The effect of exercise on pharmacokinetics of paracetamol (acetaminophen) in healthy volunteers

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Abstract

Exercise can influence a large number of physiological factors that may also affect the pharmacokinetics of various drugs. The aim of this study was to evaluate the influence of moderate-intensity exercise on the pharmacokinetics of paracetamol(acetaminophen) in healthy volunteers. Each of fourteen healthy male volunteers received a single dose of 1,000 mg of paracetamol without exercise were compared with those who received the drug before exercise by treadmill running at 5 km/hr for 30 minutes. Plasma concentrations of paracetamol were determined by HPLC. The pharmacokinetics parameters of both groups were calculated from plasma drug concentration changes during an eight-hour period. In the exercise group, the absorption rate constant (K_a) increased by about 2 fold (i.e. 4.90 ± 1.52 hr^{-1} vs 2.51 ± 1.02 hr^{-1}, P <0.01), the maximal concentration (C_{max}) increased significantly (18.64 ± 0.70 ug/ml vs 17.24 ± 1.06 ug/ml, P<0.01) whereas the time to reach maximal concentration (T_{max}) decreased by about 0.7 fold (0.86 ± 0.11 hr vs 1.25 ± 0.11 hr, P<0.01) and the absorption half-life ($t_{1/2}$(abs) decreased by about 0.5 fold (0.15 ± 0.05 hr vs 0.31 ± 0.09 hr, P<0.01). However, the area under the concentration-time curve (AUC), elimination rate constant (K_e), elimination half-life ($t_{1/2}$), apparent volume of distribution (Vd/f) and clearance(Cl/f) were not significantly different. In conclusion, moderate exercise increased the rate of paracetamol absorption but had no effect on distribution, metabolism and excretion of the drug. The increased rate of paracetamol absorption was supposed to be due to the increase in gastric emptying rate.

Key word   Exercise, Paracetamol, Acetaminophen, Pharmacokinetics, Healthy volunteers

Introduction

More and more people are getting involved in exercise to control their weight or improve their personal health or quality of life. Not only normal healthy individuals but also those who are taking medications are exercising to benefit their health or disease states.

Exercise can produce dramatic changes in the pharmacokinetic variables of certain drugs and result in alteration of the clinical responses as the blood or target tissue concentration is higher or lower than the therapeutic levels(Sweeney,1981; Van Baak, 1990). The magnitude of the changes depend on factors that pertain to the characteristics of each drug as well as exercise-related factors such as exercise intensity, mode and duration of exercise (Ciccone, 1995).

Exercise may affect many physiological factors which are important in the regulation of drug absorption, distribution, metabolism and excretion. These factors include gastric emptying rate, gastrointestinal transit, intestinal blood flow, gastrointestinal pH, plasma protein level, hepatic and renal blood flow etc.

Neufer *et al.* (1989) reported that gastric emptying was increased during treadmill exercise at moderate intensity of exercise but decreased during high intensity of 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. Moore et al. (1990) also reported that walking on an exercise treadmill at 3.2 km/hr or at 6.4 km/hr significantly increased gastric emptying.

Gastrointestinal transit is accelerated during mild exercise (treadmill walking at 5.6 km/hr for 15 minutes) from 87 ± 7 minutes at rest to 63 ± 5 minutes during exercise ($P < 0.05$) (Harris and Martin, 1993).

Exercise may shift blood flow away from the gastrointestinal tract towards the active muscle and the lungs (Brouns and Becker, 1993) and result in removal of drug from the absorption site. 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. Submaximal exercise reduced splanchnic blood flow by approximately 43% (Perko et al. ,1998). At maximal exercise intensity, splanchnic blood flow may reduced by about 80% (Clausen, 1977). So absorption of those drugs which have rate-limited absorption from the gastrointestinal tract, such as midazolam, may be reduced. As shown by Stromberg et al (1992) who reported that absorption of midazolam was impaired during the treadmill running. However, exercise may result in increasing of the absorption rate of some drugs such as cardiac glycoside : digoxin (Jogestrand and Andersson , 1989) and some antimcrobial agents (sulphamethizole, tetracycline and doxycycline) (Ylitalo et al , 1977). Hence, exercise can produce variable effects on absorption following oral administration depending on the characteristics of the drugs, intensity or type and duration of exercise.

