablets, soluble tablets, pediatric soluble tablets, extended-release tablets, fruit-flavored chewable tablets, pediatric elixirs, suspensions, and drops. The strength of solid oral dosage forms ranges from 80 mg to 650 mg. The strengths of paracetamol tablets USP include 325 mg, 500 mg, and 650 mg. The usual strength of paracetamol tablets BP 500 mg. The strength of liquid oral dosage forms ranges from 120 mg to 250 mg per 5 ml. In the USA, drops are available containing 100 mg/ml.

2. Rectal forms

Suppositories are available containing 80 mg to 650 mg paracetamol in the USA and 125 mg or 500 mg paracetamol in UK.

Generally, paracetamol preparations should be stored in airtight containers. Liquid preparations, in particular, should be protected from light. Suppositories

should be stored in a cool place. Paracetamol is available in combination with, for example, aspirin, codeine phosphate, caffeine, dextromethorphan, propoxyphene hydrochloride, dihydrocodeine tartrate, diphenhydramine, doxylamine, ephedrine, scopolamine, isometheptene mucate, pentazocine hydrochloride, phenylephrine, phenylpropanolamine, pholcodine, promethazine, and pseudoephedrine.

The conventional oral dose of paracetamol is 325 to 1,000 mg (625 mg rectally); the total daily dose should not exceed 4,000 mg. For children, the single dose is 40 to 480 mg, depending upon age and weight; no more than five doses should be administered in 24 hours. A dose of 10 mg/kg may also be used. Paracetamol should not be administered for more than 10 days or to young children except upon advice of a physician.

Effects of Exercise on Pharmacokinetics

Exercise can produce dramatic change in the pharmacokinetic variables of certain drugs, resulting in altered clinical responses because the amount of drug reaching the bloodstream and ultimately reaching target tissues is excessively high or excessively low (Sweeney, 1981; Van Baak, 1990). The magnitude of these changes is dependent on factors that pertain to the characteristics of each drug as well as exercise-related factors such as exercise intensity, mode, and duration (Ciccone, 1995).

1. Exercise and Absorption

Exercise can affect absorption in two primary ways. First, increased tissue heat during exercise will increase kinetic molecular movement and thus increase diffusion of drug molecules across biological membranes. Second, drug dispersion away from the drug delivery site can be increased or decreased, depending on whether exercise increases or decreases blood flow to the site of drug administration (Ciccone, 1995).

1.1 Absorption from the Gastrointestinal Tract

Exercise may influence a number of factors which are important in the regulation of the absorption of drugs from the gastrointestinal tract, including gastric emptying, gastrointestinal transit, intestinal blood flow, gastrointestinal pH, changes in nervous activity, hormones and peptides.

1.1.1 Gastric emptying

Gastric emptying regulates the rate of drug delivery to the absorption site (the small intestine for most drugs). Exercise can either enhance or delay gastric emptying such as in the study of Neufer *et al.* (1989) who examined the gastric emptying during treadmill exercise performed over a wide range of intensities relative to resting conditions, 10 men ingested 400 ml of water prior to each of six 15 min exercise bouts or 15 min of seated rest. Three bouts of walking exercise (1.57 m/s) were performed at increasing grades eliciting approximately 28%, 41% or 56% of $\dot{V}O_{2max}$. On a separate day, three bouts of running (2.88 m/s) exercise were performed at grades eliciting approximately 57%, 65% or 75% of $\dot{V}O_{2max}$. Gastric emptying was increased during treadmill exercise at all intensities excluding 75% $\dot{V}O_{2max}$ as compared to resting group. Gastric emptying was similar for all intensities during walking and at 57% and 65% $\dot{V}O_{2max}$ during running. These data demonstrate that gastric emptying is similarly increased during both moderate intensity (approximately 28%-65% $\dot{V}O_{2max}$) walking or running exercise as compared to resting conditions. However, gastric emptying decreases during high intensity exercise. Increases in gastric emptying during moderate intensity treadmill exercise may be related to increases in intragastric pressure brought about by contractile activity of the abdominal muscles (Neufer *et al.*, 1989).

Moore *et al.* (1990) reported that exercise (walked on an exercise treadmill at 3.2 km/hr or at 6.4 km/hr) significantly increased gastric emptying (at rest emptying half-time ($t_{1/2}$) = 72.6 $\pm$ 7.6 min; 3.2 km/hr $t_{1/2}$ = 44.5 $\pm$ 3.9 min, P =

0.005; 6.4 km/hr $t_{1/2}$ = 32.9 ± 1.9 min, P = 0.005). The 6.4 km/hr emptying time was significantly faster than the 3.2 km/hr emptying.

Cammack *et al.* (1982) studied the effect of intermittent moderate exercise on the passage of a solid meal, labelled with radioactive Technetium sulphur colloid, through the stomach and small intestine in seven healthy volunteers. Measurements of gastric radioactivity and breath hydrogen excretion were recorded every 10 minutes while subjects exercised in a controlled manner while seated on a bicycle ergometer at a constant rate of 33 pedal revolutions per minute for six hours. These were compared with values obtained during a separate experiment while the same subjects sat upright in a chair. Exercise significantly accelerated gastric emptying (control $t_{1/2}$ = 1.5 ± 0.1 hr; exercise $t_{1/2}$ = 1.2 ± 0.1 hr; P < 0.02) but had no significant effect on small bowel transit time.

1.1.2 Gastrointestinal transit

gastrointestinal transit regulates the time the drug stays at the absorption site. Exercise reduces the intestinal transit time. This effect is important for those drugs which are primarily absorbed from the intestine. For example, Oettle (1991) assessed the effect of moderate exercise (running and riding) on whole gut transit. The study was divided in to three one week periods. During each week the subjects either ran on a treadmill, or cycled on a bicycle ergometer, or rested in a chair for 1 hour every day. The exercise was performed at 50% $\dot{V}O_{2max}$ (moderate exercise). Transit time was dramatically accelerated by moderate exercise (both running and riding). Whole gut transit changed from 51.2 hours (41.9-60.5 hr) at rest to 36.6 hours (31.6-39.2 hr) when riding and

34.0 hours (28.8-39.2 hr) when running. Riding and running both differed significantly from resting ($P < 0.01$); the difference between riding and running was not significant. The mechanism of acceleration of transit by moderate exercise is unclear. The main possibility is through a reduction in visceral blood flow. Visceral blood flow falls with exercise. At level of exertion close to maximum the bowel may only receive 20% of its resting flow, though at 50% $\dot{V}O_{2max}$ (as in this study) gut blood flow is maintained at 70% of normal.

William *et al.* (1987) showed that the gastrointestinal transit is accelerated by approximately 23% during mild exercise (treadmill walking at 5.6 km/hr for 15 minutes).

Harris and Martin (1993) reported that the gastrointestinal transit is accelerated during mild exercise (treadmill walking at 5.6 km/hr). Transit time was 87 ± 7 min at rest, 63 ± 5 min in exercise ($P < 0.05$).

1.1.3 Intestinal blood flow

Intestinal blood flow regulates the removal of drug from the absorption site. Exercise may result in shifting of blood flow away from the gastrointestinal tract towards the active muscle and the lungs (Brouns and Beckers, 1993).

Osada *et al.* (1999) showed that splanchnic blood flow is reduced by approximately 36% during right-legged knee extension-flexion exercise at very low intensity [peak heart rate 76 beats/min] every 6 seconds for 20 minutes. Perko *et al.* (1998) reported that submaximal exercise reduced splanchnic blood flow approximately 43%. Rowell and Colleagues (1964) found that a 60-70% decrease in splanchnic blood flow in humans exercising at 70% of maximal oxygen consumption ($\dot{V}O_{2max}$). At maximal exercise intensity, splanchnic blood

flow may be reduced by about 80% (Clausen, 1977). From these data it is clear that exercise may reduce the absorption rate of those drugs showing a perfusion rate-limited absorption from the gastrointestinal tract such as midazolam (Stromberg *et al.*, 1992).

1.1.4 Gastrointestinal pH

Nielsoen *et al.* (1995) found that maximal ergometer rowing for 30 min decreases the pH of both gastric mucosa from 7.25 (7.04-7.48) to 6.79 (6.67-6.85) ($P < 0.05$) and arterial blood from 7.42 (7.41-7.44) to 7.29 (7.26-7.33) ($P < 0.05$). The later study found that the gastric pH were no differences between the pre-exercise, during exercise (high intensity ergometer cycling) and the post-exercise episodes (Van Nieuwenhoven *et al.*, 1999). This change in pH may alter drug ionization and polarity. Drug absorption may be increased or decreased depending on the nature of the drug molecule and its pK_a.

1.1.5 Neurogenic

Exercise is a known stimulant of the autonomic nervous system and much is known about its effects on gastrointestinal function. During exercise, increased sympathetic adrenergic activity produces vasoconstriction of, and reduced blood flow through, the splanchnic vessels (Grossman *et al.*, 1984; Kraemer *et al.*, 1985,1990; Read and Houghton, 1989; Rowell *et al.*, 1964; Schlant and Sonnenblick, 1986) which could reduce intestinal absorption.

Contractile activity within the stomach is controlled through the vagal system. Increased sympathetic tone and the release of catecholamines are responsible for the inhibition of gastric emptying with vigorous exercise

(Banister and Griffiths, 1972; Brouns *et al.*, 1987; Costil and Saltin, 1974; Galbo *et al.*, 1975).

1.1.6 Hormones and peptides

Moderate exercise can elevated some gastrointestinal hormones and peptides such as motilin an enkephalins. These hormones and peptides are known to increase gastrointestinal motility.

Worobetz and Gerrard (1988) reported that exercise for 2 hr on a treadmill which set at a workload for 50% of their maximum oxygen uptake induced increase in serum motilin. There is evidence that plasma concentration of enkephalins increases with exercise (Grossman and Sulton, 1985). Conversely four other studies have failed to show any alteration in motilin and enkephalins during exercise (Hvidsten *et al.*, 1986; Keeling *et al.*, 1990; Soffer *et al.*, 1993, 1994).

Endogenous opioids such as β-endorphins are released from the pituitary after moderate levels of exercises and β-endorphins delay gastric emptying by decreasing the gastric emptying rate (Konturek, 1980). However, it should bbe noted that increases in plasma β-endorphins are generally reported to occure after, and not during exercise (Farell, 1985; Goldfarb *et al.*, 1987).

Submaximal or maximal exercise can elevated some gastrointestinal hormones and peptides include somatostatin (Hilsted *et al.*, 1980; O'Connor *et al.*, 1995), gastrin (Brandsborg *et al.*, 1978; O'Connor *et al.*, 1995) and cholecystokinin (O'Connor *et al.*, 1995). Changes in hormones and peptides lead to decreases in gastrointestinal motility (Khazaeinia and Ramsey, 2000).

On the other hand, exercise may theoretically increase the absorption rate of those drugs for which diffusion is the rate-limiting step. Diffusion results from the movement of molecules due to their kinetic energy. Exercise increases body temperature in proportion to the relative exercise intensity (Gisolfi and Wenger, 1984; Saltin and Hermansen, 1966) and may thus increase the kinetic energy of drug molecules, consequently speeding up their diffusion rate (Van Baak, 1990). However, it is unlikely that a temperature increase of 1 to 2 °C, such as that is found during exercise, will cause biologically meaningful changes in absorption rate.

The effect of exercise on the drug absorption has been evaluated in several studies, there are evidences of both increased and decreased, as well as of unchanged, plasma drug concentrations such as the study of Aslaksen and Aanderud (1980) which designed a study to investigate the absorption during exercise of 3 different drugs: the antiarrhythmic drug: quinidine sulphate (5 mg/kg), sodium salicylate (10 mg/kg) and the antimicrobial agent: sulphadimidine (10 mg/kg). Exercise was performed as 'interval exercise' (5 minutes' work, 5 minutes' rest) for 3 hours on a bicycle ergometer, the work load was 450 kpm for females and 600 kpm for males. The plasma concentrations of the 3 drugs were not altered significantly by exercise, the authors concluded that there was no significant effect on the absorption rate of these drugs.

Ylitalo *et al.* (1977) examined the effect of exercise which consisted of 50 minutes per hour of playing basketball for 4 hours (mean heart rate 130 to 140 beats/min) on absorption rate of antimicrobial agents (sulphamethizole,

tetracycline and doxycycline). The absorption rate of the drugs was increased, because plasma concentrations of the drugs were higher on the exercise day than on the rest day. The peak plasma concentration of sulphamethizole was increased by approximately 70%, that of tetracycline by 20%, and that of doxycycline by 40%. The authors suggested that the changes in plasma concentrations was due to acute reduces in the volume of distribution of these drugs.

Jogestrand and Andersson (1989) showed that the plasma concentration of the cardiac glycoside digoxin increased more rapidly during 30 and 45 min after oral administration when exercise was performed (the subjects exercised intermittently on a bicycle ergometer for 8 hours) in comparison with supine rest. Two and 4 hr after the intake of digoxin, the serum digoxin concentration was significantly lower during exercise than during rest. Muscle biopsies showed that the concentration of digoxin in skeletal muscle was increased. The most probable reason for these changes in the pharmacokinetics is increased binding of digoxin to exercising muscles.

Stromberg *et al.* (1992) examined the effects of the absorption of midazolam (a sedative-hypnotic agent) during 50 minutes of treadmill running in 6 healthy volunteers. The authors stated that midazolam absorption was impaired during exercise because the peak plasma concentration was significantly lower than during a control, nonexercise period. The authors suggested that at this exercise intensity decrease in splanchnic blood flow would be responsible for slower absorption (Van Baak, 1990).

Schmid *et al.* (1996) studied the effect of physical exercise using cycle ergometry for 1 hour ($\dot{V}O_{2max}$ = 53.4 ± 11.0 ml/min/kg, HR_{max} = 186 ± 7 beats/min) on ferric sodium citrate absorption in eight healthy male subjects. During physical exercise, serum iron increased significantly after administration of 100 mg ferric sodium citrate compared with the control group. The authors concluded that 1 hour of moderate exercise enhanced the rate of iron absorption.

Fujisawa *et al.* (1993) studied the impact of exercise on the intestinal absorptive capacity of fructose in ten healthy male volunteers. The exercise consisted of two 30-min bouts of exercise of increasing intensity on a motor-driven treadmill, separated by a 30-min rest. The intestinal transit time is reduced and the absorption of fructose was decreased as a result of exercise. The authors suggested that exercise reduced intestinal transit time, can cause incomplete absorption of fructose.

Collomp *et al.* (1991) studied the effect of exercise using cycle ergometry at 30% of $\dot{V}O_{2max}$ (moderate exercise) for 1 hour on the pharmacokinetics of caffeine in 12 healthy volunteers. Exercise did lead to a significant rise in plasma concentration from 7.28 ± 0.5 mg/l at rest to 10.45 ± 0.4 mg/l ($P < 0.05$) and reduced the volume of distribution (37 ± 3.46 l vs 20.9 ± 2.34 l; $P < 0.05$). The authors suggested that the changes in plasma concentrations due to the volume of distribution was reduced.

Barclay and Turnberg (1988) studied the effect of moderate exercise on jejunal absorption in seven healthy subjects. Moderate exercise on a bicycle ergometer at a constant 15 km/hr for 50 minutes significantly reduced net absorption of water from 32.0 ± 4.0 ml to 16.2 ± 6.1 ml ($P < 0.02$), sodium from

2.4 ± 0.4 mmol to 0.5 ± 0.9 mmol ($P < 0.05$), chloride from 2.0 ± 0.4 mmol to 0.3 ± 0.7 mmol ($P < 0.05$) and potassium from 0.20 ± 0.02 mmol to 0.01 ± 0.04 mmol ($P < 0.01$). The authors suggested that moderate exercise can influence jejunal absorption of salt and water in man, because the first, during exercise, increased sympathetic adrenergic activity produces vasoconstriction of, and reduced blood flow through, the splanchnic vessels which could reduce intestinal absorption and the second, changes in small intestinal motility and transit may have influenced mucosal transport. It is also feasible that changes in muscle 'tone', possibly induced by exercise, may influence the area of mucosa available for absorption.

