Effects of Cimetidine on the Pharmacokinetics of Mefloquine

Phongphan Chamnongchob

Master of Science Thesis in Biological Sciences

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Author Miss Phongphan Channongchob

Major Biological Sciences

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หัวข้อวิทยานิพนธ์	ผลของยาไซเมทิดีนต่อเภสัชจลนศาสตร์ของยาเมโฟลควิน
ผู้เขียน	นางสาวผ่องพรรณ จำนงชอบ
สาขาวิชา	วิทยาศาสตร์ชีวภาพ
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บทคัดย่อ

ยาเมโฟลควิน (mefloquine) เป็นยาที่พัฒนาขึ้นมาโดยมีสูตรโครงสร้างคล้ายยาควินิน (quinine) ยานี้มีประสิทธิภาพสูงในการรักษาโรคมาลาเรียที่เกิดเนื่องจากเชื้อปลาสโมเดียม ฟัลซิปารั่ม (Plasmodium falciparum) ดื้อต่อยารักษาหลายชนิด ซึ่งยานี้ได้ถูกใช้อย่างแพร่หลายทั่วประเทศไทย ในรูปยารวมกับซัลฟาดอกซิน (sulfadoxine) และ ไพริเมทามีน (pyrimethamine) ยาไซเมทิดีน (cimetidine) เป็นยาที่ใช้ได้ผลดีในการรักษาแผลในลำไส้เล็กส่วนต้น (duodenal ulcer) แผลในกระเพาะอาหาร (gastric ulcer) หลอดอาหารอักเสบ (peptic esophagitis) แผลในทางเดินอาหารที่เกิดจากภาวะเครียด (stress ulcer) และ เลือดออกจากกระเพาะอาหาร และลำไส้เล็กส่วนต้น ในกรณีที่เกิดจากมีกรดในกระเพาะมากเกินไป ซึ่งยานี้มีผลข้างเคียงน้อยมาก จึงเป็นที่นิยมใช้ทั่วไป และในปี 2529 วรรณวิมลรักษ์ และคณะได้รายงานการเปลี่ยนแปลงทางเภสัชจลนศาสตร์ ของยาควินิน ในอาสาสมัครไทย ภายหลังได้รับควินินร่วมกับไซเมทิดีน (cimetidine) โดยพบว่าค่าครึ่งชีวิตการกำจัดยา ($t_{1/2}$) และพื้นที่ใต้กราฟ (AUC) ของยาควินินเมื่อได้รับร่วมกับไซเมทิดีนมีค่าเพิ่มขึ้น จากการศึกษาเภสัชจลนศาสตร์ของยาเมโฟลควินในอาสาสมัครชายไทย 10 คนที่ได้รับเมโฟลควินเพียงอย่างเดียวในขนาด 500 มิลลิกรัมครั้งเดียวโดยการรับประทาน และภายหลังจากได้รับร่วมกับไซเมทิดีนในขนาด 800 มิลลิกรัมต่อวันเป็นเวลา 28 วัน โดยเก็บตัวอย่างเลือด มาวิเคราะห์ปริมาณยาด้วยวิธีเทคนิค High Performance Liquid Chromatography (HPLC) และหาค่าพารามิเตอร์ที่สำคัญทางเภสัช-จลนศาสตร์ พบว่าไซเมทิดีนไม่มีผลเปลี่ยนแปลงความเข้มข้นสูงสุด (C_{max}) เวลา

ที่ให้ความเข้มข้นสูงสุด (t_{max}) ปริมาตรของการกระจาย (Vd) และพื้นที่ใต้กราฟของยาเมโฟลควิน แต่มีผลทำให้ค่าคงที่ของอัตราการดูดซึมของยา (K_a) เพิ่มขึ้นจาก 0.493 ต่อชั่วโมงเป็น 0.886 ต่อชั่วโมง ($p < 0.05$) ค่าครึ่งชีวิตการดูดซึม ($t_{1/2}$ abs) ลดลงจาก 1.406 ชั่วโมงเป็น 0.782 ชั่วโมง ($p < 0.05$) ค่าครึ่งชีวิตการกำจัดยาเพิ่มขึ้นจาก 9.625 วัน เป็น 14.438 วัน ($p < 0.05$) ค่าคงที่ของอัตราการกำจัดยา (K_e) ลดลงจาก 0.003 ต่อชั่วโมงเป็น 0.002 ต่อชั่วโมง ($p < 0.05$) และค่าอัตราการชำระยา (Cl) ลดลงจาก 0.051 ลิตรต่อชั่วโมงต่อกิโลกรัมเป็น 0.031 ลิตรต่อชั่วโมงต่อกิโลกรัม ($p < 0.05$) นั่นคือการที่เมโฟลควินถูกกำจัดได้ช้าลงน่าจะมีผลทำให้ระยะเวลาในการออกฤทธิ์นานขึ้น

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ABSTRACT

Mefloquine, a structural analog of quinine is effective single dose therapy for multidrug resistant falciparum malaria The drug has been used widely in Thailand as a combination with sulfadoxine and pyrimethamine tablet. Cimetidine is a potent H_2-receptor antagonist to be introduced for general clinical use, won rapid acceptance for the treatment of duodenal ulcers and other gastric hypersecretory conditions and became one of the most widely prescribed of all drugs. Wanwimolruk et al. (1986) have shown that in healthy Thai volunteers the co-administration of quinine with cimetidine resulted in a longer terminal half-life ($t_{1/2}$) and greater area under the curve (AUC) of quinine. The present study reports on the pharmacokinetics of mefloquine in ten male Thai volunteers before and after a 28-day course of cimetidine (800 $mg.day^{-1}$). Mefloquine was administered as a single 500 mg oral dose. The mefloquine concentrations were determined by high performance liquid chromatography (HPLC). Peak plasma mefloquine concentration (C_{max}), time to peak concentration (T_{max}), volume of

distribution(Vd), and AUC were not altered after cimetidine. There were significant ($p < 0.05$) reduction in the drug clearance of mefloquine (0.051 ± 0.026 $l.hr^{-1}.kg^{-1}$ VS 0.031 ± 0.015 $l.hr^{-1}.kg^{-1}$, mean $\pm$ s.d.) and significant increase ($p < 0.05$) in the mean elimination half-life (9.625 days VS 14.438 days) after cimetidine. These findings suggest that mefloquine have a longer duration of action after concomitantly administered with cimetidine.