Exercise may also influence protein binding of some drugs. During exercise, the plasma protein concentration increases due to movement of plasma water from vasculature to intracellular and interstitial spaces at the onset of intense exercise (Hyyppa and Poso, 1998; Van Beaumont et al., 1973). The volume of distribution (Vd) of some drugs have been shown to be reduced during exercise. 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 miles per hour for 20 minutes. Schlaeffer et al. (1984) reported a 50 %

lower volume of distribution of theophylline in healthy volunteers exercising at 50 % of VO_{2max} for 2 hours but the Vd was not affected by exercise at 30 % of VO_{2max}. Jogestrand and Sundqvist (1981) demonstrated that the plasma concentration of digoxin decreased by 37% during exercise (1 hour cycle ergometry at a heart rate of 120 −140 beats/min.) but the concentration of the drug in skeletal muscle was increased.

During exercise, hepatic blood flow is reduced in proportion to the relative exercise intensity (Van Baak, 1990). At a moderate exercise intensity i.e. at 50 % of VO_{2max} , hepatic blood flow is reduced by approximately 30 % while at 70 % of VO_{2max} , the reduction of blood flow was about 50 %. At maximal exercise, the hepatic blood flow was reduced by approximately 80 % (Swartz et al., 1974). Therefore , exercise may reduce the hepatic clearance of drugs with high hepatic extraction ratio and hepatic clearance is blood flow-dependent. Low hepatic extraction drugs will probably not be affected during exercise because clearance of these drugs depends on the metabolic capacity of the liver rather than on hepatic blood flow (Dossing,1985). Theilade et al. (1979) found that the hepatic clearance of phenazone (a low hepatic extraction ratio drug) was not changed during exercise (9-hour march at 4.6 km/hr) compared with supine bed rest.

Total clearance and biliary clearance of paracetamol were significantly increased in exercised rats while the volume of distribution and elimination half-lives were not different between the exercise and the sedentary groups. This may be due to elevated bile acid secretion and an increase number of organic anion/bile acid transporters (Watkins,1994) which can not be compensated for by decreased hepatic blood flow. However, there is not enough data to support this conclusion , especially in human.

Therefore , the aim of this study was to evaluate the influence of moderate-intensity exercise on the pharmacokinetics of paracetamol in healthy volunteers.

Paracetamol (acetaminophen), the active metabolite of phenacetin, is the most widely used antipyretic-analgesic drug throughout all over the world. Paracetamol is rapidly absorbed from gastrointestinal tract. The proportion of the dose reaching the systemic circulation appears to depend on the dose administered e.g. 90% after 1-2 g and 68% after 0.5 g. (Rawlins et al., 1977). Peak blood concentrations are usually reached in 30-60 minutes and the plasma half-life is about 2 hours after a therapeutic dose(Paul, 1991). The usual therapeutic dose is 10-20 mg/kg which gives a plasma concentration of 5-20 μg/ml. After 8 hours, only a small amount of unchanged paracetamol is detectable in plasma.

The rate of paracetamol absorption seems to be predominantly dependent upon the rate of gastric emptying, food, posture, some drugs, diseases or other conditions which can alters the rate of gastric emptying. Dietary fiber could reduce the rate of absorption of paracetamol (Holt et al., 1979a). 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 ≤ 0.05) and increased time to reach maximal plasma concentration (0.25-2 hr to 0.75-3 hr). Nimmo and Prescott (1978) reported that the rate of paracetamol absorption was markedly reduced when subjects lay on their left hand side compared with when ambulant. They suggested that the alteration of absorption rate was caused by changing in gastric emptying time.

Paracetamol is slightly bound to plasma protein (Donald,1992). Its apparent volume of distribution is about 1 L/kg. It is metabolized predominantly in the liver. At therapeutic dose, it is metabolized to glucuronide and sulfate conjugates, which comprise 90-95 % of the total excreted metabolites. Cytochrome P-450-dependent glutathione (GSH) conjugate pathway accounts for the remaining 5-10 %. The half-life of paracetamol is 2-3 hours and may be increased two fold or more with toxic dose or in liver disease.