Larsen *et al.* (1999) studied the interaction of sulfonylureas (7 mg glibenclamide) and exercise using cycle ergometry for 60 min at 57 ± 3% of $\dot{V}O_{2max}$ on glucose homeostasis in type 2 diabetic patients. The rate of decrease in glucose during exercise was higher ($P < 0.05$) on days with both glibenclamide and exercise, compared with days with glibenclamide alone and days with exercise alone (-0.035 ± 0.009 mmol/l/min vs -0.016 ± 0.002 mmol/l/min and -0.022 ± 0.005 mmol/l/min, respectively). Consequently, the glucose was lower on days with glibenclamide and exercise than on days with glibenclamide or exercise alone (6.7 ± 1.1 mmol/l vs 8.1 ± 0.9 mmol/l and 7.6 ± 1.0 mmol/l, respectively; $P < 0.05$). The authors concluded that the hypoglycemic action of glibenclamide and exercise is enhanced when the treatments are combined. The interaction reflects an increased inhibition by glibenclamide-enhanced insulin levels of hepatic glucose production when hepatic glucose production is accelerated by exercise. The findings indicate that

in physically active type 2 diabetic patients, just as in type 1 diabetic patients, antidiabetic medication, extent of exercise, and intake of meals should be mutually adjusted.

Hence, exercise can produce variable effects on absorption following oral administration, and these effects are probably depend on the characteristics of the drug and the intensity, duration, and type of exercise.

1.2 Absorption from Subcutaneous and Intramuscular Sites

Absorption from intramuscular and subcutaneous sites is usually perfusion rate-limited. Exercise increases the blood flow to active tissue and reduces to inactive tissue in an exercise intensity-related fashion (Brouns and Beckers, 1993). Thus, absorption from sites in active tissue may be increased during exercise, while that from sites in inactive tissues may be reduced (Van Baak, 1990). This observation may be explained by the fact that transmembrane diffusion and blood flow are both increased in exercising tissues and the drug is absorbed more quickly and dispersed more rapidly away from the injection site and into the systemic circulation.

Three studies have addressed the effect of exercise on absorption from subcutaneous sites of insulin (Ferrannini, *et al.*, 1982; Kemmer, *et al.*, 1979; Koivisto and Felig, 1978). After subcutaneous injection of insulin in the thigh, an increased absorption of this agent (measured as the disappearance rate of ^{125}I labelled drug) during moderate and intensive leg exercise has been found. Plasma insulin concentrations were increased by 12% (Koivisto and Felig, 1978) to 25% (Ferrannini *et al.*, 1982) during leg exercise. Increased absorption was

found only when insulin was injected into the active leg, not when arm or abdominal injections were used (Ferrannini *et al.*, 1982; Kemmer *et al.*, 1979; Koivisto and Felig, 1978). Ferrannini *et al.* (1982) found no significant increase in subcutaneous blood flow in the thigh during exercise to explain the increased absorption. The authors suggested that the increased absorption may be due to the massage effect of contracting muscle. External massage of the injection site has been shown to enhance the absorption of insulin, without a concomitant rise in subcutaneous blood flow (Linde, 1986). The authors concluded that (a) intense physical exercise of short duration can accelerate the absorption of subcutaneously injected insulin; (b) the effect is more pronounced at injection sites near the exercising parts; (c) an increase in subcutaneous blood flow is not the main reason for this effect.

Mundie *et al.* (1988) found a tendency for higher serum concentrations of atropine after intramuscular injection of atropine sulfate in the biceps femoris of exercising sheep (treadmill running 20 min at 3-4 mph). The peak atropine concentration was increased by 37% (9.7 $\pm$ 1.3 ng/ml vs 7.1 $\pm$ 2.9 ng/ml). The authors concluded that the absorption rate was significantly increased.

1.3 Transdermal Absorption

Percutaneous absorption may be influenced by skin temperature, the hydration state of the skin and cutaneous blood flow (Van Baak, 1990). Exercise initially increase skin temperature (Saltin and Hermansen, 1966). Diffusion through the skin, as elsewhere, is a temperature-dependent process. Raising the skin temperature should enhance thermodynamic drive and thus increase the

percutaneous absorption rate of drug with diffusion rate-limited absorption (Van Baak, 1990). Sweating enchances skin hydration and therefore would be expected to increase percutaneous absorption of certain drug with diffusion rate-limited absorption characteristics. The overall effect of changes in skin temperature and sweating during exercise on the percutaneous absorption rate of drugs with diffusion rate-limited absorption will depend on the relative contribution of these 2 factors.

Cutaneous blood flow is increased during exercise (Johnson, 1998). An increased cutaneous blood flow will increase the percutaneous absorption of those drugs which show perfusion rate-limited absorption characteristics.

Danon *et al.* (1986) studied the effect of exercise (45 min/hr at 30% of maximal oxygen uptake for 6 hours at ambient temperatures of 22°C or 40°C) on the absorption of methyl salicylate, administered by applying over the chests and backs of the subjects. The absorption of methyl salicylate was increased to more than 3-times above control in subjects exercising in the heat. The authors concluded that exercise and heat exposure, by increasing skin temperature, hydration and blood flow, enhance the percutaneous absorption of methyl salicylate.

Barkve *et al.* (1986) showed that the peak plasma concentration of nitroglycerine administered in a transdermal patch was higher in asymptomatic volunteers undergoing cycling exercise for 20 minutes (heart rate at least 110 beats/min, average 130 beats/min) than in nonexercising subjects.

Weber *et al.* (1987) demonstrated that the plasma concentration of nitroglycerine after transdermal administration during exercise; exercise was

performed on a bicycle ergometer, the workload being adjusted to maintain a heart rate of 110 beats/min was increased. The authors suggested that the increased concentration was mainly due to exercise-induced reduction in hepatic blood flow (Dossing, 1985), which can decrease clearance, prolong the half-life and increase plasma levels of high clearance, hepatic blood flow dependent drug such as nitroglycerine. Another moderate exercise increase cutaneous blood flow and therefore has the potential to increase transdermal nitroglycerine absorption.

Klemsdal *et al.* (1995) studied the effect of physical exercise (moderate bicycle exercise for 20 min) on plasma nicotine concentrations in eight healthy subjects treated with a nicotine patch releasing 14 mg/24 hr. Mean plasma nicotine concentration increased from 9.8 to 11.0 mg/ml during physical exercise compared to rest. The authors suggested that exercise-induced increase in blood flow in the patch area and therefore has the potential to increase transdermal nicotine absorption.

1.4 Inhalation Absorption

Schmekel *et al.* (1992) investigated whether a constant submaximal exercise challenge affected the plasma pharmacokinetics of inhaled terbutaline in healthy nonsmokers. The rate of increase of plasma concentrations and the maximal plasma concentrations were higher during exercise than during rest. The plasma concentration fell rapidly after cessation of the exercise and approached those obtained at rest. The authors suggested that increased pulmonary and/or bronchial blood flow and reduced surface tension of the liquid

lining of the air space may contribute to the enhancement of absorption of this hydrophilic compound during exercise.

Ghosh *et al.* (1994) investigated the effect of physiological manoeuvres on plasma nedocromil concentration in eight healthy subjects after inhalation of 1 ml nedocromil solution (1% w/v) via a Wright nebuliser. These manoeuvres included steady state treadmill exercise at a submaximal workload for 6-8 min (until heart rate increased above 75% age related maximum predicted value). There were significant increases in plasma drug concentration following exercise. During exercise increased breathing frequency and lung volumes. The results suggest that certain manoeuvres increase the absorption of nedocromil sodium was probably due to increased breathing frequency and lung volumes may accelerate the absorption of drug from the lung and exercise may alter its disposition.

1.5 Intravenous Absorption

Dyke *et al.* (1998a) examined the effects of maximal exercise on the pharmacokinetics of bromsulphalein (BSP) in six adult thoroughbreds (4 mares, 2 geldings). Three interventions were studied: resting on the treadmill (REST), exercised then standing on the treadmill for 30 minutes (MS), and exercised then walking at 2 m/s for 30 minutes (MW). At 60 seconds after completion of exercise, bromsulphalein (BSP) was infused IV. Plasma BSP concentration was higher after exercise. Median hepatic blood flow (BSP clearance) decreased significantly from 23.8 ml/min/kg (REST) to 20.7 ml/min/kg (MS) and 18.7 ml/min/kg (MW). Median steady-state volume of distribution of BSP decreased

from 47.6 ml/kg (REST) to 42.7 ml/kg (MW) and 40.2 ml/kg (MS). The authors concluded that hepatic blood flow and pharmacokinetics of BSP are markedly altered immediately after exercise.

2. Exercise and Distribution

Several factors determine the distribution pattern of drug, including the dilivery of drug to tissue, its ability to pass through tissue membranes and its binding to plasma proteins and to tissue components such as proteins, phospholipids or nucleoproteins. Many lipid soluble drugs are stored by physical solution in the neutral fat. The binding of a drug to plasma proteins limits its concentration in tissues, since only unbound drug is in equilibrium across membranes. Exercise may affect the volume of distribution of drugs in a mumber of ways. The haemodynamic changes that take place during exercise, an increased total blood flow and a redistribution of flow towards the active tissues to inactive tissues (Brouns and Beckers, 1993) may influence the dilivery of drug to certain tissues and also the washout of drug from tissues into which it has distributed.

Exercise may also influence binding to plasma proteins and tissues. During exercise the plasma protein concentration increases (Hyyppa and Poso, 1998; Van Beaumont *et al.*, 1973), due to plasma water moves from the vasculature to the intracellular and interstitial spaces at the onset of intense exercise. The magnitude of the plasma water loss depends on the intensity and duration of, and the intake of fluids during, the exercise. Decreases in plasma volume of up to 5.2% (Greenleaf *et al.*, 1985) to 8.5% (Gore *et al.*, 1992) have been reported.

Increases in plasma protein concentration of the same magnitude as a result of this reduced volume may lead to increased protein binding of drugs.

The volume of distribution (Vd) of a number of drugs has been shown to change during exercise (Mundie *et al.*, 1988; Schlaeffer *et al.*, 1984; Swartz and Sidell, 1973; Theilade *et al.* 1979): for most drugs, this change took the form of a reduction in volume of distribution.

Mundie *et al.* (1988) showed that the volume of distribution of atropine sulfate was reduced by 30% in exercise sheep (treadmill running at 3-4 mph for 20 min).

Schlaeffer *et al.* (1984) reported a 50% lower volume of distribution for the bronchodilator theophylline in healthy volunteers exercising at 50% of $\dot{V}O_{2max}$ for 2 hours, although during exercise at 30% of $\dot{V}O_{2max}$ the volume of distribution was unaffected.

Theilade *et al.* (1979) found that the volume of distribution of antipyrine was 11% lower during a 9 hours march (4.6 km/hr).

Collomp *et al.* (1991) showed that the volume of distribution of caffeine was reduced when subjects performing moderate exercise (30% of $\dot{V}O_{2max}$ for 1 hour) compared with when rest (20.9 ± 2.34 l vs 37 ± 3.46 l; $P < 0.05$).

Mooy *et al.* (1986) found that the volume of distribution of calcium antagonist verapamil and the β-adrenoceptor blocker propranolol (Arends *et al.*, 1986) were not significantly changed during prolonged low-intensity exercise for 7 hours. However, in a number of other studies rapid increases (ranging between 10% and 100%) in plasma concentration of β-blockers propranolol, acebutolol and of verapamil, were demonstrated during exercise (Henry *et al.*, 1981;

Hurwitz *et al.*, 1983; Powis and Snow, 1978). The authors suggested that the changes in plasma concentrations due to a reduction of the volume of distribution during exercise.

Van Baak *et al.* (1992) studied the effect of exercise (during exhaustive exercise at 70% of maximal aerobic power (W_{max}) on a cycle ergometer for 25 min) on the plasma concentrations of propranolol, atenolol and verapamil in 12 healthy volunteers. In a second study the effect of 10 min exercise at 50% of maximal aerobic power on steady state plasma concentrations of propranolol, atenolol and verapamil was compared in 7 healthy subjects. The first study, the plasma concentration of propranolol and verapamil were significantly increased. In contrast, the plasma concentration of atenolol did not change during exercise (265 $\pm$ 115 ng/ml vs 270 $\pm$ 100 ng/ml). In the second study, during the 10 min exercise period the concentrations of verapamil and propranolol increased significantly (propranolol from 51.9 $\pm$ 12.5 ng/ml to 59.6 $\pm$ 10.6 ng/ml, $P < 0.01$, verapamil from 50.9 $\pm$ 15.2 ng/ml to 70.1 $\pm$ 10.6 ng/ml, $P < 0.001$). The plasma concentration of atenolol was not significantly changed during exercise (33.7 $\pm$ 3.0 ng/ml and 33.7 $\pm$ 2.7 ng/ml). From the results it is concluded that exercise led to a reduction in the volume of distribution of propranolol and verapamil during prolonged exercise (25 min) at 70% W_{max}, which was not clearly demonstrable during 10 min exercise at 50% W_{max}. The volume of distribution of verapamil was reduced during 10 min exercise at 50% W_{max}. No change in the volumes of distribution of atenolol during exercise could be shown. The changes in the volumes of distribution of propranolol and verapamil during

exercise may contribute to preventing an increase in the half-life of these drugs in subjects performing prolonged physical exercise.

For other drugs, indications of an increase in volume of distribution during exercise have been found. Swartz and Sidell (1973) showed that the volume of distribution of the cholinesterase reactivator, pralidoxime was increased by approximately 20% during exercise (treadmill walking 4.8 km/hr, 20 minutes per half hour for 3 hours).

Jogestrand and Sundqvist (1981) demonstrated that the plasma concentration of the cardiac glycoside digoxin decreased by 37% during exercise (1 hour cycle ergometry at a heart rate of 120 to 140 beats/min). Muscle biopsies showed that the concentration of digoxin in skeletal muscle was increased. In a subsequent study, Joreteg and Jogestrand (1984) demonstrated that the erythrocyte digoxin concentration decreased during exercise (12%), indicating that the increased uptake of digoxin in skeletal muscle during exercise influenced digoxin concentration in other tissues. The same authors (1983, 1984) also showed that the increased uptake of digoxin into exercise skeletal muscle was related to the intensity of the exercise and the muscle activation frequency.

3. Exercise and Elimination

3.1 Hepatic Elimination

Although drug metabolism can take place in many organs, it is most often the liver which has the greatest metabolic capacity. Hepatic clearance is the most direct quantitative measure of the ability of the liver to eliminate a drug, and includes biliary excretory clearance and hepatic metabolic clearance. For

drugs with a high hepatic extraction ratio, clearance is rate-limited by hepatic blood flow. For drugs with a low extraction ratio, the rate-limiting process could be a slow enzymatic reaction in the hepatocyte, poor biliary transport, poor diffusion into the hepatic cell or strong plasma protein binding.

During exercise, hepatic blood flow is reduced in proportion to the relative exercise intensity (Van Baak, 1990). At a moderate exercise intensity of 50% of $\dot{V}O_{2max}$ hepatic blood flow is reduced by approximately 30%; at an intensity of 70% of $\dot{V}O_{2max}$ the reduction amounts to 50% (Van Baak, 1990); at a maximal exercise hepatic blood flow is reduced by approximately 80% (Swartz *et al.*, 1974). These data suggest that exercise may reduce the hepatic clearance of drug with a high hepatic extraction ratio whose hepatic clearance is blood flow-dependent. Low hepatic extraction drugs will probably not be affected during exercise because clearance of these drug is dependent on the metabolic capacity of the liver rather than on hepatic blood flow (Dossing, 1985).

Kemme *et al.* (2000) examined the effect of exercise-induced reduction in liver blood flow on the pharmacokinetics of recombinant tissue factor pathway inhibitor (rTFPI; rTFPI has been shown to be an effective treatment in an animal models of sepsis and is under investigation for human use). This was a two-way, open-lable, randomized crossover study in eight healthy male volunteers. The subjects in both treatment groups received a continuous intravenous infusion of rTFPI (0.2 mg/kg/hr) concurrently with intravenous sorbitol (50 mg/min) for 4 hours. Sorbitol was used as a biomarker for liver blood flow. The subjects were randomized to remain supine or to exercise on a bicycle ergometer for 30 minutes starting at the beginning of the third hour of the infusion. Exercise

reduced liver blood flow from 1.44 ± 0.06 l/min to 0.40 ± 0.03 l/min. The average clearance of rTFPI decreased from 0.73 ± 0.04 l/min in the supine position to 0.25 ± 0.02 l/min during exercise. This decrease in rTFPI clearance resulted in an 80% increase in plasma rTFPI levels during exercise. The authors suggested that reduction in liver blood flow by exercise markedly increased rTFPI concentrations.