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Phongphan Chamnongchob

CONTENTS

LIST OF ABBREVIATIONS

$t_{1/2}$ abs	=	absorption half-life
K_a	=	absorption rate constant
AUC	=	area under the curve
BUN	=	blood urea nitrogen
CNS	=	central nervous system
Cl	=	clearance
CV	=	coefficient of variation
dl	=	deciliter
°C	=	degree celcius
DNA	=	deoxyribonucleic acid
$t_{1/2}$	=	elimination half-life
K_e	=	elimination rate constant
GC-ECD	=	gas chromatography-electron capture detection
GC-MS	=	gas chromatography-mass spectrometery
g	=	gram
HPLC	=	high performance liquid chromatography
hr	=	hour
i.m.	=	intramuscular
i.v.	=	intravascular
kg	=	kilogram
l	=	liter
MQ	=	mefloquine
MSP	=	mefloquine-sulfadoxine-pyrimethamine

LIST OF ABBREVIATIONS (CONT.)

ug	=	microgram
ul	=	microliter
mg	=	milligram
ml	=	milliliter
mm	=	millimeter
mM	=	millimolar
min	=	minute
ng	=	nanogram
N	=	normality
OCS	=	oral contraceptive steroid
C_{max}	=	peak plasma drug concentration
%	=	percent
rpm	=	round per minute
SGOT	=	serum glutamic oxaloacetic transaminase
SGPT	=	serum glutamic pyruvic transaminase
s.d.	=	standard deviation
TLC	=	thin layer chromatography
T_{max}	=	time to reach peak concentration
UV	=	ultraviolet
UNDP	=	United Nations Development Programme
u/L	=	unit per liter
Vd	=	volume of distribution
wk	=	week
WHO	=	World Health Organization

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INTRODUCTION

Mefloquine, a synthetic antimalarial drug, is a 4-quinoline methanol, chemically related to quinine (Katzung, 1992 : 728). Following initial development and testing of mefloquine by the United States Army in the 1960s, the drug has been developed further through a collaborative effort involving the UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases, the Walter Reed Army Institute of Research and Hoffmann-La Roche of Basle, Switzerland (WHO scientific Group, 1984 : 101-126). It has strong schizonticidal activity against all species of malarial parasites infecting humans including multi-drug-resistant Plasmodium falciparum but is not active against the hepatic stages of infection and thus cannot produce radical cure of Plasmodium vivax.

Because mefloquine is effective against most resistant strains of Plasmodium falciparum and because it produces fewer adverse effects than quinine, the drug is an important advance in the treatment of falciparum malaria (Katzung, 1992 : 728-730).

The results of acute, subacute and chronic toxicity studies of mefloquine in the rat, dog, monkey and mouse showed that the drug was not mutagenic. There were no teratological changes at doses that were tolerated by adult female animals, and the drug was not carcinogenic in rats or

mice (UNDP/World Bank/WHO Update, 1983 : 169-178). Recent results of reproductive trials comparing mefloquine with chloroquine have shown that mefloquine is less toxic for the foetus than chloroquine (Harinasuta, 1992 : 99).

The frequency and intensity of adverse reactions to mefloquine are dose-related. In prophylactic trials, the minor and transient adverse effects include gastrointestinal disturbances (nausea, vomiting, epigastric pain, diarrhea), headache, dizziness, syncope, and extrasystoles. Transient leukocytosis, thrombocytopenia and transaminase elevations have been reported. With treatment doses, particularly those over 1000 mg, gastrointestinal symptoms and fatigue are more likely and the incidence of neuropsychiatric symptoms (dizziness, headache, visual disturbances, vertigo, tinnitus, insomnia, restlessness, anxiety, depression, confusion, disorientation, acute psychosis, or seizures) may be as high as 1%. Other infrequent to rare toxic reactions are bradycardia, pruritus, myalgia, fever, chills, skin rash, and hair loss. Reactions have sometimes occured as long as 2-3 weeks after the last dose of mefloquine (Katzung, 1992 : 729).

Mefloquine is available either as the hydrochloride salt alone, or in a combined preparation with sulfadoxine and pyrimethamine (Karbwang and White, 1990: 264-279). It can only be given orally because intense local irritation occurs with parenteral use. Studies in experimental animals have demonstrated that mefloquine is

well absorbed after oral administration and 99 percent of the drug is protein bound (WHO Scientific Group, 1984: 101-125). Peak plasma concentrations are attained in a few hours and decline slowly over a period of several days. It is excreted predominantly in the feces and bile. Very little of the administered dose is excreted unchanged in the urine (Stern (letter), 1988). Five metabolites have been isolated and the structures of two are identified as 2, 8 bistrifluoromethyl-quinoline-4-methanol and carboxylic acid metabolite (UNDP/World Bank/WHO Update, 1983 : 169-178).

Mefloquine has the important advantage of providing cure following a single dose. Dose-finding studies have indicated that mefloquine is effective and well tolerated at the therapeutic dosages of 750-1250 mg. For prophylaxis, mefloquine is used at a dose of 250 mg weekly for adults and children of more than 45 kg body weight. It should be taken at least one week before entering an endemic area and continued for another 4 weeks ofter leaving the area (Karbwang and Harinasuta 1992 : 122).

Cimetidine is a potent H_2-receptor antagonist, and has been widely used since 1976 for the treatment of patients with duodenal ulcer, Zollinger-Ellison syndrome, systemic mastocytosis, reflux esophagitis and gastric ulcers. It also reduces duodenal ulcer recurrence.

The first H_2-receptor antagonists, burinamide and metiamide, were withdrawn from clinical trials due to serious complications. Cimetidine was then developed and

has been used extensively. The incidence of serious side effects is low.