Methods

Subjects

Fourteen Thai male volunteers were enrolled in this study. The mean (range) age was 29 (20-36) years, bodyweight 61.4 (57.0-68.3) kg , height 163.6 (158-171) cm. and body mass index (BMI) 23.03 (20.18-25.91) kg/m^2. All subjects were none-smoker and non-alcoholic. Medication was stopped for at least 1 week before and during the entire period of the study. They had no history of adverse drug reactions to paracetamol. The subjects were considered to be healthy as determined by medical history, physical examination and laboratory tests (fasting blood sugar, liver and renal function tests and complete blood count). The study was approved by the Ethical Committee of the faculty of Science, Prince of Songkla University. All subjects had voluntarily signed the written informed consent to participate in the study.

Protocol

Pharmacokinetics of paracetamol was studied on two separate occasions with a 1-week washout period in a crossover manner. In the first occasion , each subject of the control group received 1,000 mg of paracetamol (500 mg/tablet, 2 tablets) with 200 ml of water. No food was permitted for 2 hours after the dose. Water or soft drinks was allowed if the subjects had sign and symptom of hypoglycemia. Since the absorption of paracetamol is altered by posture and activity (Rumble et al., 1991); therefore 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 the tested group , each subject was assessed for vital signs 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 paracetamol intake. It consisted of two 15-minute sessions of treadmill-running (5 km/hr) with about 5-minute break for blood collection. Thus the total exercise time was 30 minutes. This exercise pattern was chosen because of a moderate level of exercise as determined 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. In the second occasion, the subjectes in each group were crossovered between the controlled and tested group and were treated by the same procedures mentioned above.

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 after paracetamol administration. Blood samples were centrifuged at 3,000 rpm for 30 minutes and plasma was separated and stored at -70° C for 4 weeks until analysis.

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). The instrumentation consisted of a Jascoo PU-980 pump fitted with the Waters 717 plus autosampler (Waters Associates, Milford, MA, U.S.A.), a guaard-pak precolumn, a μ-Bondapak C18 column (30 c, x 3.9 mm I.D.)(Waters Assoc., Milfopd, MA, U.S.A.) a variable UV detector set at 254 nm and a Jasco 807-IT integrator (Tokyo, Japan). The mobile phase was 25% methanol in 75% 0.1 M disodium hydrogen orthophosphate (adjusted pH to 4.7 with 85% orthophosphoric acid). The flow rate of the mobile phase was 2.0 ml/min. Samples were prepared by adding 450 μl of 10% perchloric acid to 450 μl of plasma which contained 300 μg/ml of 3-hydroxy acetanilide (used as internal standard), vortexing for 30 second then centrifuging at 14,000 rpm for 15 minutes then 20 μl of the supernatant was injected on to the column by an automatic injector. The method provided good linearity of response with correlation coefficient (r) more than 0.99 over the range of 1.0 – 25.0 mg/L. The assay detection limits for paracetamol in plasma was 0.5 mg/L.

Data Analysis

Pharmacokinetic Calculations

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

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.

Statistical Analysis

All results are expressed as means $\pm$ S.D. Differences in paracetamol pharmacokinetic parameters between the control and the 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.

Results

All fourteen volunteers were well tolerated to exercise and paracetamol throughout the study. Exercise caused significant elevation of heart rate (from 74 ± 5 to 126 ± 6 beats/min.), systolic blood pressure (from 117 ± 5 mmHg to 127 ± 5 mmHg), diastolic blood pressure (from 76 ± 5 mmHg to 81 ± 2 mmHg) and respiratory rate (from 20 ± 3 /min. to 30 ± 4/min.). But the body temperature was not significantly changed.

The semi-logarithmic mean plasma paracetamol concentration-time profile in fourteen healthy volunteers receiving a single oral dose of paracetamol without exercise(control group) and exercise after paracetamol ingestion(tested group) was shown in figure 1.