Exercise may influence the plasma protein binding of certain drugs and the diffusion across membranes. Changes in these factors could affect the hepatic clearance of drugs with a low hepatic extraction ratio in which these factors are rate-limiting. Enzymatic reactions are temperature-dependent, suggesting that the increase in body temperature during exercise might increase the enzyme activity and thus the metabolic clearance rate of low extraction drugs in which the enzymatic capacity of the liver is rate-limiting. Exercise may increase bile flow and secretion, thus increasing hepatic clearance of drugs whose clearance is biliary excretion-dependent (Van Baak, 1990).

Sweeney (1981) investigated the effect of exercise (cycle ergometry for 1 hour) on the plasma concentration of the antiarrhythmic drug lidocaine (lignocaine). A 50% increase was found in the plasma concentration of lidocaine during and after exercise. The author suggested that exercise may indeed reduce the hepatic clearance of drugs with a high hepatic extraction ratio.

Two studies investigated the effects of prolonged moderate exercise (20 minutes' cycling at 50% of $\dot{V}O_{2max}$ and 35 minutes' walking per hour for 7 hours) on the disposition of the high extraction drugs verapamil and propranolol (Arends *et al.*, 1986; Mooy *et al.*, 1986). No significant change in clearance was

found on the exercise day compared with the rest day, despite the fact that indocyanine green clearance, as a marker of hepatic blood flow, was significantly reduced during the cycle ergometry periods. It seems unlikely that an increased clearance during the walking periods would have compensated for a reduced clearance during the cycling episodes. Another explanation could be that a reduced hepatic clearance is compensated by an increased nonhepatic clearance.

Theilade *et al.* (1979) investigated the influence of exercise on the hepatic clearance of drug with a low hepatic extraction ratio (phenazone). The authors found that the hepatic clearance was not changed during exercise (9-hour march at 4.6 km/hr) compared with supine bed rest. Swartz *et al.* (1974) also found no effect of a combination of low intensity exercise and environmental heat on clearance of phenazone.

Schlaeffer *et al.* (1984) studied the effect of 2 hours of moderate intensity exercise at 50% of $\dot{V}O_{2max}$ at 22°C and 30% of $\dot{V}O_{2max}$ at 22 °C and 40°C on the clearance of theophylline. Plasma clearance were significantly reduced at the exercise sessions compared with at rest (0.75 ± 0.09, 0.70 ± 0.09, 0.62 ± 0.1 vs 0.99 ± 0.13 ml/min/kg, respectively).

Swartz *et al.* (1974) investigated the effect of exercise conditions (walking on a treadmill at 3 mph for 20 minutes of each half hour for 3 hours) on the elimination and distribution of compounds metabolized by the liver in normal healthy volunteers. Indocyanine green (ICG) and antipyrine (AP) were used as respective examples of compounds rapidly and relatively slowly eliminated by the liver. The plasma half-life for ICG increased significantly under exercise conditions when compared to rest (3.5 min vs 2.3 min). The volume of

distribution changed only slightly (35.6 ml/kg vs 36.3 ml/kg). The plasma clearance reduced by approximately 60% of control (7.3 ml/kg/min vs 11.4 ml/kg/min). The authors suggested that exercise may reduce the hepatic clearance of ICG with a high hepatic extraction ratio because during exercise hepatic blood flow is reduced. The absorption half-life for antipyrine reduced to less than 20% of the control value (2.0 min vs 10.6 min). The total volume of distribution ($Vd = V_1+V_2$) decreased during exercise (505 ml/kg vs 600 ml/kg). The plasma clearance did not change significantly during exercise (0.65 ml/min/kg vs 0.60 ml/min/kg). The authors suggested that factors other than liver plasma flow must be involved in the removal of antipyrine. One is that the hepatic extraction (i.e., the hepatic arteriovenous difference) of antipyrine may be enhanced by the slower perfusion of the liver under conditions of reduced liver plasma flow. Enhanced hepatic extraction of antipyrine would increase the observed clearance rate and partially compensate for lowered liver plasma flow. A second factor is suggested by the kinetic analysis of these data. The apparent volume of distribution for antipyrine in V_2 actually increased under exercise conditions, even though V_1 and Vd (total volume of distribution) decreased. The higher initial plasma concentrations and the more rapid initial disappearance rate under exercise suggest an altered distribution of antipyrine from a contracted central compartment (V_1) to an expanded peripheral compartment (V_2).

Yoon *et al.* (1997) studied the effects of acute physical exercise on the paracetamol-induced hepatotoxicity in adult female rats. Rats were forced to move at a speed of 10 m/min for 2 hr in a rotation cage. Immediately following the exercise bout rats were treated with paracetamol (APAP; 700 mg/kg, i.p.).

The physical exercise enhanced the hepatotoxicity of APAP as shown by increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities measured 24 hr following the treatment. A significant decrease in hepatic glutathione (GSH) was observed in the rats forced to exercise. The authors suggested that the enhancement of APAP hepatotoxicity was associated with the depression of this endogenous tripeptide. Lew and Quintanilha (1991) shown that the same amount of submaximal exercise, trained rats are able to maintain their levels of glutathione or their glutathione redox status (in the liver, heart, skeletal muscle and plasma) in contrast to their untrained counterparts. Also, upon administration of paracetamol, trained rats show a less pronounced depletion in liver glutathione than untrained rats, that training significantly increases (50-70%) glutathione peroxidase and reductase, glucose-6-phosphate dehydrogenase, and catalase activity. The authors concluded that endurance training tissues will develop mechanisms to prevent glutathione depletion.

Villa *et al.* (1998) studied the effect of physical conditioning on antipyrine clearance in two groups of subjects. Healthy men not engaged in the systematic practice of any sport were compared with endurance runners (defined as men running > 80 km/week). Antipyrine clearance was also significantly elevated and antipyrine half-life reduced in runners. The authors suggested that aerobic conditioning increased hepatic oxidative metabolism of antipyrine (low clearance drug). The same authors (1999) investigated the effects of aerobic conditioning on the different metabolic pathways of antipyrine by comparing the production clearances of antipyrine metabolites. Antipyrine clearance was significantly higher and antipyrine half-life significantly lower (-31%) in runners than in the

controls. There was no significant change with training in the renal clearance of antipyrine or in the norantipyrine (NORA) formation clearance but significant increases were observed in hydroxymethylantipyrine (HMA) and 4-hydroxyantipyrine (OHA) formation clearance (+42% and +37%, respetively). The findings indicate that aerobic conditioning leads to the alteration of the disposition of antipyrine and to a preferential stimulation of its hydroxylation metabolic routes.

Dyke *et al.* (1998b) studied the effects of exercise training on the plasma clearance of antipyrine (20 mg/kg i.v.) in adult mares that either underwent treadmill training for 5 wk (n = 7) or remained in box stalls for the same time period (n = 6). Training consisted of treadmill exercise at 60% (12 min/day) and 90% (3 min/day) of pretraining maximal oxygen consumption for 6 days/wk for 5 wk. The plasma clearance and volume of distribution of antipyrine increased significantly in trained group (from 5.5 to 6.4 ml/min/kg and from 813 to 881 ml/kg, respectively) and decreased significantly in the untrained group. Elimination half-lives did not change neither in the training or box rest. Increases in plasma antipyrine clearance were indicative of an increase in hepatic metabolism of antipyrine. Increases in the volume of distribution of antipyrine suggest that total body water increases as a result of exercise training.

3.2 Renal Elimination

The elimination of a drug into urine is the net result of filtration, secretion and reabsorption. Exercise has been shown to reduce renal blood flow. The reduction is related to the intensity of exercise. It may fall to 25% of the resting

value when strenuous work is performed. The reduction of renal blood flow during exercise produces a concomitant effect on the glomerular filtration rate, though the latter decreases relatively less than the former during exertion. However, the degree of hydration has an important influence on the glomerular filtration rate (Poortmans, 1984). Clearance of drugs that undergo flow-dependent elimination by the kidneys (high-extraction drugs), therefore, can be decreased during exercise because less of the drug is reaching the nephron (Van Baak, 1990).

For the vast majority of drugs, tubular reabsorption is a passive process. The degree of reabsorption depends on the polarity of the drug, the state of ionisation and urine flow. The urinary pH may decrease during exercise (Ylitalo *et al.*, 1977), and therefore the reabsorption of nonpolar weak acids is increased and that of nonpolar weak bases decreased.

Swartz and Sidell (1973) showed that the renal clearance of pralidoxime, a cholinesterase reactivator, tended to be reduced by approximately 10% during exercise (20 minutes per half-hour treadmill walking at 4.8 km/hr for 3 hours). Plasma half-life values for pralidoxime increased with exercise conditions compared to rest (87.7 ± 14.7 min vs 71.2 ± 7.4 min). The authors suggested that the decrease in renal blood flow during exercise affects the excretion of drugs, such as pralidoxime, which are eliminated primarily through the kidneys.

Mason *et al.* (1980) found that the renal clearance of β-blocker atenolol was reduced by approximately 8% during exercise. The authors suggested that decrease in the renal clearance of the drug was probably due to decreased renal blood flow during exercise.

Ylitalo and Hinkka (1985) demonstrated a significant reduction (16%) of the renal clearance of the weak base procainamide during a 4-hours basketball game. Urinary pH and flow were significantly reduced. Distal tubular reabsorption is insignificant in the case of procainamide. In the same study it was found that the renal clearance of the antimicrobial drug sulphadimidine was reduced by 89% and that of its metabolite acetyl-sulphadimidine by 48%. The authors suggeted that exercise suppresses their excretion in urine, occasionally even more than what would be expected on the basis of the decrease in the glumerular filtration rate.

Eddington *et al.* (1998) examined the effect of exercise training on the pharmacokinetics of procainamide and its active metabolite, N-acetylprocainamide (NAPA). Male Sprague Dawley rats were randomly assigned to three testing groups: (1) sedentary, (2) 4 weeks of exercise training and (3) 8 weeks of exercise training. Treadmill speed and exercise duration were gradually increased, reaching a final rate of 24 m/min for an hour by the end of the 4-week or 8-week period. Sedentary and exercise trained rat received a single i.p. dose of procainamide (100 mg/kg). The $t_{1/2}$ of procainamide was significantly ($P < 0.05$) higher in the 8 week exercise group (331 min) as compared to the sedentary group (77 min). In addition, there was a significant reduction in the amount of N-acetylprocainamide formed after 8 weeks of exercise (AUCNAPA = 739 ng/ml/min). Results of this study suggest that prolonged exercise (8 weeks of training) alters the pharmacokinetics of procainamide by modifying the amount of active metabolite formed.

Jogestrand and Andersson (1989) demonstrated that the renal excretion of digoxin over an 8-hour period after intake of the drug was significantly reduced (14%) during exercise.

Piatkowski *et al.* (1993) studied the effect of exercise on renal paracetamol metabolism in Fischer-344 male rats. The exercise consisted of treadmill running at a moderate intensity ($\dot{V}O_{2max}$ 70%) for 8 weeks. Exercise was found to increase renal deacetylation of paracetamol to the nephrotoxic metabolite p-aminophenol by 54% in young and 26% in middle-aged rats and renal microsomal cytochrome P-450 levels were increased 60% and 37% in young and middle-aged runners, respectively. The authors concluded that exercise increased renal paracetamol metabolism, any increase in renal metabolism that is accompanied by a hepatic decrease as occurs with exercise may enhance the importance of the kidney in this process. Thus, implicating the kidney as the second organ whose metabolic capacity is altered by running exercise.

Mauriz *et al.* (2000) investigated the effects of engagement in a program of regular physical exercise on the clearance and metabolite excretion of antipyrine, a marker of oxidative metabolism, in elderly subjects. The metabolites were studied in 37 elderly women (mean age 66 years). Subjects attended 60-min sessions three time a week for 12 weeks. Each session consisted of both aerobic (training of cardiorespiratory capacity) and nonaerobic exercises performed at 50-75% of maximum oxygen uptake. Antipyrine was administered orally and pharmacokinetics parameters were obtained from saliva and urine samples. After 3 months of participation in the exercise program, saliva antipyrine clearance was significantly increased by 17% (0.42 $\pm$ 0.02 vs 0.36 $\pm$ 0.02

ml/min/kg; $P < 0.05$) and the half-life of antipyrine was significantly reduced by 18% (17.9 ± 1.1 hr vs 22.3 ± 1.3 hr; $P < 0.05$). No significant change with exercises was observed in the renal clearance of antipyrine or in the norantipyrine formation clearance, but significant increases were found for hydroxymethylantipyrine (42 ± 5 vs 32 ± 4 μl/kg/min; $P < 0.05$; +31%) and 4-hydroxyantipyrine (243 ± 18 vs 194 ± 17 μl/kg/min; $P < 0.05$; +25%) formation clearances. These finding indicate that regular exercise leads to increased disposition of antipyrine in the elderly and that the main metabolic pathways of the compound are changed differentially.

3.3 Pulmonary Elimination

Lorino *et al.* (1989) investigated the effects of a constant load and prolonged exercise on pulmonary clearance of aerosolized ^{99m} Tc-DTPA (diethylenetriaminepentaacetate) in seven healthy nonsmoking volunteers. The exercise was performed on a treadmill for 75 min, corresponding to 75% of maximal oxygen uptake. After exercise, total clearance were significantly increased ($P < 0.01$). The authors suggested that two mechanisms may be responsible for exercise-induced increase in clearance rate, e.g., an increase in the surface available for diffusion of aerosol particles or changes in integrity of the pulmonary epithelium.

CHAPTER 3

MATERIALS AND METHODS

Chemical and Reagents

The standard paracetamol (Lot No. A 5000) and 3-hydroxy acetanilide (Lot No. A 4911) were purchased from Sigma Chemical Co., St. Louis, U.S.A. Paracetamol (Tylenol®, 500 mg/tablet Lot No. B 045039) was obtained from OLIC (Thailand) Ltd. Methanol (HPLC grade), di-sodium hydrogen orthophosphate (analytical grade), 85% orthophosphoric acid (analytical grade) and 65% perchloric acid were purchased from J.T. Baker Inc.; Univar; Merck and Carlo Erba, respectively. Water was purified for HPLC by the Milli Q Water Purification System (Millipore, Milford, MA, U.S.A.)

Equipments

The HPLC system consisted of a Waters 515 pump, the automated injection system was Waters 717 plus Autosampler (Waters Associates, Milford, MA, U.S.A.). The detector was Jasco UV-975. Detection was made with the variable-wavelength UV detector set at 254 nm and peak area was measured with a Jasco 807-IT integrator (Tokyo, Japan). A Jasco recorder attenuation was set at 32 mV.F.S. and chart speed was 1 mm/min. Separation was achieved on a reversed-phase μ-Bondapak C_{18} column (30 cm × 3.9 mm I.D., particle size 10 μm, Waters Associates). A guard-pak precolumn module was used to obviate the effect of rapid column degeneration.

Methods

1. Subjects

Fourteen Thai male volunteers aged 20-36 yr, weight 57.0-68.3 kg, height 158-171 cm and BMI 20.18-25.91 kg/m^2 were enrolled in this study. All subjects were non-smoker and non-alcoholic. Medication was stopped for at least 1 week before and during the entire period of the study. They also were excluded if they had known history of adverse reactions to paracetamol. The subjects were considered to be healthy as determined by medical history, physical examination, and essential laboratory tests (complete blood count, liver and renal function tests, and fasting blood sugar). The protocol of the studies and the possible side effects of the drug used were explained to the subjects and then they would give written informed consent to the study which was approved by the Ethics Committee, Faculty of Science, Prince of Songkla University, Hat Yai, Thailand.

2. Protocol

Pharmacokinetics of paracetamol were studied on two separate occasions with a 1-week washout period. In occasion 1, each subject received 1,000 mg of paracetamol (500 mg/tablet, 2 tablets) with 200 ml of water. No food was allowed at least 3 hours after drug ingestion. Water or soft drinks was allowed if the subjects had sign and symtom of hypoglycemia. Since the absorption of paracetamol is altered by posture and activity, the subjects were requested to sit upright in their chairs for the first 2 hours and only modest activity was allowed

for the next 2 hours. In occasion 2, each subject was assessed vital signs (body temperature, heart rate, respiratory rate, blood pressure) before and after exercise and received 1,000 mg of paracetamol (500 mg/tablet, 2 tablets) with 200 ml of water just before starting exercise. The trial exercise was started after the intake of paracetamol. It consisted of two 15-minute sessions of treadmill-running (5 km/hr) with 5-minute break for blood sampling. Thus the total excercise time was 30 minutes. This exercise pattern was chosen because of a moderate level of exercise as dertermined by HR_{max}(Anderson, 1978), an attempt to mimic usual daily life exercise (Weber *et al.*, 1987) and it could easily be sustained throughout the entire period of this study.