Cimetidine may be given orally or parenterally by intravenous or intramuscular routes. The drug is rapidly and well absorbed from the GI tract after oral administration. Peak plasma drug concentration (C_{max}) is 1.44 $\pm$ 0.36 $mg.l^{-1}$. Time to reach peak concentration (T_{max}) is 1.9 $\pm$ 0.9 hrs after oral administration of a 300 mg tablet of cimetidine. The mean oral bioavailability ranged from 58 to 89% (Lin, 1991 : 218-236). Cimetidine is widely distributed throughout the body and is 15-20% bound to plasma proteins. Animal studies indicate that the drug crosses the placenta. Cimetidine is distributed into milk (McEvoy, 1989 : 1609-1614). Therapeutic concentration of the drug in plasma usually is in the range of 0.5 to 1.5 $ug.ml^{-1}$ (Moffat, 1986 : 468).

Most of the dose of cimetidine is recovered in the urine within 24 hours, about 50-70% as unchanged drug. Following administration, about 30-40% of the dose is metabolized in the liver. The sulfoxide is the major metabolite (Sewester, et al. 1991 : 1451-1459). Up to about 10% of the dose is eliminated in the faeces (Moffat, 1986 : 468). The elimination half-life is 1.5-2 hrs (Benitz and Tatro, 1988 : 389-390).

Adverse reactions to cimetidine are infrequent and are usually reversible following a reduction of dosage or withdrawal of therapy. The most frequently reported

side-effects are headache, tiredness, diarrhoea, muscular pain, skin rash and dizziness (Brogden, et al. 1978 : 122). Reversible confusional states, especially in the elderly or in seriously ill patients such as those with renal failure, have occasionally occurred (Langman, 1988 : 784). Information on the acute toxicity of cimetidine is limited. Doses of up to 15 g have not been associated with any untoward effects (Sewester, et al. 1991 : 1451-1459). Cimetidine increases plasma prolactin levels; gynecomastia and, rarely, galactorrhea may ensue. Depression of sperm count and impotence have been noted particularly with long-term high-dose cimetidine therapy (Dukes, 1988 : 784).

Cimetidine inhibits the cytochrome P 450 oxidase system that affects metabolism of other drugs e.g., warfarin, theophylline, several oral anticonvulsants, several β-blockers, several calcium antagonists, several antiarrhythmic agents and several antimalarial drugs (chloroquine, quinine, quinidine) (Sewester et al. 1991 : 1451-1459). Like quinine and chloroquine, mefloquine is a blood schizontocidal drug and it is a structural analog of quinine (WHO Scientific Group, 1984 : 101-125), therefore cimetidine could inhibit the metabolism of mefloquine theoretically, delaying elimination and increasing the plasma concentration of mefloquine. Concomitant administration of cimetidine with mefloquine may result in mefloquine increased pharmacological effects or toxicity.

The purpose of this investigation was to study the pharmacokinetics of mefloquine in healthy volunteers when this drug was administered alone and concomitantly with cimetidine. Because of the lack of previous studies of the effects of cimetidine on the pharmacokinetics of mefloquine, the pharmacokinetic data from this study should be important for the clinicians to set up a required dosage adjustment.

LITERATURE REVIEW

MEFLOQUINE

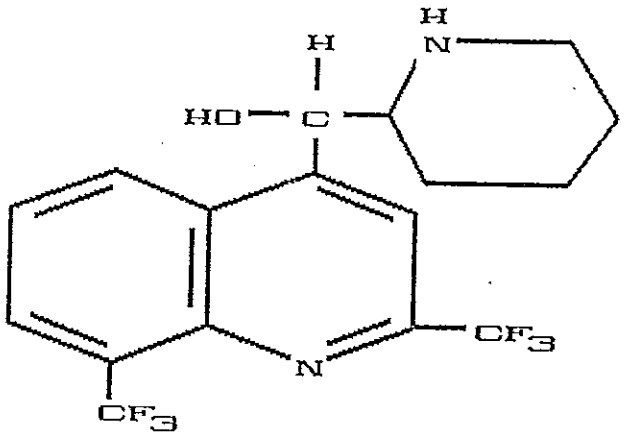

Figure 1 Structural Formula of Mefloquine

Chemical Name : dl-Erythro-α-(2-piperidyl)-2,8-bis (trifluoromethyl)-4-quinoline methanol

Molecular Formula : $C_{17}H_{16}F_6N_2O$

Trademark : Lariam

CHEMICAL AND PHYSICAL PROPERTIES

Molecular Weight : 414.79

Melting Point : 257-259 °C

Description : White, odorless, bitter-tasting powder.

Solubility : Very soluble in methanol, ethanol, acetone.
Moderately soluble in chloroform.
Insoluble in water, petroleum ether, benzene.

Storage : Mefloquine hydrochloride tablets should be kept in well-closed containers protected from moisture (Stern (letter), 1988)

PHARMACODYNAMIC PROPERTIES

1. Mechanism of Action

The exact mechanism of action of mefloquine is not known. Its activity shows some similarities to quinine or quinine-related drugs (Strickland, 1991 : 605).

In some respects, mefloquine behaves like quinine, but it does not intercalate with DNA. It has been shown to associate strongly with membrane phospholipids (Strickland, 1991 : 605). This may be an important feature of its activity, although its major mode of action is probably involved with parasite hemoglobin digestion (WHO Scientific Group, 1984 : 101-125).

Mefloquine has strong blood schizonticidal activity against Plasmodium falciparum and Plasmodium vivax but is not active against Plasmodium falciparum gametocytes or the hepatic stages of Plasmodium vivax. There was no evidence of effectiveness against Plasmodium malariae or Plasmodium ovale but theoretically the drug should be

effective against circulating schizonts of these species (Katzung, 1992 : 728-730).