The pharmacokinetic parameters (mean $\pm$ S.D.), estimated from the plasma concentration-time data of paracetamol are shown in Table 1. The results showed that Ka, $t_{1/2}$ (abs), T_{max} and C_{max} were significantly different between the two groups while

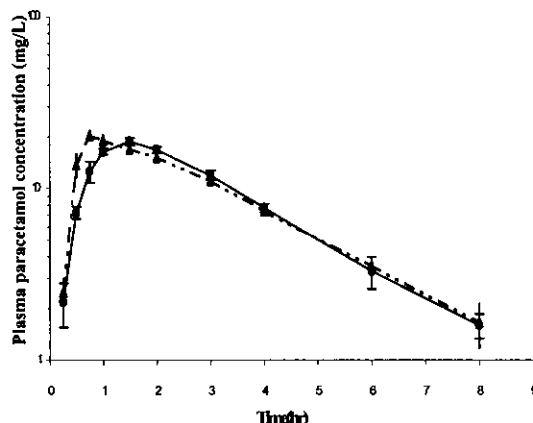there were no significant difference in AUC, Ke, $t_{1/2}$, Vd/f, Cl/f and the lag times

Figure 1 Semi-logarithmic mean plasma paracetamol concentrations in 14 healthy volunteers receiving a single oral dose of paracetamol 1,000 mg without exercise or control group (---●----); and with exercise after paracetamol treatment or tested group (...Δ....).

Table 1 Pharmacokinetic parameters (mean $\pm$ S.D.) of paracetamol in fourteen subjects receiving a single oral dose of 1,000 mg paracetamol without exercise or exercise after paracetamol treatment.

Parameters	Paracetamol without exercise (Control gr.)	Paracetamol with exercise (Tested gr.)	Paired student's t-test
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

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 and in plasma were in the range of 0.30 - 1.31% and 1.07 - 3.25 %; and 0.10 - 2.45% and 1.54 - 4.03 % respectively. While the coefficient of variation for intra- and inter-assay variance of six different internal standard concentrations (3-hydroxy acetanilide) in distilled water and in plasma were in the range of 0.32 - 0.80 % and 1.38 - 3.15 %; and 0.44 - 1.26 % and 1.05 - 2.13 % respectively. 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. The lower detection limit for paracetamol was 0.5 µg/ml. The recovery of standard paracetamol and 3-hydroxy acetanilide (internal standard) in plasma were in the range of 97.90 - 99.93% and 96.98 - 98.41 %, respectively.

Discussion

The semi-logarithmic mean plasma paracetamol concentration-time profile in the study has shown that the data were well described by a one compartment open model with first-order kinetics for both absorption and elimination which was similar to other studies (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). This may indicated that there is no significant difference of pharmacokinetics of paracetamol among races.

In this study, the absorption rate was significantly enhanced in the exercise group as shown by 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 ($C_{max.}$). This was supposed to be due to the increase in gastric emptying rate. Since gastric emptying regulated the rate of drug delivery to the absorption site, i.e. small intestine for paracetamol. Paracetamol absorption in man is related to the rate of gastric emptying (Clements *et al.* (1978); Heading *et al.* (1973) and Holt *et al.* (1979a)). Exercise significantly accelerated gastric emptying from 1.5 ± 0.1 hr. to 1.2 ± 0.1 hr.; $P < 0.02$) (Cammack *et al.* (1982). Moore et al. (1990) also demonstrated that exercise by walking on an exercise treadmill at 3.2 km/hr or at 6.4 km/hr significantly increased gastric emptying i.e. gastric emptying half-time ($t_{1/2}$) at rest ,walking at3.2 km/hr and walking at 6.4 km/hr were 72.6 ± 7.6 min. ; 44.5 ± 3.9 min and 32.9 ± 1.9 min. respectively.

However, distribution ,metabolism and excretion of the drug were not significantly changed. It is generally accepted that exercise redistributes blood flow away from the gastrointestinal tract (Horvath S., 1979) towards the active muscles and lungs and results in a reduction in splanchnic-hepatic blood flow (Wade *et al.*, 1956). Reduction of splanchnic-hepatic blood flow is related to the relative intensity of the exercise (Rowel LB, 1974). This finding may indicated that moderate exercise, used in this study, did not significantly affect hepatic nor renal blood flow. Judy (1984) has shown

that mild to moderate level of exercise did not change renal blood flow and there were no significant differences in the urinary concentrations of paracetamol, its glucuronide and sulfate conjugates in exercise v.s. sedentary rats (Watkins III JB. Et al., 1994)

In conclusion, exercise under the condition of this study : moderate exercise, increased the rate of paracetamol absorption but did not increase the total amount absorbed and neither did affect distribution, metabolism nor excretion.

Additional researches on the effect of exercise on the pharmacodynamics of the drug might be relevant for patients who exercise while on drug administration.

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