Blood Sample Collection

Paracetamol was administered after an over night fasting, an indwelling heparin-lock catheter was placed in a vein in the forearm of each subject. Serial blood samples (5 ml) were drawn immediately before paracetamol administration and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 hr post paracetamol administration in to heparinized tubes (50 µl of 100 units/ml heparin). Blood samples were centrifuged at 3,000 rpm for 30 minutes and plasma was separated and stored at -70°C for 4 wks until analysis.

3. Sample Analysis

The plasma paracetamol concentrations were measured by a high performance liquid chromatographic (HPLC) method (modified by the method of Adriaenssens *et al.*, 1978).

3.1 Mobile Phase

The mobile phase was 25 ml methanol in 0.1 M di-sodium hydrogen orthophosphate and adjusted to pH 4.70 with 85% orthophosphoric acid. The mobile phase was freshly prepared in each day and was filtered through 0.45 micropore filtered paper and degased before using. The mobile phase was pumped at 2.0 ml/min. All analysis were performed at room temperature.

3.2 Stock Standard Solution

Standard solution of paracetamol was prepared by dissolving 12.5 mg standard paracetamol in 25 ml distilled water. The stock solution was stored at 4 C and aliquot of the stock solution was used for preparing the working standard paracetamol (10, 25, 50, 100, 200, 300 μg/ml) in solution (deionized water) and plasma (Appendix-2), which were used to run the calibration curves in each day.

3.3 Calibration Curves

The calibration curves were prepared by adding working standard paracetamol solutions and 300 μg/ml of 3-hydroxy acetanilide as internal standard to blank human plasma so that the final concentrations of paracetamol were 2.5, 5.0, 10.0, 15.0, 20.0 and 25.0 μg/ml. The calibration curves of paracetamol (by using peak area ratio between paracetamol and internal standard) was linear in the range of 2.5-25.0 μg/ml.

3.3.1 Recovery

Potential loss of paracetamol during the 10% perchloric acid precipitation

was determined by comparing the peak area of paracetamol extracted from plasma sample in the range of 2.5-25.0 μg/ml with that of an equal concentration of standard paracetamol prepared in distilled water. The percent recovery was calculated as follow:

$$\% \text{ recovery} = \frac{\text{peak area of standard paracetamol or 3-hydroxy acetanilide in plasma}}{\text{peak area of standard paracetamol or 3-hydroxy acetanilide in distilled water}} \times 100$$

3.3.2 Precision and Variability

To determine intra-day precision and variability, the standard paracetamol was spiked in blank plasma at concentration 2.5, 5.0, 10.0, 15.0, 20.0 and 25.0 μg/ml and 5 replicates of each concentration were carried out on one day. All should be of ± 10% of spiked value and the coefficient of variation (CV) of each concentration should be less than 10%.

To determine inter-day precision and variability, the standard paracetamol was spiked in blank plasma at concentration 2.5, 5.0, 10.0, 15.0, 20.0 and 25.0 μg/ml and each concentration was carried out on 10 different days. Accuracy should be of ± 10% of spiked value and the coefficient of variation (CV) of each concentration should be less than 10%.

3.3.3 Sample Preparation

A 100 µl of internal standard (300 µg/ml of 3-hydroxy acetanilide in distilled water) was added to 450 µl of plasma. The mixture was precipitated with 550 µl of 10% perchloric acid. After mixing for 30 second and centrifuging at 14,000 rpm for 15 minutes, the 20 µl supernatant was injected by an automated injection.

4. Data Analysis

4.1 Pharmacokinetic Calculations

The following parameters were calculated by using Winnonlin® software program, 1995.

The maximum plasma paracetamol concentration (C_{max}), the time to reach C_{max} (T_{max}), the absorption rate constant (Ka), the absorption half-life ($t_{1/2}$abs), the elimination rate constant (Ke), the elimination half-life ($t_{1/2}$), the area under the concentration-time curve (AUC) and the lag times.

The apparent oral clearance (Cl/f) was calculated as dose/(AUC x body weights).

The apparent volume of distribution (Vd/f) was calculated as Cl/f devided by Ke.

4.2 Statistical Analysis

All results are expressed as means ± S.D. Differences in paracetamol pharmacokinetic parameters among control and exercise groups were tested for statistical significance by Student's paired t-test with P value less than 0.05 taken as the minimum levels of significance.

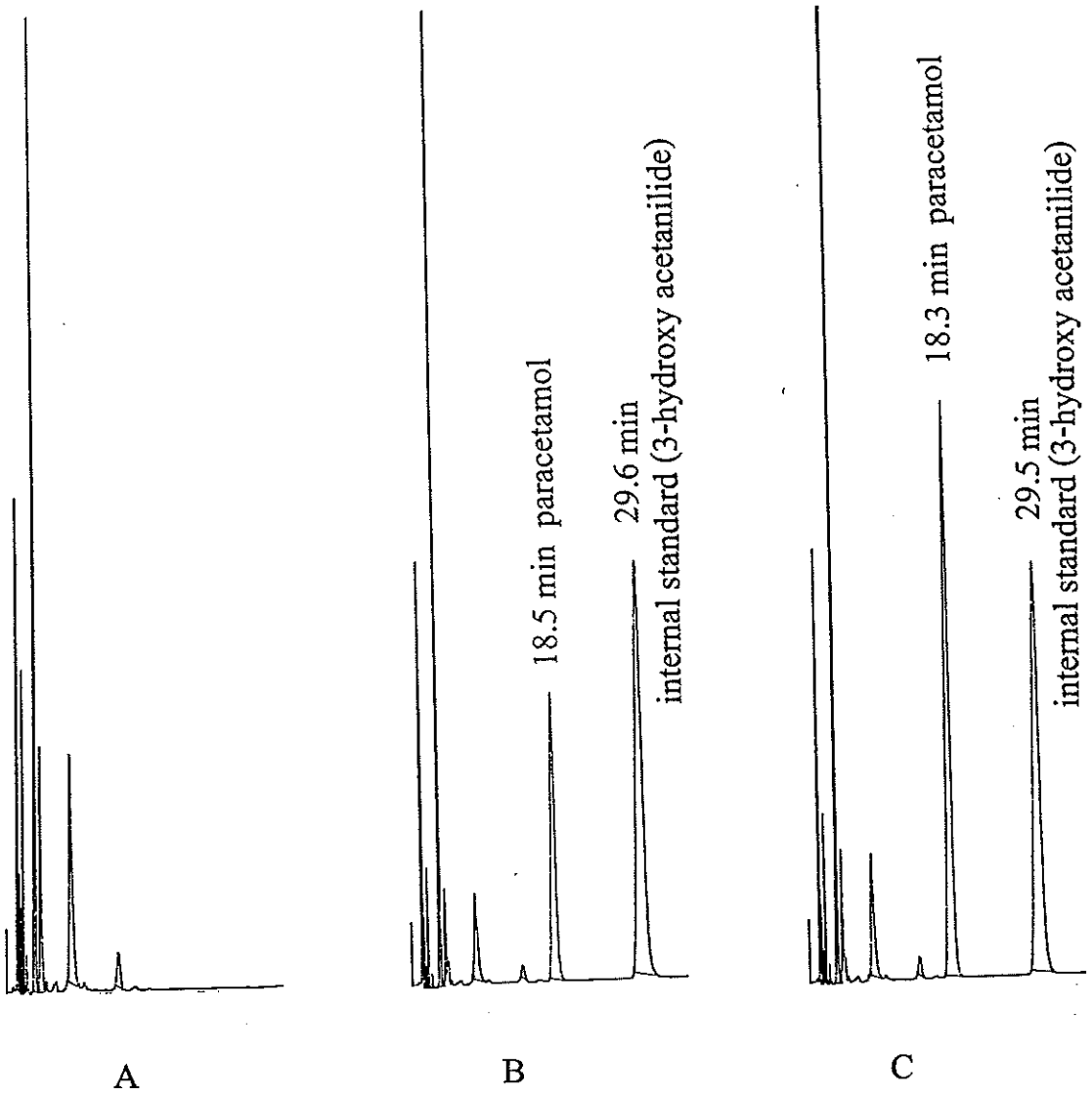

Figure 3 Representative chromatograms of a standard paracetamol and 3-hydroxy acetanilide (internal standard) in a 20 µl human plasma sample. (A) blank; (B) spiked with a standard paracetamol 10 µg/ml and an internal standard (3-hydroxy acetanilide); (C) spiked with a standard paracetamol 20 µg/ml and an internal standard. The mobile phase was 25 ml methanol in 0.1 M di-sodium hydrogen orthophosphate pH 4.70 at a flow rate of 2.0 ml/min. Chart speed was 1 mm/min. Attenuation was 32 mVF.S.

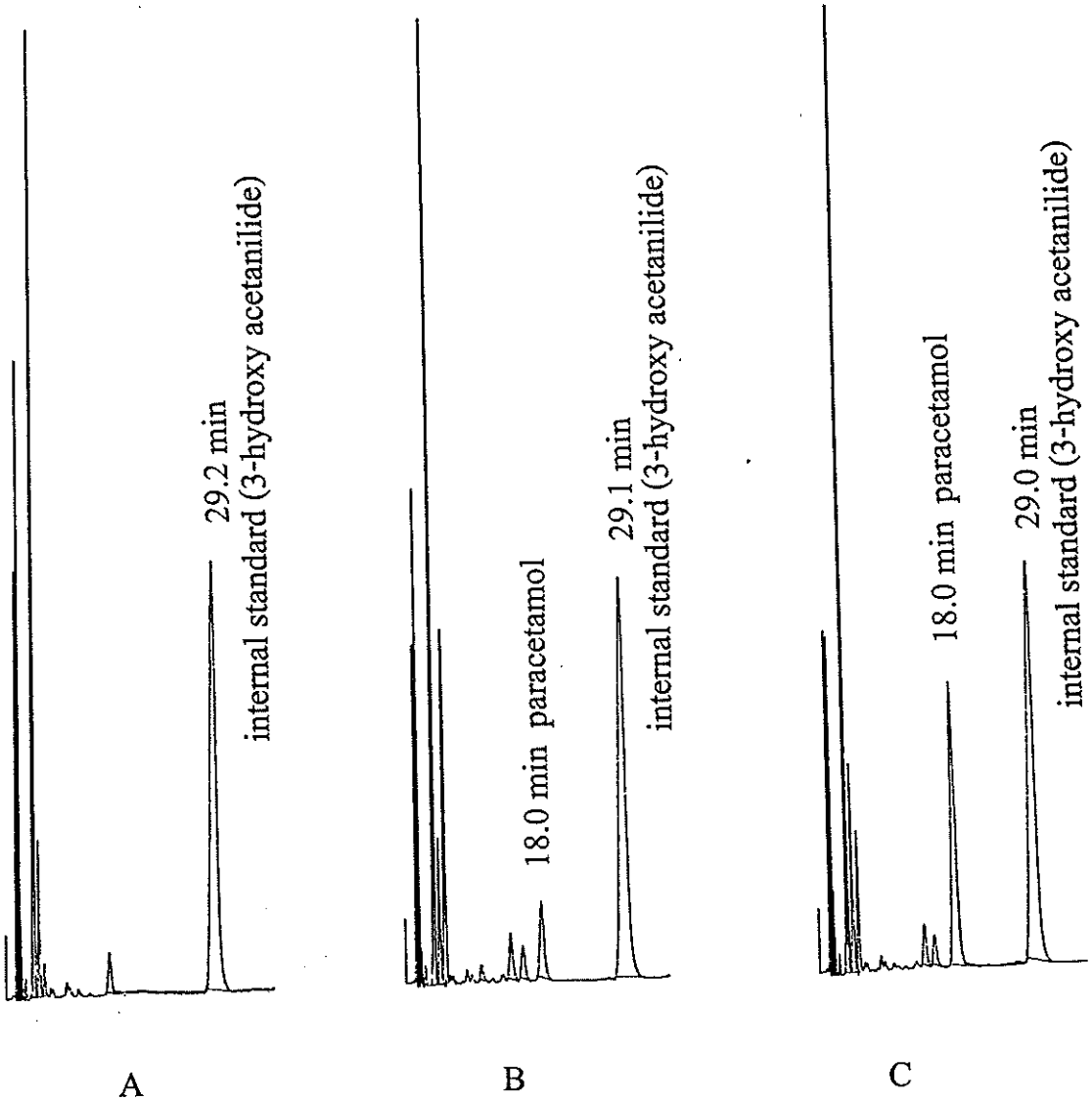

Figure 4 Representative chromatograms of paracetamol in a 20 µl human plasma sample of healthy subject after orally given 1,000 mg paracetamol. (A) before ingestion of paracetamol; (B) 15 min after receiving paracetamol; (C) 30 min after receiving paracetamol. The mobile phase was 25 ml methanol in 0.1 M di-sodium hydrogen orthophosphate pH 4.70 at a flow rate of 2.0 ml/min. Chart speed was 1 mm/min. Attenuation was 32 mVF.S.

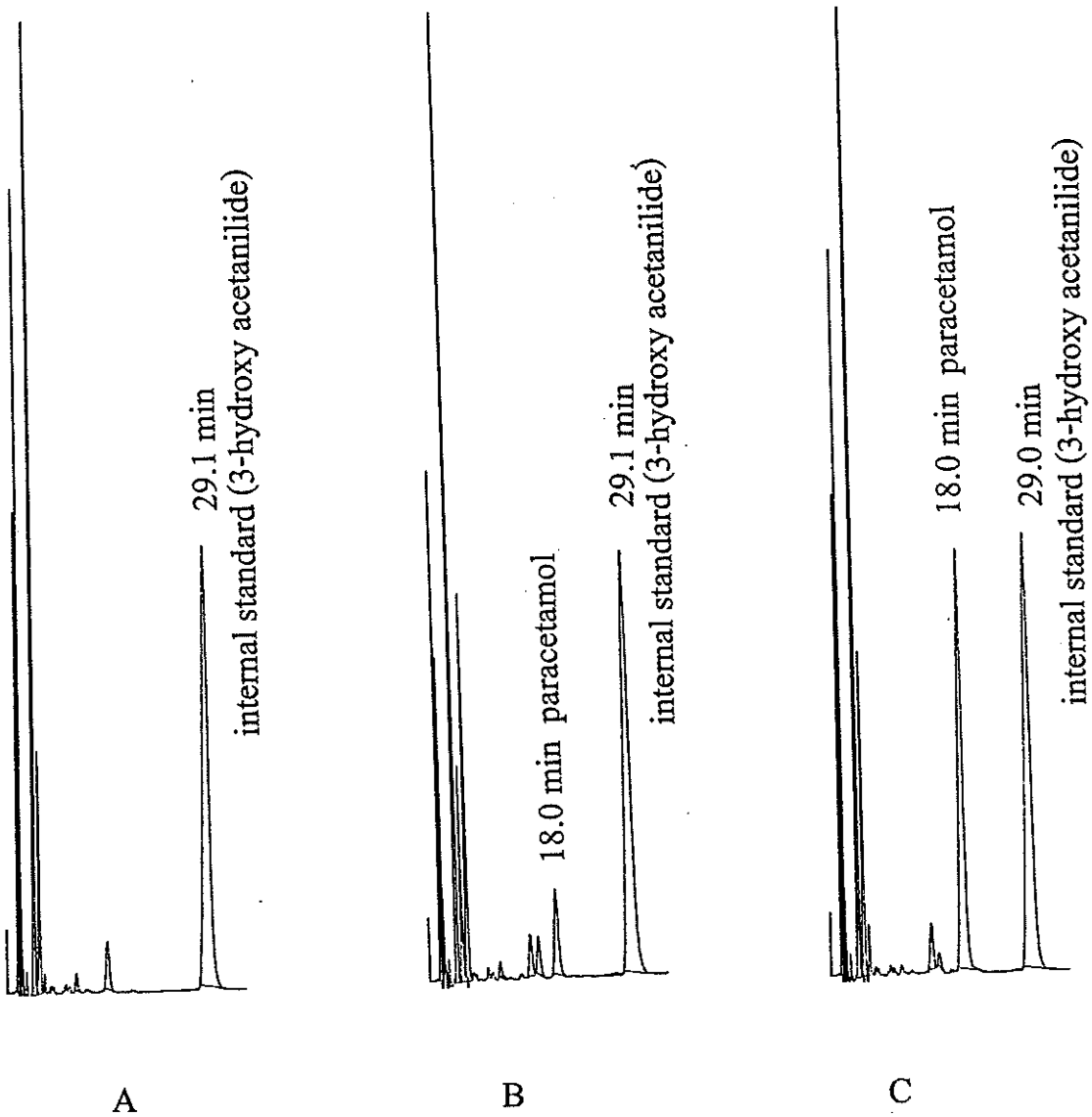

Figure 5 Reprersentative chromatograms of paracetamol in a 20 μl huma plasma sample of healthy subject receiving 1,000 mg paracetamol and follow exercise. (A) before exercise; (B) 15 min after exercise; (C) 30 min after exercise. The mobile phase was 25 ml methanol in 0.1 M di-sodium hydrogen orthophosphate pH 4.70 at a flow rate of 2.0 ml/min. Chart speed was 1 mm/min. Attenuation was 32 mVF.S.