2. Pharmacologic Effects

Like quinine, mefloquine can slow cardiac conduction. Studies in animals have shown antifibrillary action and an increase in the pulse rate interval. The effect of mefloquine on the compromised cardiovascular system in humans has not been evaluated (Katzung, 1992 : 729)

PHARMACOKINETIC PROPERTIES

Mefloquine hydrochloride is a synthetic 4-quinoline methanol derivative, chemically related to quinine. The drug was developed for human administration. It can only be given orally either as a tablet or as a crystalline aqueous suspension because intense local irritation occurs with parenteral use. Consequently, most kinetic data are derived from studies following oral administration, and the estimates of apparent volume of distribution and clearance are all corrected for the unknown fraction of the drug absorbed. The metabolism of mefloquine has been studied mainly in animals (Karbwang and White, 1990 : 264-279). It is well absorbed, and peak plasma concentrations are reached within 2-12 hours. A single oral dose of 250 mg. results in a plasma concentration of 290-340 $ng.ml^{-1}$. Plasma levels of 200-300 $ng.ml^{-1}$ may be necessary to achieve chemosuppression in Plasmodium falciparum infections (Katzung, 1992 : 728-730). The drug is 98% bound to plasma

proteins (Karbwang and White, 1990 : 264-279), concentrated in red blood cells, and is extensively distributed to the tissues, including the central nervous system. It is metabolized primarily to one component devoid of antiplasmodial activity and accumulates in the plasma. It undergoes extensively to biliary and gastric secretion, followed by reabsorption (Strickland, 1991 : 605). Most of the drug and its metabolites are slowly excreted, mainly in the feces. It has a long but variable elimination half-lives, ranging from 13 days to 33 days, which tends to be shortened in patients with acute malaria. The drug can be detected in the blood for months after dosing ceases (Katzung, 1992 : 728-730).

Schwartz et al. (1980) studied the pharmacokinetics of mefloquine in dogs and in man. Comparing the areas under the mefloquine curve following oral and i.v. administration in dogs, the bioavailability of the drug from tablets was found to range between 67 and 90% of the dose (mean 78%). Assuming that the absorption of mefloquine is also almost complete in man, first estimates of its volume of distribution and total clearance were attempted.

Single Dose Pharmacokinetics in Healthy Subjects

Desjardins et al.(1979) studied the pharmacokinetics of mefloquine hydrochloride in 20 healthy male subjects and used a HPLC technique to assay whole blood mefloquine concentrations and derived pharmacokinetic parameters in 4

groups of volunteers receiving a single oral dose of 250, 500, 1000 or 1500 mg (Table 1) given as tablets or in aqueous suspension form. Absorption was considerably more rapid from an aqueous suspension (mean absorption half-life = 1.1 hr) compared with that from tablets (mean absorption half-life = 3.8 hr). The area under the whole blood concentration-time curve (AUC) was 35% greater with the suspension than with tablet form, suggesting greater oral bioavailability. The total apparent volume of distribution (Vd) was large (13.3 $\pm$ 3.3 $l.kg^{-1}$), and the terminal elimination half-life varied from 6.5 to 22.7 days (mean 13.9 days). These data suggest a low intrinsic clearance with a very small first-pass effect.

Schwartz et al. (1982) studied the single-dose kinetics of mefloquine in 16 male volunteers. Plasma concentrations were measured by gas chromatography. The administration of mefloquine hydrochloride equivalent to 250 mg base (= 1 tablet) produced maximum plasma levels of 290-320 $ng.ml^{-1}$ within 4-6 hr while a 1000 mg-dose (= 4 tablets) resulted in some of the same subjects in plasma level maxima of 1010-1030 $ng.ml^{-1}$ within 2-12 hr. They measured both plasma and whole blood concentrations and found that absorption was rapid, with absorption half-life values between 22 and 120 minutes. Plasma terminal elimination half-life ranged between 15.6 and 33 days. Apparent volume of distribution estimates ranged between 13.5 and 29.1 $l.kg^{-1}$, and total clearance estimates ranged

between 18 and 40 $ml.min^{-1}.kg^{-1}$. Urinary excretion accounted for between 1.5 and 8.7% of unchanged mefloquine.

Riviere et al. (1985) studied the pharmacokinetics of mefloquine after oral administration of 750 mg to six volunteers. Plasma drug concentrations were analysed by HPLC. The absorption was apparently slow. Plasma mefloquine concentrations at 24 hr. (559 $\pm$ 181 $ng.ml^{-1}$; mean $\pm$ s.d.) greater than that at 6 hr (459 $\pm$ 166 $ng.ml^{-1}$). The elimination half-life, total clearance, and apparent volume of distribution were 373 $\pm$ 249 hr, 5.90 $\pm$ 2.71 $ml.hr^{-1}$ and 35.7 $\pm$ 30.7 $l.kg^{-1}$ respectively.

Karbwang et al. (1987b) studied the pharmacokinetics of a single oral dose of mefloquine 750 mg when given alone or in combination with sulfadoxine-pyrimethamine (Fansimef$^{(R)}$: sulfadoxine 1.5 g and pyrimethamine 75 mg) in 12 healthy Thai male and 12 healthy Thai female volunteers. Plasma concentrations of mefloquine were measured by HPLC at intervals for 42 days. Comparing the data from the individual groups, the time to peak (t_{max}) in female subjects receiving Fansimef$^{(R)}$ was less than that in male subjects receiving Fansimef$^{(R)}$ ($P < 0.05$) and in female subjects given mefloquine alone ($P < 0.05$). In the male subjects receiving mefloquine alone, peak concentrations ranged between 638 and 2494 $ng.ml^{-1}$ with a mean concentration of 1442 $ng.ml^{-1}$ which were higher compared to previously published data on mefloquine concentrations in

healthy Caucasian male subjects (Riviere, et al. 1985) receiving the same dose.

Mansor et al. (1989) studied the pharmacokinetics of a single dose of 500 mg mefloquine given in combination with sulfadoxine-pyrimethamine (Fansimef$^{(R)}$) to 10 healthy adult male Malaysian volunteers. The dose consisted of two tablets containing 500 mg mefloquine base, 1 g sulphadoxine base and 50 mg pyrimethamine base. Plasma concentrations of mefloquine were measured by GC-ECD. The mean peak concentration (C_{max}) was 1010 mg.l^{-1} and time to peak concentration 5.70 $\pm$ 0.95 hr (mean $\pm$ s.d.). The elimination half-life ($t_{1/2}$) for mefloquine was 387 $\pm$ 98 hr. The results of this study suggest that the pharmacokinetics of mefloquine be not significantly altered when administered as a triple combination.