Table 1 The intra-assay variance of six different paracetamol concentrations in distilled water

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 5)	CV[b](%)
2.5	65117 ± 854	1.31
5.0	137549 ± 415	0.30
10.0	287490 ± 2043	0.71
15.0	430642 ± 2746	0.64
20.0	584609 ± 3068	0.52
25.0	842536 ± 6886	0.82

[a]Various concentrations of standard paracetamol were directly injected into HPLC system

[b]Standard deviation divided by mean, expressed in percent

Table 2 The inter-assay variance of six different paracetamol concentrations in distilled water

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 10)	CV[b](%)
2.5	64785 ± 1493	2.31
5.0	135915 ± 2956	2.17
10.0	284807 ± 6163	2.16
15.0	429344 ± 8088	1.88
20.0	569580 ± 18527	3.25
25.0	810419 ± 8693	1.07

[a]Various concentrations of standard paracetamol were directly injected into HPLC system

[b]Standard deviation divided by mean, expressed in percent

Table 3 The intra-assay variance of six different paracetamol concentrations in plasma

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 5)	CV[b](%)
2.5	62237 ± 762	1.22
5.0	133722 ± 129	0.10
10.0	278725 ± 6835	2.45
15.0	420124 ± 5905	1.41
20.0	571672 ± 9873	1.73
25.0	787584 ± 1913	0.24

[a]Various concentrations of standard paracetamol were added to drug-free plasma sample prior to precipitation with perchloric acid

[b]Standard deviation divided by mean, expressed in percent

Table 4 The inter-assay variance of six different paracetamol concentrations in plasma

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 10)	CV[b](%)
2.5	64832 ± 1806	2.79
5.0	134148 ± 2711	2.02
10.0	278832 ± 4418	1.58
15.0	423451 ± 6507	1.54
20.0	564865 ± 14449	2.56
25.0	764778 ± 30819	4.03

[a]Various concentrations of standard paracetamol were added to drug-free plasma sample prior to precipitation with perchloric acid

[b]Standard deviation divided by mean, expressed in percent

Table 5 Relative recovery of standard paracetamol in plasma

Concentration[a] (μg/ml)	Peak area in distilled[b] water (Mean ±S.D.) (n = 10)	Peak area in plasma[c] (Mean ± S.D.) (n = 10)	% Recovery[d]
2.5	64785 ± 1493	64732 ± 1806	99.92
5.0	135915 ± 2956	134148 ± 2711	98.70
10.0	284807 ± 6163	278832 ± 4418	97.90
15.0	429344 ± 8088	423451 ± 6507	98.63
20.0	569580 ± 18527	564865 ± 14449	99.17
25.0	765299 ± 20352	764778 ± 30819	99.93

[a]Various concentrations of standard paracetamol in distilled water were directly injected

[b]Various concentrations of standard paracetamol were added to distilled water and followed by perchloric acid

[c]Various concentrations of standard paracetamol were added to drug-free plasma sample prior to precipitation with perchloric acid

[d]Mean peak area in plasma divided by mean peak area in distillled water expressed in percent

Table 6 The intra-assay variance of six different 3-hydroxy acetanilide concentrations in distilled water

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 5)	CV[b](%)
2.5	656216 ± 2627	0.40
5.0	680862 ± 2152	0.32
10.0	615750 ± 2830	0.46
15.0	684688 ± 5342	0.78
20.0	674919 ± 3750	0.56
25.0	650900 ± 5221	0.80

[a]Various concentrations of standard paracetamol were directly injected into HPLC system

[b]Standard deviation divided by mean, expressed in percent

Table 7 The inter-assay variance of six different 3-hydroxy acetanilide concentrations in distilled water

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 10)	CV[b](%)
2.5	669001 ± 18301	2.74
5.0	674383 ± 9313	1.38
10.0	666339 ± 20975	3.15
15.0	671900 ± 10092	1.50
20.0	676354 ± 15934	2.37
25.0	660874 ± 13312	2.01

[a]Various concentrations of standard paracetamol were directly injected into HPLC system

[b]Standard deviation divided by mean, expressed in percent

Table 8 The intra-assay variance of six different 3-hydroxy acetanilide concentrations in plasma

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 5)	CV[b](%)
2.5	663203 ± 4295	0.65
5.0	646406 ± 2840	0.44
10.0	652115 ± 6227	0.95
15.0	650053 ± 4224	0.65
20.0	649599 ± 4376	0.67
25.0	646782 ± 8117	1.26

[a]Various concentrations of standard paracetamol were added to drug-free plasma sample prior to precipitation with perchloric acid

[b]Standard deviation divided by mean, expressed in percent

Table 9 The inter-assay variance of six different 3-hydroxy acetanilide concentrations in plasma

Concentration[a] (μg/ml)	Mean peak area ± S.D. (n = 10)	CV[b](%)
2.5	654919 ± 8511	1.30
5.0	655738 ± 13974	2.13
10.0	651068 ± 6842	1.05
15.0	653496 ± 9516	1.46
20.0	652035 ± 9055	1.39
25.0	650365 ± 7696	1.18

[a]Various concentrations of standard paracetamol were added to drug-free plasma sample prior to precipitation with perchloric acid

[b]Standard deviation divided by mean, expressed in percent

Table 10 Relative recovery of standard 3-hydroxy acetanilide in plasma

Concentration[a] (μg/ml)	Peak area in distilled[b] water (Mean ±S.D.) (n = 10)	Peak area in plasma[c] (Mean ± S.D.) (n = 10)	% Recovery[d]
2.5	669001 ± 18301	654919 ± 8511	97.90
5.0	674383 ± 9313	655738 ± 13974	97.24
10.0	666339 ± 20975	651068 ± 6842	97.71
15.0	671900 ± 10092	653496 ± 9516	97.26
20.0	672354 ± 15934	652035 ± 9055	96.98
25.0	660874 ± 13312	650365 ± 7696	98.41

[a]Various concentrations of standard paracetamol in distilled water were directly injected

[b]Various concentrations of standard paracetamol were added to distilled water and followed by perchloric acid

[c]Various concentrations of standard paracetamol were added to drug-free plasma sample prior to precipitation with perchloric acid

[d]Mean peak area in plasma divided by mean peak area in distillled water expressed in percent

CHAPTER 4

RESULTS

The assay validation of the experimental method demonstrated that the coefficient of variation for intra- and inter-assay variance of six different paracetamol concentrations in distilled water were in the range of 0.30-1.31% and 1.07-3.25%, respectively (Table 1-2). The coefficient of variation for intra- and inter-assay variance of six different paracetamol concentrations in plasma were in the range of 0.10-2.45% and 1.54-4.03%, respectively (Table 3-4). The coefficient of variation for intra- and inter-assay variance of six different internal standard concentrations (3-hydroxy acetanilide) in distilled water were in the range of 0.32-0.80% and 1.38-3.15%, respectively (Table 6-7). The coefficient of variation for intra- and inter-assay variance of six different internal standard concentrations (3-hydroxy acetanilide) in plasma were in the range of 0.44-1.26% and 1.05-2.13%, respectively (Table 8-9). The linearity of the standard curve of paracetamol concentration range of 0.5-25.0 μg/ml was used as the standard curve for each day, and it was linear with the correlation coefficient (r) of 0.9999 (Figure 6). The lower detection limit for paracetamol was 0.5 μg/ml. The recovery of standard paracetamol and 3-hydroxy acetanilide in plasma were in the range of 97.90-99.93% and 96.98-98.41%, respectively (Table 5 and Table 10). The representative chromatograms in Figure 3 showed that a peak of paracetamol and 3-hydroxy acetanilide were well separated from the other peaks in plasma.

Fourteen adult healthy Thai male volunteers who were non-smoker, non-alcoholic and unregistered drugs in this study, were enrolled and totally completed in this study. These subjects were well tolerated to exercise and paracetamol throughout the study. The mean plasma paracetamol concentrations versus time profiles and standard deviation at each point of time are illustrated in Figure 7. The pharmacokinetic parameters (mean ± S.D.), estimated from the plasma concentration-time data of paracetamol are shown in Table 11-12. The results showed that Ka, $t_{1/2}$ (abs), T_{max} and C_{max} were significantly different between parameters of paracetamol alone and exercise after paracetamol treatment while there were no significant difference in AUC, Ke, $t_{1/2}$, Vd/f, Cl/f and the lag times (Table 13). The values (mean ± S.D.) for Ka, $t_{1/2}$ (abs), Ke, C_{max}, T_{max}, $t_{1/2}$, Vd/f, Cl/f, AUC and lag times in subjects receiving paracetamol alone were 2.51 ± 1.02 hr^{-1}, 0.31 ± 0.09 hr, 0.38 ± 0.04 hr^{-1}, 17.24 ± 1.06 μg/ml, 1.25 ± 0.11 hr, 2.02 ± 0.09 hr, 0.67 ± 0.08 l/kg, 0.25 ± 0.02 l/hr/kg, 64.83 ± 2.88 mg/l.hr and 0.31 ± 0.08 hr, respectively; whereas in exercise after paracetamol treatment subjects were 4.90 ± 1.52 hr^{-1}, 0.15 ± 0.05 hr, 0.39 ± 0.05 hr^{-1}, 18.64 ± 0.70 μg/ml, 0.85 ± 0.11 hr, 1.99 ± 0.17 hr, 0.71 ± 0.05 l/kg, 0.25 ± 0.02 l/hr/kg, 66.10 ± 3.37 mg/l.hr, and 0.24 ± 0.05 hr, respectively.

The semi-logarithmic mean plasma paracetamol concentration-time profile in fourteen healthy volunteers receiving a single oral dose of paracetamol alone and exercise after paracetamol ingestion (Figure 8) and paracetamol plasma concentration-time profile from one subject (subject number 12) (Figure 9) receiving paracetamol alone have shown that the plasma concentration declined monoexponentially and were fitted to a one compartment open model. The

summary data (Table 14) are compared to other published data of the pharmacokinetics of paracetamol in human volunteers. In the present study, The pharmacokinetic parameters of paracetamol in our subjects receiving paracetamol alone are similar to other reports.

The moderate exercise utilized in exercise group caused significant elevation of respiratory rate, heart rate, systolic pressure and diastolic pressure compared to control group (30 $\pm$ 4 beats/min, 126 $\pm$ 6 beats/min, 127 $\pm$ 5 mmHg, 81 $\pm$ 2 mmHg *versus* 20 $\pm$ 3 beats/min, 74 $\pm$ 5 beats/min, 117 $\pm$ 5 mmHg, 76 $\pm$ 5 mmHg, respecctively) while the body temperature did not change (Table 15).

Table 11 Pharmacokinetics parameters of paracetamol in subjects receiving a single oral dose of 1,000 mg paracetamol alone.

Subject No.	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	AUC (mg/l.hr)	Ka (hr^{-1})	Ke (hr^{-1})	$t_{1/2}$ (abs) (hr)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (µg/ml)	Vd/f (l/kg)	Cl/f (l/hr/kg)	Lag time (hr)
1	25	58.3	160.0	22.77	66.87	4.69	0.34	0.15	2.07	1.02	18.30	0.76	0.26	0.41
2	29	60.7	163.0	22.85	66.43	2.37	0.36	0.29	2.01	1.16	17.20	0.68	0.25	0.23
3	36	68.0	167.0	24.38	61.70	1.88	0.39	0.37	1.96	1.27	16.04	0.61	0.24	0.22
4	25	65.5	159.0	25.91	66.23	2.33	0.41	0.30	2.01	1.30	18.54	0.57	0.23	0.39
5	27	56.3	163.0	21.19	68.59	4.79	0.33	0.15	2.12	1.01	18.41	0.79	0.26	0.41
6	21	58.4	169.0	20.45	65.20	2.19	0.44	0.32	2.08	1.29	19.18	0.60	0.26	0.37
7	20	58.3	170.5	20.06	68.82	2.77	0.33	0.25	2.09	1.26	17.08	0.75	0.25	0.38
8	35	68.3	163.0	25.71	68.64	2.02	0.38	0.34	2.15	1.37	17.55	0.57	0.21	0.34
9	27	61.0	158.0	24.44	62.36	1.66	0.41	0.42	1.91	1.35	16.06	0.65	0.26	0.23
10	32	60.2	168.0	21.33	64.45	1.69	0.39	0.41	2.07	1.35	16.26	0.66	0.26	0.22
11	22	59.0	171.0	20.18	63.08	2.00	0.37	0.35	2.04	1.24	16.15	0.71	0.27	0.22
12	35	62.5	156.0	25.68	63.91	2.49	0.39	0.28	2.07	1.25	17.77	0.64	0.25	0.37
13	36	63.0	159.0	24.92	60.95	1.55	0.44	0.45	1.89	1.36	16.19	0.60	0.26	0.22
14	32	60.5	164.0	22.49	60.43	2.72	0.38	0.25	1.83	1.21	16.68	0.72	0.27	0.37
Mean	28.9	61.4	163.6	23.03	64.83	2.51	0.38	0.31	2.02	1.25	17.24	0.67	0.25	0.31
S.D.	5.9	3.7	4.9	2.15	2.88	1.02	0.04	0.09	0.09	0.11	1.06	0.08	0.02	0.08

Table 12 Pharmacokinetics parameters of paracetamol in subjects receiving a single oral dose of 1,000 mg paracetamol with exercise.

Subject No.	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	AUC (mg/l.hr)	Ka (hr^{-1})	Ke (hr^{-1})	$t_{1/2}$ (abs) (hr)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (µg/ml)	Vd/f (l/kg)	Cl/f (l/hr/kg)	Lag time (hr)
1	25	58.3	160.0	22.77	62.48	4.48	0.38	0.16	1.80	0.83	19.07	0.72	0.28	0.23
2	29	60.7	163.0	22.85	69.01	6.94	0.32	0.10	2.17	0.70	18.97	0.75	0.24	0.23
3	36	68.0	167.0	24.38	68.11	6.36	0.42	0.11	2.19	0.73	18.39	0.68	0.22	0.23
4	25	65.5	159.0	25.91	66.19	6.39	0.42	0.11	2.17	0.73	18.03	0.72	0.23	0.24
5	27	56.3	163.0	21.19	65.64	6.85	0.45	0.10	2.00	0.70	19.39	0.78	0.27	0.24
6	21	58.4	169.0	20.45	57.60	4.62	0.42	0.15	1.67	0.80	18.87	0.71	0.30	0.23
7	20	58.3	170.5	20.06	69.08	4.62	0.34	0.15	2.04	0.84	19.11	0.73	0.25	0.23
8	35	68.3	163.0	25.71	70.59	4.01	0.35	0.17	2.01	0.89	19.32	0.60	0.21	0.22
9	27	61.0	158.0	24.44	66.17	3.91	0.46	0.18	1.92	0.91	18.74	0.69	0.25	0.23
10	32	60.2	168.0	21.33	68.39	3.71	0.32	0.19	2.15	0.93	17.48	0.75	0.24	0.21
11	22	59.0	171.0	20.18	62.85	3.16	0.47	0.22	1.89	0.99	17.34	0.74	0.27	0.21
12	35	62.5	156.0	25.68	66.15	7.20	0.34	0.10	2.03	0.85	19.41	0.71	0.24	0.41
13	36	63.0	159.0	24.92	65.06	2.92	0.40	0.23	1.73	1.01	19.03	0.61	0.24	0.22
14	32	60.5	164.0	22.49	68.07	3.49	0.34	0.20	2.06	0.97	17.86	0.72	0.24	0.23
Mean	28.9	61.4	163.6	23.03	66.10	4.90	0.39	0.15	1.99	0.85	18.64	0.71	0.25	0.24
S.D.	5.9	3.7	4.9	2.15	3.37	1.52	0.05	0.05	0.17	0.11	0.70	0.05	0.02	0.05

Table 13 Pharmacokinetic parameters (mean ± S.D.) of paracetamol in fourteen subjects receiving a single oral dose of 1,000 mg paracetamol alone or exercise after paracetamol treatment.

Parameters	Paracetamol alone	Paracetamol + Exercise	Paired student's t-test
Age (yr)	28.9 ± 5.9	28.9 ± 5.9	-
Weight (kg)	61.4 ± 3.7	61.4 ± 3.7	-
Height (cm)	163.6 ± 4.9	163.6 ± 4.9	-
BMI (kg/m^2)	23.03 ± 2.15	23.03 ± 2.15	-
AUC (mg/l.hr)	64.83 ± 2.88	66.10 ± 3.37	NS
Ka (hr^{-1})	2.51 ± 1.02	4.90 ± 1.52	$P < 0.01$
Ke (hr^{-1})	0.38 ± 0.04	0.39 ± 0.05	NS
$t_{1/2}$ (abs) (hr)	0.31 ± 0.09	0.15 ± 0.05	$P < 0.01$
$t_{1/2}$ (hr)	2.02 ± 0.09	1.99 ± 0.17	NS
T_{max} (hr)	1.25 ± 0.11	0.85 ± 0.11	$P < 0.01$
C_{max} (μg/ml)	17.24 ± 1.06	18.64 ± 0.70	$P < 0.01$
Vd/f (l/kg)	0.67 ± 0.08	0.71 ± 0.05	NS
Cl/f (l/hr/kg)	0.25 ± 0.02	0.25 ± 0.02	NS
Lag time (hr)	0.31 ± 0.08	0.24 ± 0.05	NS

NS; no significant difference from control

Table 14 Paracetamol pharmacokinetic data are compared to other published data.

Data	Sources					
	El-Azab 1996	Ismail 1995	Kamali 1993	Pantuck 1984	Ridtitid 1998	Present study[a]
Subjects	8 men	8 men	5 men and 5 women	10 men	7 men	14 men
Age (yr)	13.7 ± 3.1	19-41	20-29	24-37	21-33	20-36
Dose (mg)	1000	1000	1500	1000	1000	1000
Route	oral	oral	oral	oral	oral	oral
C_{max} (μg/ml)	17.1 ± 3.9	14.5 ± 5.8	18.2 ± 1.9	21.8 ± 2.1	18.9 ± 7.0	17.24 ± 1.06
T_{max} (hr)	1.4 ± 0.7	1	1.0 ± 0.2	0.8 ± 0.1	0.8 ± 0.4	1.25 ± 0.11
$t_{1/2}$ (hr)	2.4 ± 0.3	3.7 ± 1.1	2.1 ± 0.2	2.3 ± 0.1	2.2 ± 0.3	2.02 ± 0.09
Vd/f (l/kg)	-	1.2 ± 0.7	1.0 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.67 ± 0.08
Cl/f (l/hr/kg)	-	0.2 ± 0.1	0.4 ± 0.1	-	0.2 ± 0.1	0.25 ± 0.02

[a] calculation of pharmacokinetic data based on subjects receiving paracetamol alone

Table 15 Average measurements of body temperature, respiratory rate, heart rate and blood pressure in fourteen healthy volunteers in control and exercise groups.

Vital sign	Control group	Exercise group	Paired student's t-test
Body temperature (°C)	36.7 ± 0.2	36.8 ± 0.2	NS
Respiratory rate (beats/min.)	20 ± 3	30 ± 4	$P < 0.01$
Heart rate (beats/min.)	74 ± 5	126 ± 6	$P < 0.01$
Blood pressure (mmHg)			
Systolic	117 ± 5	127 ± 5	$P < 0.01$
Diastolic	76 ± 5	81 ± 2	$P < 0.01$

Results are expressed as mean ± S.D.

NS; no significant difference from control

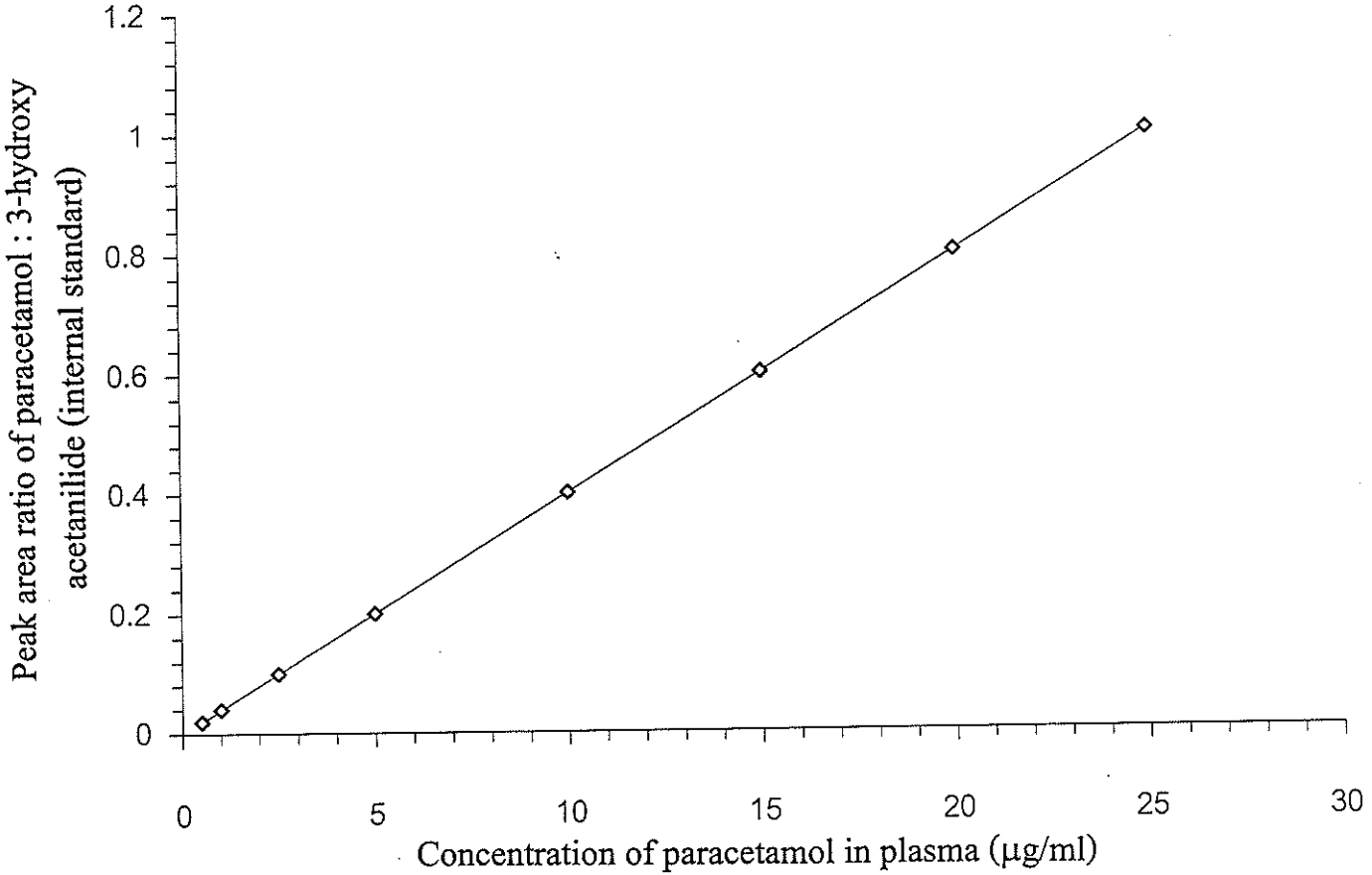

Figure 6 Correlation between peak area ratio of paracetamol : 3-hydroxy acetanilide (internal standard) and concentration of paracetamol in plasma, correlation coefficient (r) = 0.9999

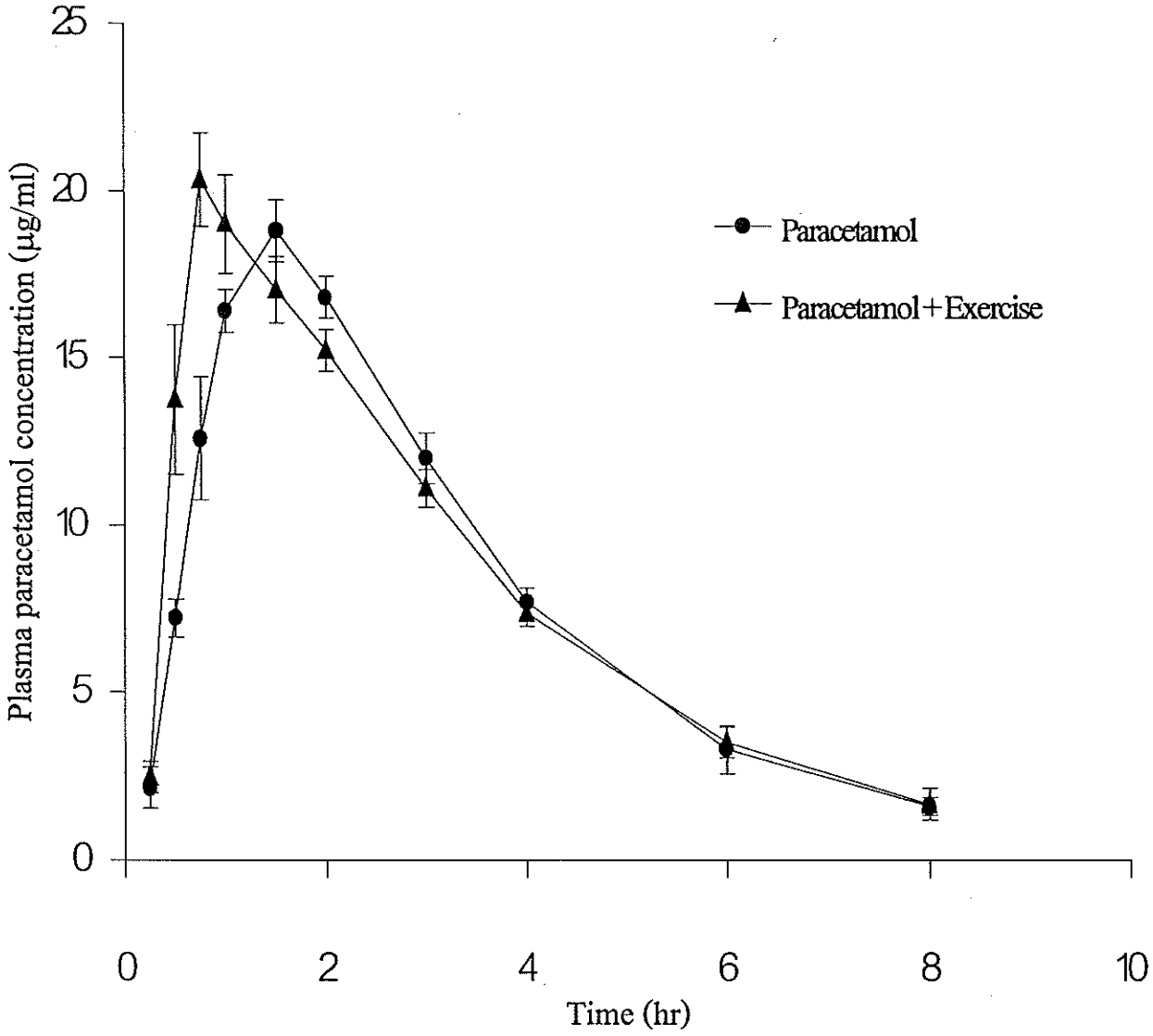

Figure 7 Mean plasma paracetamol concentrations in 14 healthy volunteers receiving a single oral dose of paracetamol 1,000 mg alone (●); and exercise after paracetamol treatment (▲). Each point represents mean ± S.D.

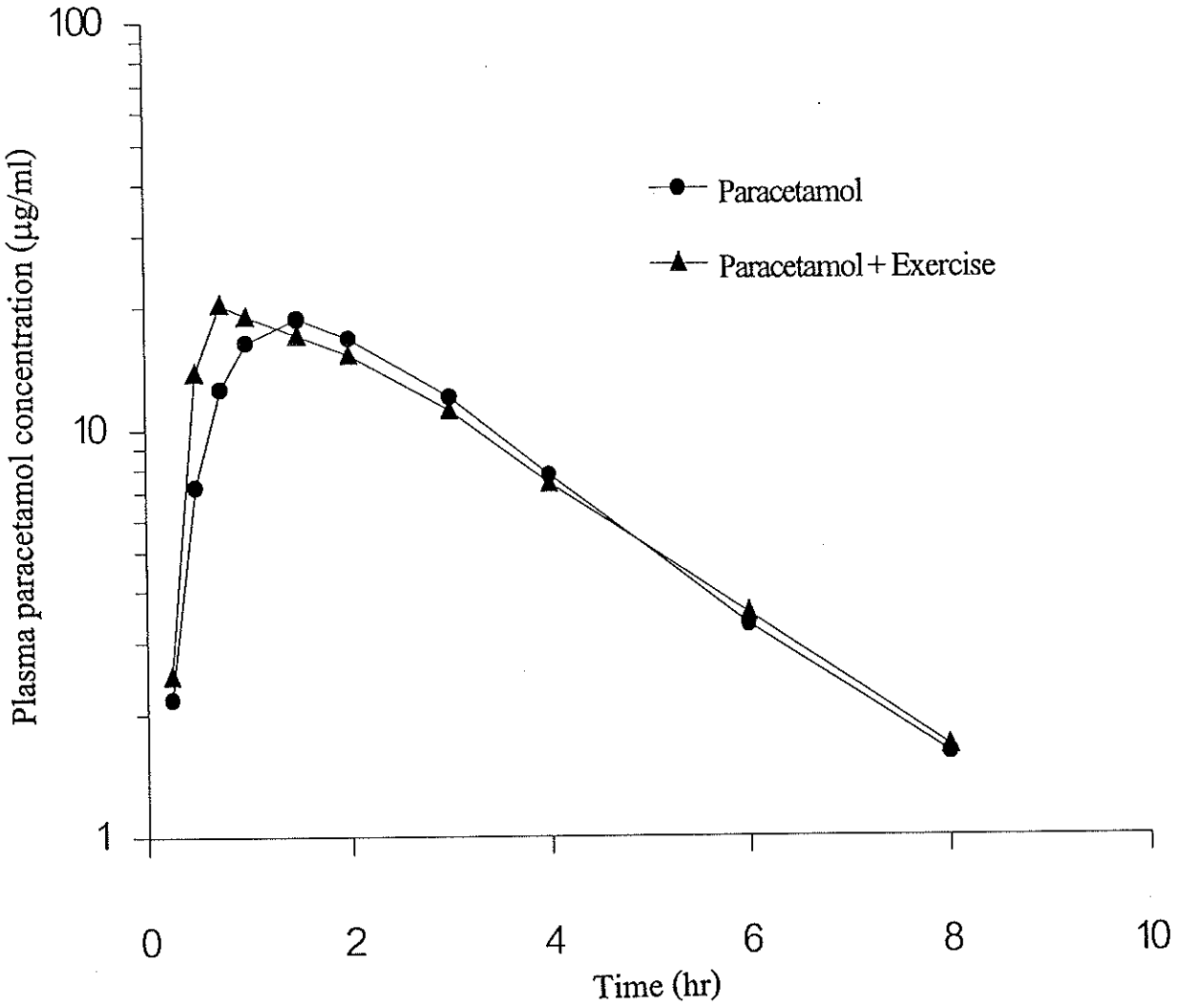

Figure 8 Semi-logarithmic mean plasma paracetamol concentrations in 14 healthy volunteers receiving a single oral dose of paracetamol 1,000 mg alone (●); and exercise after paracetamol treatment (▲).