Franssen et al. (1989) studied the pharmacokinetics of mefloquine, given orally in divided-doses to healthy Caucasian volunteers. The subjects received 500 or 750 mg followed by 500 mg 8 hr later. Mefloquine was measured in whole blood and plasma for 50 days by HPLC. Maximum blood and plasma mefloquine concentrations of 1872 $\pm$ 362 ng.ml^{-1} (mean $\pm$ s.d.) and 1900 $\pm$ 434 ng.ml^{-1}, respectively, were found within 6-10 hr. after the second dose. The terminal plasma elimination half-life was 20.1 $\pm$ 3.7 days (mean $\pm$ s.d.) and the clearance was 22.3 $\pm$ 6.7 ml.hr^{-1}.kg^{-1} (mean $\pm$ s.d.). The differences in the pharmacokinetic parameters

derived from plasma or blood concentration profiles were not statistically significant.

Multiple Dose Pharmacokinetics in Healthy Subjects

Mimica et al. (1983) studied the multiple dose pharmacokinetics of mefloquine in 5 healthy adult volunteers who received a dosage of 250 mg weekly for 21 weeks. Blood samples were collected just before administration of the next dose and plasma mefloquine and metabolite concentrations were analysed by TLC and UV-absorption. The mean plasma level of mefloquine measured at steady state, ranged from 560-1250 $ug.l^{-1}$ and that of the metabolite from 1470-5550 $ug.l^{-1}$. The elimination half-life at the end of drug administration was between 14.7 and 30.0 days.

Karbwang et al. (1991a) carried out a study of the multiple dose pharmacokinetics of Fansimef$^{(R)}$ (mefloquine-sulfadoxine - pyrimethamine) in 9 healthy border police volunteers who were working on the Thai-Cambodia border. Mefloquine 375 mg as Fansimef$^{(R)}$ tablets was given as a loading dose, followed by mefloquine 250 mg every 4 weeks for 4 doses. Whole blood concentrations of mefloquine were measured by HPLC at intervals for 19 weeks. The mean maximum concentration (C_{max}) was 420 $\pm$ 141 $ug.l^{-1}$ (mean $\pm$ s.d.), time to peak concentration (t_{max}) 12 $\pm$ 8 hr (mean $\pm$ s.d.), terminal half-life 14.93 $\pm$ 4.43 days (mean $\pm$ s.d.), apparent volume of distribution (Vd) 16.5 $\pm$ 5.6 $l.kg^{-1}$ (mean $\pm$ s.d.) and total clearance 0.99 $\pm$ 0.62 $ml.min^{-1}.kg^{-1}$

(mean ± s.d.). The mean minimum whole blood mefloquine concentration derived from the study was approximately 100 $ug.l^{-1}$ which was considered to be low for treatment.

Nosten et al. (1990) studied the pharmacokinetics of mefloquine in 20 Karen women in the third trimester of pregnancy receiving antimalarial prophylaxis with mefloquine. Ten of them received 250 mg mefloquine base weekly and the rest received identical tablets of 125 mg-base. $week^{-1}$. Whole blood mefloquine concentrations were determined by HPLC. The median time to peak mefloquine concentration was 6 hr (range 3-24). The mean peak blood mefloquine concentrations were 722 ± 279 $ng.ml^{-1}$ (mean ± s.d.) for the 250 mg-dose and 390 ± 86 $ng.ml^{-1}$ for the 125 mg-dose. The median volume of distribution was estimated to be 13.6 $l.kg^{-1}$, the mean total clearance was 0.047 ± 0.016 $l.hr^{-1}.kg^{-1}$ and the apparent terminal elimination half-life ($t_{1/2}$) was 11.6 ± 7.9 days.

Pharmacokinetics in Patients with Falciparum Malaria

In Thailand most studies of mefloquine pharmacokinetics have used a randomized clinical trial design to compare patients with malaria and healthy volunteers. Looareesuwan et al. (1987) studied mefloquine bioavailability and kinetics using a stable isotope technique. Five male Thai patients with falciparum malaria and six healthy male Swiss volunteers received 250 mg of mefloquine and 250 mg of deutero mefloquine base. Mefloquine and its deuterium labelled analogue were measured simultaneously by gas chromatography with mass spectrometry. The peak plasma mefloquine concentrations were approximately three times higher in the Thai patients (1004 $\pm$ 276 $ng.ml^{-1}$ mean $\pm$ s.d. for tablet and 1085 $\pm$ 280 $ng.ml^{-1}$ mean $\pm$ s.d. for the suspension) compared with the Swiss volunteers (319 $\pm$ 73 $ng.ml^{-1}$ mean $\pm$ s.d. for the tablet, and 369 $\pm$ 121 $ng.ml^{-1}$ mean $\pm$ s.d for the suspension). The total clearance of unlabelled mefloquine was significantly lower (17.5 $\pm$ 4.4 $ml.hr^{-1}.kg^{-1}$ mean $\pm$ s.d.) in the Thai patients compared with 28.8 $\pm$ 3.5 $ml.hr^{-1}.kg^{-1}$ mean $\pm$ s.d. in the Swiss volunteers ($p < 0.05$). Terminal elimination half-lives were significantly shorter in the Thai patients (10.3 $\pm$ 2.5 days mean $\pm$ s.d.) than in the Swiss volunteers (16.7 $\pm$ 1.9 days mean $\pm$ s.d.) ($p < 0.005$)

Karbwang et al. (1987a) studied the pharmacokinetics of mefloquine in the combined preparation of mefloquine-sulfadoxine-pyrimethamine (MSP) (Fansimef$^{(R)}$) in

9 Thai patients with uncomplicated chloroquine-resistant falciparum malaria. All patients received 11.2-16.7 mg of mefloquine base per kilogram body weight as MSP tablets. Mefloquine was assayed by HPLC. The mean apparent absorption half-life ($t_{1/2}$ abs) of mefloquine was 4.89 hr (range 2.25-9.72) and mean peak plasma concentration was 1815 $ng.ml^{-1}$ (range 725-3368). The authors found no difference between whole blood and plasma mefloquine concentrations during the first 48 hr of treatment.