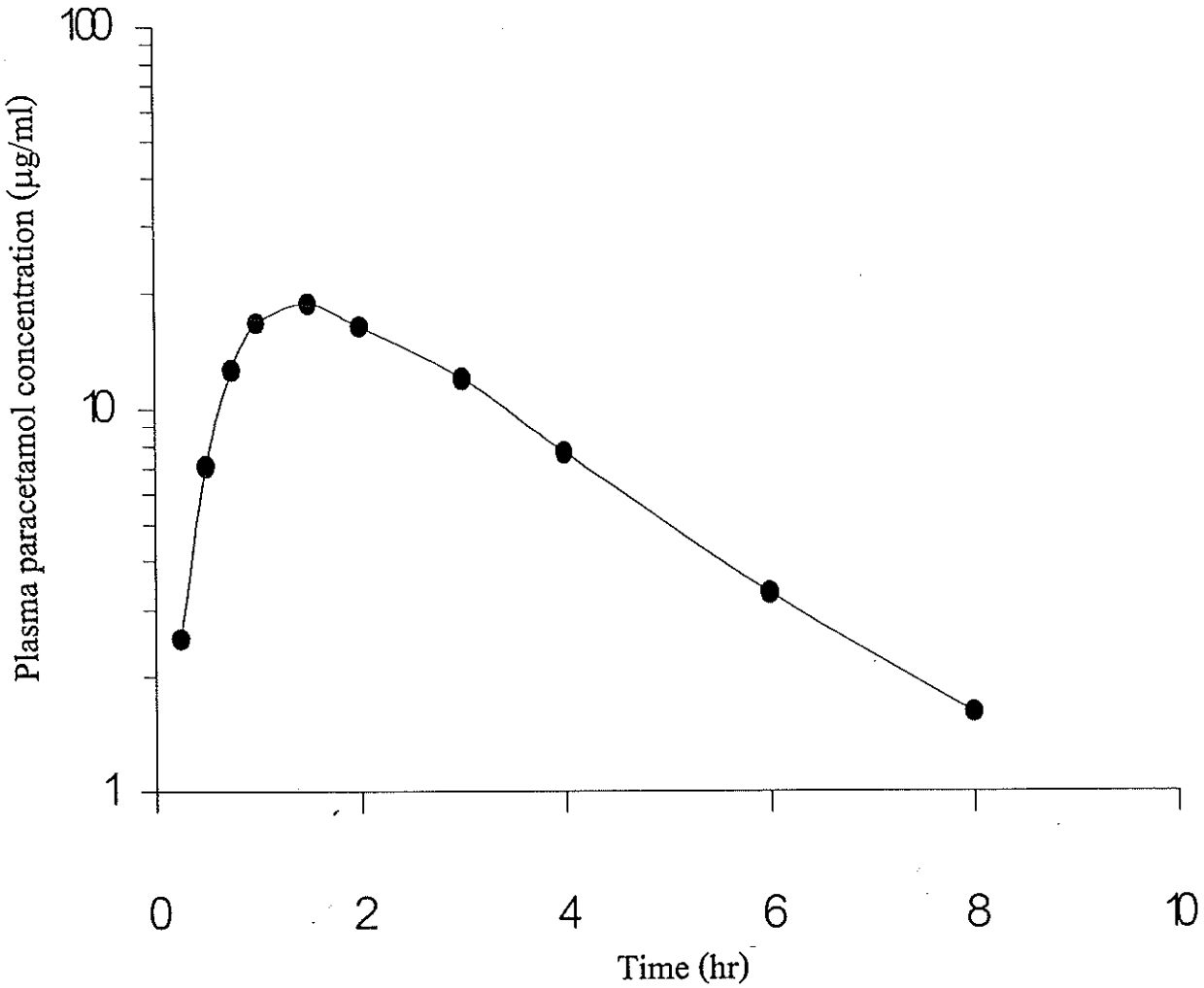

Figure 9 Semi-logarithmic plasma paracetamol concentration-time profile following an oral administraion of a single 1,000 mg dose of paracetamol alone (subject number 12)

CHAPTER 5

DISCUSSION

As paracetamol is the non-prescription antipyretic-analgesic drug that has been widely used for relieving pain and fever, while exercise is getting more popular among people since it has a positive impact on health and quality of life. However, these population may have fever or headache, and may need paracetamol to relieve their pain and fever. Exercise can influence a number of physiological factors such as haemodynamics, metabolism, urinary pH, body temperature and gastrointestinal function (Van Baak, 1990) that may affect the pharmacokinetics of drugs. The effect of physical activity on drug pharmacokinetics has been evaluated by several studies, there are evidences of both increased and decreased, as well as of unchanged, plasma drug concentrations during or after exercise (Henry *et al.*, 1981; Hurwitz *et al.*, 1983; Mason *et al.*, 1980; Powis and Snow, 1978; Sweeney, 1981; Van Baak, 1990; Weber *et al.*, 1987; Ylitalo and Hinkka, 1985; Ylitalo *et al.*, 1977). The magnitude of these changes depends on factors that pertain to the characteristics of each drug as well as exercise-related factor such as exercise intensity, mode and duration (Ciccone, 1995). Exercise may affect the pharmacokinetics of paracetamol. Therefore, we investigated the effect of exercise on the pharmacokinetics of paracetamol in normal healthy volunteers.

The profile of plasma paracetamol concentration and the derived pharmacokinetic parameters in this study were similar to those previously

reported following oral paracetamol except for the volume of distribution (Table 14) (El-Azab, 1996; Ismail, 1995; Kamali, 1993; Pantuck, 1984; Ridtitid *et al.*, 1998). The mean volume of distribution in this study was lower than those reported by previous investigators. The reasons might be due to differences in age, number of subject, body weight, race and pharmacokinetic calculations method. The subjects in this study had a lower body weight than subjects in other studies. Since the volume of distribution of paracetamol seemed to be predominantly depend on body weight. The volume of distribution was greater in obese than in control men (Abernethy *et al.*, 1982). In the present study there were considerable interindividual variability in plasma concentration profiles, and as a consequence there were large variations in the derived pharmacokinetic parameters as seen in previous reports (Heading *et al.*, 1973; Paintaud *et al.*, 1998).

The semi-logarithmic mean plasma paracetamol concentration-time profile in the fourteen healthy volunteers receiving a single oral dose of paracetamol alone and exercise after paracetamol ingestion (Figure 8) and paracetamol plasma concentration-time profile from one subject (subject number 12) (Figure 9) receiving paracetamol alone have shown that the data were well described by a one compartmental open model with first-order kinetics for both absorption and elimination which was similar to the study of Alam *et al.* (1977); Levy *et al.* (1975); Miller *et al.* (1976); Prescott *et al.* (1993); Ridtitid *et al.* (1998) and Schuitmaker *et al.* (1999). The pharmacokinetic parameters such as the absorption rate constant (Ka), the absorption half-life ($t_{1/2}$(abs)), the time to reach the maximal concentration

(T_{max}) and the maximal concentration (C_{max}) of the subjects who exercise after paracetamol treatment were significantly different from those receiving paracetamol alone (4.90 ± 1.52 hr^{-1}, 0.15 ± 0.05 hr, 0.85 ± 0.11 hr and 18.64 ± 0.70 μg/ml *versus* 2.51 ± 1.02 hr^{-1}, 0.31 ± 0.09 hr, 1.25 ± 0.11 hr and 17.24 ± 1.06 μg/ml, respectively; $P < 0.01$). These findings suggest that exercise has a pronounced effect on the pharmacokinetics of paracetamol (Table 13).

In the present study, moderate exercise appeared to accelerate the absorption of paracetamol as indicated by Ka, $t_{1/2}$ (abs), T_{max} and C_{max} values. Exercise produced significantly higher maximal concentration (C_{max}) and the absorption rate constant (Ka) by about 1.08-fold and 1.95-fold, respectively (8.12% and 95.18%, respectively) and shorter the time to reach the maximal concentration (T_{max}) and the absorption half-life ($t_{1/2}$ (abs)) by about 0.68-fold and 0.50-fold, respectively (31.97% and 50.00%, respectively). These results suggest that physical exercise performed under the conditions of this study may influence the gastric emptying time. The rate of gastric emptying determines the rate of absorption of orally administered paracetamol (Heading *et al.*, 1973). In previous studies, paracetamol absorption in man is related to the rate of gastric emptying (Clements *et al.*, 1978; Heading *et al.*, 1973; Holt *et al.*, 1979a). Gastric emptying is accelerated by mild to moderate exercise such as in the study of Cammack *et al.* (1982) who reported that exercise significantly accelerated gastric emptying than control subjects (1.2 ± 0.1 hr *versus* 1.5 ± 0.1 hr; $P < 0.02$). Moore *et al.* (1990) demonstrated that exercise (walked on an exercise treadmill at 3.2 km/hr or at 6.4 km/hr) significantly increased gastric emptying (emptying half-time ($t_{1/2}$) at rest = 72.6 ± 7.6 min; $t_{1/2}$ of walking at

3.2 km/hr = 44.5 ± 3.9 min; while $t_{1/2}$ of walking at 6.4 km/hr = 32.9 ± 1.9 min). The 6.4 km/hr emptying time was significantly faster than 3.2 km/hr emptying time. Neufer *et al.* (1989) found that gastric emptying were increased during walking exercsie at 28%, 41% or 56% of $\dot{V}O_{2max}$ and running at 57% or 65% of $\dot{V}O_{2max}$ compared to resting conditions, high intensity and exhaustive exercise above 75% of $\dot{V}O_{2max}$ appeared to delay the gastric emptying time (Feldman and Nixon, 1982; Fordtran and Saltin, 1967; Murray, 1987; Ramsbottom and Hunt, 1974; Rechrer *et al.*, 1989). In the present study, all of our subjects exercise (treadmill-running 5 km/hr) at 70% of maximal heart rate (mean heart rate ± S.D. = 74 ± 5 beats/min in control group and 126 ± 6 beats/min in exercise group) for 30 minutes (approximately 55% $\dot{V}O_{2max}$) (Anderson, 1978). Heart rate is a good measure of relative workload (Bloom *et al.*, 1976). There is a consistent linear relation between heart rate and oxygen consumption (Scheuer and Tipton, 1977; Shephard, 1987). None of our subjects were exhausted by the protocol as determined by interviewing the subjects. Due to the short duration of the exercise period, all of our subjects actually achieved a moderate level of exercise, hence more rapid gastric emptying but unfortunately, we could not confirm this as no independent measure of gastric emptying was made. The increase in the gastric emptying rate implies that the rate of paracetamol absorption was increased in the exercise subjects.

The mechanism of the acceleration of gastric emptying by mild to moderate exercise is unclear. These effects are probably related to the simply mechanical, neurogenic and homonally mediated.

Increases in gastric emptying during moderate intensity exercise may be related to increase in intragastric pressure brought about by contractile activity of the abdominal muscles (Neufer, 1989).

Exercise is a known stimulant of the autonomic nervous system and much is known about its effects on cardiac, respiratory, gastrointestinal function and endocrine function (Grossman *et al.*, 1984; Read and Houghton, 1989). There is evidence that psychological stress increases parasympathetic (Carruthers and Taggart, 1973) as well as sympathetic tone, and it has been suggested that the variable physiological responses to physiological stress depend on the relative dominance of parasympathetic and sympathetic tone. If this is true, then it is likely that responses to physical stress such as exercise will also vary according to whether the sympathetic or parasympathetic tone is dominant. Thus the reduction in the half time for gastric emptying, induced by mild to moderate exercise (Cammack *et al.*, 1982; Read and Houghton, 1989), may be explained by a relative dominance in parasympathetic tone, while the delay in gastric emptying, oberved by earlier workers in response to severe or exhaustive exercise (Banister and Griffiths, 1972; Cammack *et al.*, 1982; Fordtran and Saltin, 1967; Galbo *et al.*, 1975; Read and Houghton, 1989; Rees *et al.*, 1980), may be explained by a dominance of sympathetic tone and a release of endogenous opiates from active muscles (Guillemin *et al.*, 1977).

Some hormone concentrations alter during moderate exercise, including motilin and enkephalines (Grossman and Sulton, 1985; Worobetz and Gerrard, 1988). These homonal substances increase gastrointestinal motility. However, four other studies have failed to show any alteration in motilin and

enkephalines during exercise (Hvidsten *et al.*, 1986; Keeling *et al.*, 1990; Soffer *et al.*, 1993, 1994). Whereas during submaximal exercise or maximal exercise can elevated some gastrointestinal hormones and peptides such as somatostatin (Hilsted *et al.*, 1980; O'Connor *et al.*, 1995), gastrin (Brandsborg *et al.*, 1978; O'Connor *et al.*, 1995) and cholecystokinin (O'Connor *et al.*, 1995). Changes in hormones and peptides lead to decrease in gastrointestinal motility (Khazaeinia and Ramsey, 2000).

Gastrointestinal transit is accelerated by mild to moderate exercise (Cordian *et al.*, 1986; Harris and Martin, 1993; Koffler *et al.*, 1992; Liu *et al.*, 1993; Oettle, 1991; William *et al.*, 1987). The mechanism of the acceleration of transit is unclear, although there are perhaps four main possibilities i.e. through a reduction in visceral blood flow, hormonally mediated, neurogenic or simply mechanical (Oettle, 1991). This effect is important for paracetamol which is primarily absorbed from the intestine. However, transit rate does not appear to influence small bowel absorption (Morris and Turnberg, 1981), perhaps because exchange across the mucosal cell is so fast that, even under condition of reduced contact time with the absorbing mucosa, there is still enough time for complete exchange.

Exercise may result in shifting of blood flow away from the gastrointestinal tract towards the active muscle and the lungs (Brouns and Beckers, 1993). Reduction in splanchnic blood flow is related to the relative intensity of the exercise (Rowell, 1974). Splanchnic blood flow decreases during exercise may reduce the absorption rate. However, vigorous exercise does not reduce blod flow enough to reduce the rate of either active or passive

absorption of sugar, water, or sodium (Fordtran and Saltin, 1967; Rosenbloom and Sulton, 1985) and other study has failed to show any alteration in absorption with change in intestinal blood flow (Brunsson *et al.*, 1979). Therefore, it is not likely that this is an important influence on absorption (Carter *et al.*, 1992).

During exercise, lactic acid is produced which can decrease the pH of blood and muscle. Maximal ergometer rowing for 30 min decreases the pH of both gastric mucosa from 7.25 to 6.79 ($P < 0.05$) and arterial blood from 7.42 to 7.29 ($P < 0.05$) (Nielsoen *et al.*, 1995). Conversely, the later study found that the gastric pH were no differences between the pre-exercise, during exercise (high intensity ergometer cycling) and the post-exercise episodes (Van Nieuwenhoven *et al.*, 1999). This change in pH may increase paracetamol ionization and absorption. However, gastrointestinal pH may unaffected by a moderate level of exercise by the protocol in the present study. Therefore, it is not influence on paracetamol absorption.

In the present study, the area under the concentration-time curve (AUC) values are not different between the two groups and reflect an equal extent of paracetamol absorption in two conditions.

Exercises have been shown to influence the volume of distribution of a number of drugs. Both increases and decreases volume of distribution have been found. Schlaeffer *et al.* (1984) reported that a 50% lower volume of distribution for the bronchodilator theophylline in healthy volunteers exercising at a 50% of $\dot{V}O_{2max}$ for 2 hours. In contrast, the volume of distribution for the cardiac glycoside digoxin increased during exercise (1 hour

cycle ergometry at a heart rate of 120 to 140 beats/min). Muscle biopsies showed that the concentration of digoxin in skeletal muscle was increased (Jogestrand and Sundqvist, 1981). The mechanism of the change in the volume of distribution remains unclearified. However, in the present study, the volume of distribution of paracetamol in exercise group were not different from control group (Table 13). Likewise, Schlaeffer *et al.* (1984) found that during exercise at 30% of $\dot{V}O_{2max}$ the volume of distribution of theophylline was unaffected.