Karbwang et al. (1988[a]) studied the kinetics of a single oral dose of mefloquine 750 mg in 12 Thai patients with falciparum malaria and 12 Thai healthy volunteers. Mefloquine was analysed by HPLC. There was no significant difference in peak plasma concentration, time to peak, area under the curve or apparent volume of distribution between patients and controls, but the terminal half-life ($t_{1/2}$) was shorter in the patients (12.2 days) than in the volunteers (16.7 days, $p \leq 0.001$).

Karbwang et al. (1991b) carried out a comparative study of the pharmacokinetics and pharmacodynamics of mefloquine given as a single oral dose treatment of either 750 or 1250 mg to 20 Thai male patients with acute uncomplicated falciparum malaria. The level of mefloquine in whole blood was determined by HPLC method. The derived pharmacokinetic parameters of the two regimens were similar, with the absorption of mefloquine increasing linearly with dose. The AUC values obtained were increased in proportion

to the dose, which suggested that there was relatively complete absorption of the higher dose (1250 mg). However, vomiting within an hour of taking the drug reduced the whole blood mefloquine concentrations. The results did not indicate that there was any advantage in using a single dose of 1250 mg of mefloquine rather than 750 mg.

Nosten et al. (1991) studied the pharmacokinetic properties of mefloquine hydrochloride (15 mg base.kg^{-1}) in 12 Karen children (5 girls, 7 boys) aged between 5 and 10 years presenting with uncomplicated falciparum malaria. The drug was well tolerated. Mefloquine in whole blood samples was measured by HPLC. Peak concentrations (C_{max}) of 2031 $\pm$ 831 ng.ml^{-1}(mean $\pm$ s.d.), ranged from 994 to 3772 ng.ml^{-1}, were reached in a median of 8 hr (range 6-24 hr). The apparent first order absorption half-life was 2.4 $\pm$ 0.6 hr (mean $\pm$ s.d.). The values for oral clearance (Cl) were 0.523 $\pm$ 0.272 ml.min^{-1}.kg^{-1} with a range of 0.15 to 1.02 ml.min^{-1}.kg^{-1}.

METABOLISM

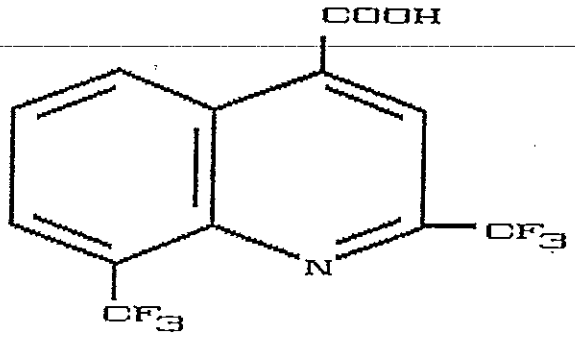

Figure 2 Structural Formula of 2,8-bis(trifluoromethyl)-4-quinoline carboxylic acid

Mefloquine is largely biotransformed into 2, 8-bis (trifluoromethyl)-4-quinoline carboxylic acid (Figure 2). Schwartz et al. (1980) studied the disposition of the carboxylic acid metabolite in human subjects given 1 g mefloquine base in the form of its hydrochloride orally. The metabolite appeared in the blood 2 to 4 hours after oral administration of mefloquine. Its concentration rose steadily to maximum values of 1.1 to 1.4 $ug.ml^{-1}$ within 1 or 2 weeks of administration and remained practically constant for about 2 to 3 weeks to decline thereafter at a rate similar to that of mefloquine. The authors compared the kinetic studies of 250 mg mefloquine and 204 mg of its metabolite in dogs, using i.v. administration. In these experiments, both compounds showed virtually the same elimination half-life but the initial plasma levels of mefloquine metabolite was about 30 times higher than those

of mefloquine. The volume of distribution of this compound was less than that of mefloquine. On comparing the AUC of metabolite formed after i.v. administration of 250 mg mefloquine with that measured after i.v. administration of 204 mg of metabolite, it was found that only 26% of mefloquine had been metabolically converted to mefloqine metabolite. Schwartz et al. (1982) studied the oral single dose kinetics of mefloquine in 16 male volunteers. Unchanged mefloquine and one of its metabolites were measured in plasma. The levels of its metabolite surpassed those of mefloquine, resulting in a 2.4-5.1 larger AUC. Franssen et al. (1989) reported that the concentration of the metabolite in whole blood was lower than that in plasma but also exceeded the whole blood concentration of mefloquine. Mimica et al. (1983) reported steady-state plasma concentration of mefloquine and carboxylic acid metabolite in 5 volunteers receiving 250 mg weekly for 21 weeks. The mean plasma levels of the metabolite ranged between 1.47 and 5.55 $ug.ml^{-1}$, while the mean metabolite to mefloquine ratio measured at steady state was found to have an interindividual range of between 2.3 and 8.6

TOXICOLOGY

UNDP/World Bank/WHO Update (1983) reported the toxicity of mefloquine in the rats, dogs, monkeys and mice. The results of acute, subacute and chronic toxicity showed that the drug did not cause mutagenic nor teratologic

changes. The toxic effects on the development of the offspring of rats were produced during the postnatal period only in those nursed by dams given very high doses of the drug. There was no evidence of toxic effects in dogs given doses ranging from 5 to 150 $mg.kg^{-1}$ body $weight.week^{-1}$ for 1 year, other than a reduction in the rate of weight gain in those receiving 25 $mg.kg^{-1}$ or more of drug per week. Epididymal lesions were seen in the male rats given 20 or 50 $mg.kg^{-1}$ of body $weight.day^{-1}$ for 90 consecutive days. Teratologic studies in female rats showed an increased incidence of externally visible soft tissue and skeletal anomalies when the drug was given 100 $mg.kg^{-1}$ of body weight from day 6 to day 15 of gestation, but no abnormalities were seen at doses of 10 or 20 $mg.kg^{-1}$. A 2-year study in rats showed that mefloquine is not carcinogenic at dose of 30 $mg.kg^{-1}$ or below. Thus, it possesses a relatively satisfactory overall profile of animal toxicity (Karbwang and White, 1990 : 264-279).

ADVERSE EFFECTS

In the clinical trials of mefloquine conducted to date, no serious adverse reactions have been observed. The main adverse reactions reported following the use of mefloquine 250 mg weekly prophylactic regimen are diarrhoea, nausea, vomiting, headache, and dizziness. Serious neurological reaction are rare with this regimen for up to 6 weeks of prophylaxis (Karbwang et al. 1992 : 118). These

side effects recorded have generally been mild and transient, self-limiting and required no specific treatment. These symptoms did not correlate with blood concentrations of mefloquine, although they were associated with the higher dose. (Karbwang et al. 1991c : 207-212). The pattern of adverse reactions seen in healthy volunteers was similar to that seen in patients (WHO Scientific Group, 1984 : 117).

Asymptomatic sinus bradycardia was found in patients receiving a single oral dose of 500, 750 or 1000 mg of mefloquine (Harinasuta et al. 1983). The bradycardia started between day 4 and 7 and the pulse rate of 46-50 per minute returned to normal within 14 days without treatment. Sinus arrhythmia was observed in 20 Thai male patients with acute uncomplicated falciparum malaria after 750 mg or 1250 mg of mefloquine. The arrhythmia occurred in three patients of the 750 mg group and four of the 1250 mg group (10 patients in each group). (Karbwang et al. 1991c : 207-212) This asymptomatic was also observed in 84 children with acute uncomplicated falciparum malaria (Chongsuphajaisiddhi et al. 1987 : 223-226). The arrhythmia occurred in 56 patients but it was not clear if this was drug-related.

THERAPEUTIC USES

Mefloquine is restricted to the prophylaxis and treatment of chloroquine-resistant and multidrug-resistant falciparum malaria. (Webster 1985 : 1029-1048). The drug is effective in prophylaxis against most strains of

chloroquine-resistant or pyrimethamine-sulfadoxine-resistant Plasmodium falciparum and is curative when taken weekly for 4 weeks after leaving an endemic area. On the other hand, the drug is indicated for oral treatment of mild to moderate mefloquine-susceptible Plasmodium falciparum infections (Katzung 1992 : 728-730). Mefloquine has been registered in Thailand and deployed in the malaria control program as a fixed combination with sulfadoxine and pyrimethamine (Fansimef$^{(R)}$). This combination is available commercially in tablets containing mefloquine 250 mg, sulfadoxine 500 mg and pyrimethamine 25 mg. The current standard regimen for radical treatment of falciparum cases in Thailand is 3 tablets taken as a single dose for adult patients (Pinichpongse et al.1987). There is an experimental evidence that mefloquine and mefloquine-sulfadoxine-pyrimethamine combination are equally effective in the treatment of acute uncomplicated falciparum infections, and cause similar in the incidence of mild side effects. In order to delay the development of mefloquine resistance, WHO are recommending that mefloquine should not be freely available. It should be distributed only to the Malaria Division, government hospitals, refugee medical organizations, and military and security forces (Pinichpongse et al. 1987).

DRUG INTERACTIONS

Sulfadoxine-pyrimethamine

Mefloquine is marketed in Thailand in combination with both sulfadoxine and pyrimethamine (Fansimef$^{(R)}$). In a recent study comparing the effects of mefloquine alone with those of mefloquine plus sulfadoxine-pyrimethamine, both regimens are equally effective in producing cure (Pinichpongse et al. 1987). There was significant difference in the half-life for patients who received mefloquine alone and for those receiving mefloquine-sulfadoxine-pyrimethamine. The derived mean half-life of mefloquine was longer following ingestion of 'Fansimef' compared to that following mefloquine alone. This suggest that sulfadoxine and/or pyrimethamine may influence mefloquine elimination (Karbwang et al. 1987^{b} : 173-177).

Quinine

Quinine should not be used concurrently with mefloquine. It can potentiate the dose-related adverse effects of mefloquine. If this compound is to be used in the initial treatment of severe malaria, mefloquine should not be administered within 12 hours of the last dose of quinine. (Stern (letter), 1988 : 16)

Metoclopramide

A study of the pharmacokinetics of 750 mg mefloquine when administered concomitantly with metoclopramide showed

that metoclopramide increased maximum concentration of mefloquine and AUC. The incidences of dizziness, nausea and abdominal pain were higher than mefloquine alone. (Nabangchang et al. 1991 : 639-641).

Oral Contraceptive Steroids

The effects of oral contraceptive steroids on the pharmacokinetics of a single oral dose mefloquine (750 mg) were studied in six healthy Thai women volunteers who regularly used oral contraceptive steroids (OCS) and in twelve Thai women patients with falciparum malaria, six of whom were also using OCS. The pharmacokinetic parameters of mefloquine were not significantly different in the two patient groups. The study suggested that the oral contraceptive steroids had no effect on the pharmacokinetics of mefloquine. (Karbwang et al. 1988b : 763-767).

Ampicillin

There was a study of the pharmacokinetics of a single oral dose of mefloquine in healthy Thai volunteers who took either mefloquine alone or in combination with ampicillin showed a significantly higher maximum whole blood mefloquine concentration after coadministration with ampicillin, significantly reduced terminal half-life and increased in mean residence time and increased volume of distribution at steady state (Karbwang et al. 1991b : 631-633).

Primaquine

A study was conducted to examine the pharmacokinetics of mefloquine in healthy Thai men who received either mefloquine alone or mefloquine and primaquine. The results suggested that primaquine did not alter the pharmacokinetics of mefloquine in Thai volunteers (Karbwang et al. (letter), 1992 : 559-560).

CIMETIDINE

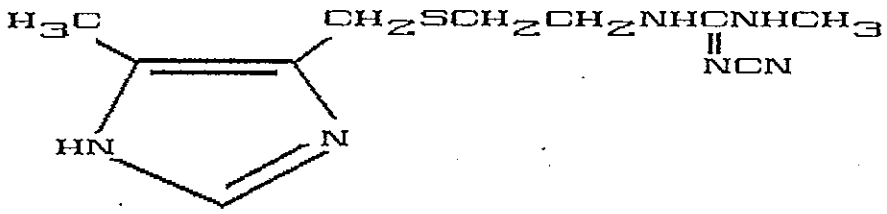

Figure 3. Structural Formula of Cimetidine

Chemical Name : 2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl) methyl] thio] ethyl] guanidine

Molecular Formula : $C_{10}H_{16}N_6S$

Trademark : Tagamet

CHEMICAL AND PHYSICAL PROPERTIES

Molecular Weight : 252.3

Melting Point : About 142 °C

pK_a 7.09

Description : White to off-white, crystalline powder; odorless, or having a slight mercaptan odor.