During exercise, hepatic blood flow is reduced in proportion to the relative exercise intensity (Van Baak, 1990). These data suggest that exercise may reduce the hepatic clearance of drugs with high hepatic extraction ratio whose hepatic clearance is blood-flow dependent. Low hepatic extraction drugs will probably not be affected during exercise because clearance of the drug is dependent on the metabolic capacity of the liver rather than on hepatic blood flow (Dossing, 1985). In the present study metabolism of paracetamol is unaffected by moderate exercise. Likewise, Swartz *et al.* (1974) found that the hepatic elimination of antipyrine (low clearance druge) did not change during treadmill walking for 3 hours. Klotz and Lucke (1978) showed that the biotransformation of another low clearance drug, diazepam, did not differ among 4 subjects undertaking maximum physical exercise on a bicycle ergometer for 5 minutes.

With normal therapeutic doses, paracetamol is excreted in urine approximately 85-95% (Forrest *et al.*, 1979; Prescott, 1980). Exercise has been shown to reduce renal blood flow. The reduction is related to the intensity of

exercise and renal blood flow may fall to 25% of the resting value when strenuous work is performed (Poortman, 1984). The renal clearance of β-blocker atenolol was reduced by approximately 8% during exercise. The authors suggested that decrease in the renal clearance of the drug was probably due to decreased renal blood flow during exercise (Mason *et al.*, 1980). However, in the present study, after receiving paracetamol with exercise subjects, the clearance were not different from those receiving paracetamol alone (Table 13). The possible explanation is that a moderate level of exercise by the protocol did not alter renal blood flow from resting conditions. During severe exercise the renal blood flow decreases approximately 20% but during mild to moderate level of exercise, the renal blood flow did not change from resting value (Judy, 1984; Manohar *et al.*, 1995; Parks and Manohar, 1983). After moderate exercise has ceased, most kidney functions return to normal resting values within an hour of recovery (Wesson, 1960), but prolonged exercise may cause change resting up to 10 hours after exercise (Castenfor, 1997).

In previous study of Abernethy *et al.* (1982) paracetamol pharmacokinetics seemed to be predominantly dependent on obesity. They reported that absolute metabolic clearance was greater in obese than in control men (484 and 323 ml/min, $P < 0.05$) and in obese than in control women (312 and 227 ml/min, $P < 0.05$). In the present study, all subjects were non-obese as determined by body mass index (BMI) (BMI = 20.18-25.91 kg/m^2). The BMI was calculated as weight in kilograms divided by the square of height in meters. Normal BMI ranges for adults are 19 to 25; a BMI of more than 27.8

for men and 27.3 for women is defined as obesity (Vander *et al.*, 1994). The latter implies that these values of BMI for all subjects have no effect on the pharmacokinetics of paracetamol.

In conclusion, under the conditions of this study, moderate exercise increased the rate of paracetamol absorption but the total absorption was not affected. We suggest that the increase of paracetamol absorption supposed to be through the increase in the gastric emptying rate. These effects are probably related to the simply mechanical, neurogenic and hormonally mediated. The findings of this study are not applicable to clinical practice directly because paracetamol is not a drug to be used when exercise. Therefore the relevance of these findings lie in the demonstration of an interaction between exercise and paracetamol pharmacokinetics because the interaction had a surprisingly great impact on the rate of paracetamol absorption. The results found may also apply to other drugs and endogenous substances. Further study is required to investigate the effects in terms of physiology and performance of altered pharmacokinetics. Investigation of the pharmacodynamics of paracetamol during exercise should also be conducted too.

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APPENDIX

APPENDIX-1

The values of essential laboratory tests (fasting blood sugar, liver and renal function tests, and complete blood count) in fourteen healthy Thai male volunteers.

Laboratory test	Results													
	Subject number													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Blood chemistry														
- Blood sugar (mg%)	93	99	104	92	103	90	89	99	99	109	104	73	91	91
- BUN (mg%)	12	12	12	13	20	13	7	10	15	13	17	12	14	12
- Creatinine (mg%)	0.9	1.1	1.0	1.2	1.1	1.3	1.2	0.7	0.9	1.4	1.5	0.8	0.8	1.0
- SGOT (U/L)	28	26	22	27	23	27	24	18	22	38	17	22	33	19
- SGPT (U/L)	18	20	20	24	17	22	14	16	24	18	25	24	36	30
Hematology														
CBC :														
- Hb (g%)	13.7	13.1	13.7	14.7	14.7	15.1	14.1	14.7	13.3	15.1	13.7	13.1	13.3	14.0
- Hct (%)	41	39	41	44	44	45	42	44	40	45	41	40	40	42
- WBC (cell/m^3)	6,700	5,200	4,400	7,700	7,100	6,300	9,700	6,200	5,500	7,500	9,450	6,700	7,300	4,400
Differential white cell count :														
- PMN (%)	58	66	64	50	51	48	56	65	74	65	30	57	67	55
- Lymphocytes (%)	37	33	33	43	15	47	43	30	25	33	65	40	29	41
- Monocytes (%)	-	-	-	2	-	-	-	1	-	-	2	-	3	2
- Eosinophils (%)	5	1	3	5	4	5	1	4	1	2	3	2	1	2
- Basophils (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- Band (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

APPENDIX-2

Preparation of standard paracetamol in plasma blank for calibration curve.

Stock	=	Paracetamol 500 µg/ml	
2.5 µg/ml	=	275 µl of 10.0 µg/ml	+ 175 µl of plasma
5.0 µg/ml	=	220 µl of 25.0 µg/ml	+ 230 µl of plasma
10.0 µg/ml	=	220 µl of 50.0 µg/ml	+ 230 µl of plasma
15.0 µg/ml	=	165 µl of 100.0 µg/ml	+ 285 µl of plasma
20.0 µg/ml	=	110 µl of 200.0 µg/ml	+ 340 µl of plasma
25.0 µg/ml	=	91 µl of 300.0 µg/ml	+ 359 µl of plasma

APPENDIX-3

Protein precipitation

1. Take 450 µl of sample or standard solution
2. Add 100 µl of 3-hydroxy acetanilide (internal standard, 300 µg/ml in distilled water)
3. Add 550 µl 10% perchloric acid
4. Shake
5. Centrifuge at 14,000 rpm for 15 min

APPENDIX-4

Plasma concentrations of paracetamol at 0-8 hr in subjects receiving a single oral dose of 1,000 mg paracetamol alone.

Subject No.	Concentrations (μg/ml)										
	Time (hr)										
	0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00
1	0	1.40	7.60	15.20	17.60	16.90	15.00	12.00	8.00	4.50	1.50
2	0	2.20	8.35	14.85	16.65	18.00	17.40	11.35	7.80	4.80	1.80
3	0	2.65	7.00	12.00	16.80	18.60	16.40	12.00	7.00	4.20	1.40
4	0	2.65	6.90	11.30	16.30	20.50	16.80	12.80	7.20	3.65	1.60
5	0	1.80	7.80	15.70	17.10	19.30	16.10	10.50	7.90	3.50	1.80
6	0	2.50	7.00	14.10	17.10	20.10	16.90	12.70	7.00	2.70	1.60
7	0	0.60	6.80	11.10	17.20	19.10	16.00	11.40	8.40	3.90	1.90
8	0	3.00	7.80	10.60	16.70	19.10	17.20	12.10	8.00	3.00	1.90
9	0	1.80	7.30	11.30	16.50	18.50	16.80	12.20	7.70	3.30	1.00
10	0	2.00	7.40	12.20	16.10	18.60	16.30	13.00	8.00	3.10	1.60
11	0	2.65	6.60	14.40	17.30	19.80	16.00	12.70	7.40	2.60	1.60
12	0	2.50	7.10	12.60	16.70	18.80	16.40	12.00	7.70	3.30	1.60
13	0	2.50	6.10	12.10	18.70	17.90	15.60	12.10	7.60	3.20	1.50
14	0	2.10	7.50	10.10	16.80	18.50	16.40	13.50	7.00	2.40	2.10
Mean	0	2.17	7.23	12.68	16.97	18.84	16.38	12.20	7.62	3.44	1.64
S.D.	0	0.62	0.57	1.83	0.64	0.93	0.63	0.77	0.44	0.71	0.26

APPENDIX-5

Plasma concentrations of paracetamol at 0-8 hr in subjects receiving a single oral dose of 1,000 mg paracetamol with exercise.

Subject No.	Concentrations (μg/ml)										
	Time (hr)										
	0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	6.00	8.00
1	0	2.35	14.00	22.20	18.00	17.15	15.20	10.50	6.80	3.50	0.65
2	0	2.35	16.90	21.00	19.60	16.70	15.50	10.40	7.00	3.80	1.80
3	0	2.20	16.00	20.20	17.00	15.00	14.35	11.15	7.60	3.90	1.40
4	0	2.00	15.40	20.55	16.50	15.20	14.20	10.45	7.00	3.40	1.50
5	0	1.90	17.00	21.90	18.00	17.10	15.50	11.80	7.10	3.80	1.90
6	0	2.90	14.30	21.60	18.80	17.80	15.80	11.30	7.10	2.70	2.00
7	0	2.80	14.10	22.10	18.70	17.10	14.20	11.80	8.20	3.30	1.40
8	0	2.70	14.70	19.20	20.80	18.60	15.60	10.60	7.80	3.60	2.25
9	0	1.60	13.90	9.30	18.70	17.40	14.80	11.00	7.60	3.20	1.00
10	0	3.20	12.10	18.00	19.90	17.30	15.80	11.60	7.60	3.20	2.50
11	0	3.00	10.30	19.40	17.60	16.80	14.30	11.00	7.00	3.00	2.00
12	0	2.75	10.80	18.40	21.20	18.20	15.40	10.20	7.30	4.20	1.60
13	0	2.70	12.50	20.33	21.10	17.10	14.20	11.50	7.40	3.30	1.70
14	0	2.30	10.60	20.40	18.20	17.70	15.10	10.30	7.50	4.40	1.60
Mean	0	2.48	13.76	20.33	18.86	17.03	15.00	11.00	7.36	3.52	1.66
S.D.	0	0.46	2.23	1.40	1.48	0.99	0.63	0.57	0.39	0.46	0.48

APPENDIX-6

ที่ ทม 1210/ 522

คณะวิทยาศาสตร์
มหาวิทยาลัยสงขลานครินทร์
ตู้ ปณ 3 คอหงส์ 90110

หนังสือรับรองการศึกษาวิจัย

การศึกษาวิจัยที่ทำการทดลองในมนุษย์เรื่อง ผลของการออกกำลังกายต่อเภสัชจลนศาสตร์ของยาพาราเซตามอล ในอาสาสมัครสุขภาพปกติ

หัวหน้าโครงการวิจัย : ผศ.นายแพทย์วีรวัฒน์ มหัทธนตระกูล
ผู้ร่วมโครงการ.. รศ.นายแพทย์วิบูลย์ ฤทธิทิศ
ผศ.มาลินี วงศ์นาวา
อาจารย์เบญจมาศ จันทร์ฉวี

ได้ผ่านการพิจารณา และเห็นชอบจากคณะกรรมการจริยธรรม ซึ่งเป็นคณะกรรมการพิจารณาโครงการวิจัย ตลอดจนติดตามผลในส่วนของการทดลองที่กระทำต่ออาสาสมัคร ของคณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ แล้ว

ให้ไว้ ณ วันที่ 22 กันยายน 2542

.....ประธานคณะกรรมการ
(รศ.เพริศพิชญ์ คณาธารณา)
รองคณบดีฝ่ายวิจัยและบัณฑิตศึกษา

.....กรรมการ
(นายแพทย์วิบูลย์ ฤทธิทิศ)
ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์

.....กรรมการ
(นายแพทย์สมหมาย ปลอดสมบูรณ์)
ภาควิชาสรีรวิทยา คณะวิทยาศาสตร์

.....กรรมการ
(แพทย์หญิงสุวิณา รัตนชัยวงศ์)
ภาควิชาชีวเวชศาสตร์ คณะแพทยศาสตร์

.....กรรมการ
(รศ.ถาวร เกียรติทับทิว)
ภาควิชารัฐประศาสนศาสตร์ คณะวิทยาการจัดการ

.....กรรมการ
(ผศ.วุฒิพร พรหมขุนทอง)
ภาควิชาวาริชศาสตร์ คณะทรัพยากรธรรมชาติ

ใบยินยอม

Consent form

การวิจัยเรื่อง : ผลของการออกกำลังกายต่อเภสัชจลนศาสตร์ของยาพาราเซตามอลในอาสาสมัครสุขภาพปกติ

วันที่ให้คำยินยอม วันที่..... เดือน..... พ.ศ.....

ข้าพเจ้า (นาย/นาง/นางสาว)..... นามสกุล.....

ที่อยู่บ้านเลขที่..... แขวง/ตำบล.....

เขต/อำเภอ..... จังหวัด.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรือ อาการที่อาจเกิดขึ้นจากการวิจัย หรือ จากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่า จะตอบคำถามต่างๆที่ข้าพเจ้าสงสัยด้วยความเต็มใจ ไม่ปิดบัง ซ่อนเร้น จนข้าพเจ้าพอใจ

ข้าพเจ้าเข้าร่วมโครงการวิจัยนี้โดยสมัครใจและมีสิทธิ์ที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยนี้เมื่อใดก็ได้ การบอกเลิกการเข้าร่วมการวิจัยนี้จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะได้รับต่อไป

ผู้วิจัยรับรองว่า จะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย

ผู้วิจัยรับรองว่า จะดำเนินการด้วยความระมัดระวังอย่างดีที่สุด และรับรองว่า หากเกิดมีอันตรายใดๆ จากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดมูลค่า

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม..... (ผู้ยินยอม)

( )

ลงนาม..... (ผู้รับผิดชอบในการวิจัย)

( )

ลงนาม..... (พยาน)

( )

ลงนาม..... (พยาน)

( )

แบบบันทึกประวัติและการตรวจร่างกาย
ของอาสาสมัครไทย

เลขที่.....

วันที่.....

1. ประวัติส่วนตัว

ชื่อ.....นามสกุล.....

อายุ.....ปี เพศ ( ) ชาย ( ) หญิง

น้ำหนัก.....กก. ส่วนสูง.....ซม.

อาชีพ..... ที่อยู่.....

2. ประวัติการเจ็บป่วย

2.1 <u>ประวัติการเจ็บป่วยในปัจจุบัน</u>

(1).....

(2).....

(3).....

2.2 <u>ประวัติการเจ็บป่วยในอดีต</u>

( ) เคยนอนพักรักษาตัวในโรงพยาบาล ระบุชื่อโรค.....

( ) เคยได้รับการผ่าตัด ระบุชื่อโรค.....

( ) เคยเป็นโรคภูมิแพ้

( ) เคยแพ้ยา ระบุชื่อยาและอาการ.....

( ) เคยมีอาการตัวเหลือง ตาเหลือง เมื่อปี.....

3. ประวัติการเจ็บป่วยในครอบครัว

3.1 <u>ประวัติโรคกรรมพันธุ์</u>

( ) โรคภูมิแพ้

( ) โรคเบาหวาน

( ) โรคลมบ้าหมู

( ) โรคเลือด.....

3.2 <u>โรคติดเชื้อ</u>

( ) วัณโรค

( ) ตับอักเสบ

( ) อื่นๆ

4. ประวัติและอุปนิสัยส่วนตัว

บุหรี่ ( ) ไม่สูบ ( ) สูบ : จำนวน.....มวน/วัน

สุรา ( ) ไม่ดื่ม ( ) ดื่ม : จำนวน.....แก้ว/วัน

ยาที่ใช้/รับประทานเป็นประจำ ระบุชื่อยา.....

5. การตรวจร่างกาย

GA : .....

Vital Sign : BT.....°C PR.....beats/min

RR.....beats/min BP.....mmHg

Skin : .....

Heart : .....

Lung : .....

Abdomen : .....

Extremities : .....

Neuroexamination :

Conciousness : ( ) poor ( ) fair ( ) good

Pupils : diameter.....mm

RTL.....

Reflex : .....

.....

Muscle Power : .....

สรุปการตรวจร่างกาย

( ) อยู่ในเกณฑ์ปกติ

( ) ผิดปกติ

แพทย์ผู้ตรวจร่างกาย .....

6. การตรวจทางห้องปฏิบัติการ

6.1 CBC ผล.....

6.2 LFT ผล.....

6.3 RFT ผล.....

6.4 FBS ผล.....

7. สรุปผลของการตรวจร่างกาย

( ) อยู่ในเกณฑ์ปกติ

( ) ผิดปกติ ระบุ.....

ผู้บันทึก.....