Solubility : Soluble in alcohol.

Freely soluble in methanol.

Sparingly soluble in isopropyl alcohol.

Slightly soluble in water and in chloroform.

Practically insoluble in ether.

Storage : In airtight containers. Protect from light.

PHARMACODYNAMIC PROPERTIES

1. Mechanism of Action

Cimetidine competitively inhibits the action of histamine on the H_2 receptor sites on parietal cells of the stomach. It is a potent inhibitor of all phases of gastric acid secretion. The drug inhibits secretions caused by histamine, muscarinic agonists and gastrin. It also inhibits fasting and nocturnal secretions, and secretions stimulated by food, insulin, caffeine, pentagastrin and betazole. In addition, the volume and the hydrogen ion concentration of gastric secretion are reduced. Cimetidine has no effects on gastric emptying and lower esophageal sphincter pressure (Sewester et al. 1991). Cimetidine produces selective blockade of H_2 receptors and hence has no effects on symptoms of allergy (Lehne et al. 1990).

PHARMACOKINETIC PROPERTIES

1. Absorption

Cimetidine is rapidly and well absorbed following oral administration (McEvoy 1989; Jacob, 1992) About 70% of the dose administered is absorbed from the GI tract (Govoni et al. 1990). The mean oral bioavailability ranged from 60-70%. Peak plasma drug concentrations (C_{max}) occur in 0.75 to 1.5 hours after an oral dose of cimetidine 300 mg, ranged from 0.7-3.2 $ug.ml^{-1}$ (Sewester et al. 1991). The absorption of cimetidine may be decreased by concurrent administration of antacids. Antacids should be administered at least 1 hour before or 1 hour after cimetidine. If cimetidine is taken with or immediately after meals, food will delay absorption and thus drug effect is prologrged. Peak blood level of cimetidine will coincide with peak food-induced gastric acid secretion (Govoni et al. 1990).

Intramuscular absorption of cimetidine is very rapid and complete. The peak plasma drug concentrations occurred in 15 minutes following a dose of 200 to 300 mg and the bioavailability was estimated to be 90 to 100% compared with intravenous administration (Lin, 1991).

2. Distribution

Cimetidine is widely distributed throughout the body (McEvoy, 1989). The apparent volume of distribution (Vd) is 0.8-1.2 $l.kg.^{-1}$ The plasma protein binding of cimetidine is low with the degree of binding of 13-25% (Sewester et al. 1991). Animal studies indicate that the

drug crosses the placenta. Cimetidine is also found to be distributed into milk (McEvoy, 1989)

3. Elimination

Cimetidine is eliminated primarily by the kidneys within 24 hours. Approximately 40 to 60% of oral drug and 77% of parenteral drug are excreted unchanged in the urine(Govoni et al.1990). Following oral administration, about 30% to 40% is metabolized in the liver, the sulfoxide being the major metabolite (Sewester et al. 1991). Some are excreted also occurs in bile, feces and breast milk. The elimination half-life of cimetidine ranges from 1.5 to 2 hours in patients with normal renal function. The half-life increases in patients with impaired renal function (Lehne et al. 1990).

THERAPEUTIC USES

Gastric and Duodenal Ulcers. Cimetidine is indicated for the treatment of active gastric and duodenal ulcers. For these conditions, treatment with cimetidine is equivalent to intensive therapy with antacids. Low doses of cimetidine may be used for prophylaxis against recurrence of gastric and duodenal ulceration (Lehne et al. 1990).

Zollinger-Ellison Syndrome. Cimetidine is useful in the symptomatic treatment of patients with Zollinger-Ellison Syndrome, but it has no effect on tumor progression.

Esophagitis Reflux. This condition caused by reflux of gastric contents back into the esophagus. Cimetidine is a drug of choice for relieving symptoms.

Other conditions. Cimetidine has been used for treatment of stress ulcers in the severely ill or burned patient, peptic esophagitis and upper gastrointestinal hemorrhage.

DOSAGE

Adult dose for duodenal and benign active gastric ulcer is 300 mg orally, 4 times daily, with meals and at bedtime; or 800 mg at bedtime. Preventive therapy is 400 mg at bedtime. For gastric hypersecretory states, maximum daily dose is usually 2.4 gm but in some hypersecretory states up to 12 mg per day may be necessary. In patients with renal impairment, start with 300 mg every 12 hr, increasing dose as necessary and as tolerated by patient. Children are dosed at 20 to 40 $mg.kg^{-1}$ in divided doses, four times daily.

Adult dose by intramuscular, intravascular, or intravascular infusion solution is 300 mg every 6 to 8 hr. The i.v. dose should be administered over 2 min or more while the i.v. infusion is mixed in a compatible solution and given over 15 to 20 min. Patients with renal impairment receive 300 mg i.v. every 12 hr, adjusting dose and interval as necessary and tolerated. Maximum daily dose is up to 2.4 mg. Children's i.m., i.v., or i.v. infusion dosage is 5 to 10 $mg.kg^{-1}$ every 6 to 8 hr (McKenry and Salerno, 1992 : 690)

ADVERSE EFFECTS

In general cimetidine is well tolerated (Jacob, 1992 : 170). The most frequently reported adverse effects are headache, tiredness, diarrhoea, constipation, dizziness, rash, muscle pain, nausea and pruritus. When administered as an i.v. bolus, cimetidine can cause hypotension and arrhythmias; these reactions are rare and do not occur with oral drug use. Hematological effects (neutropenia, leukopenia, thrombocytopenia) occur rarely (Govoni and Hayes, 1990).

Antiandrogenic Effects. Cimetidine binds to androgen receptors, producing receptor blockade. This action may result in gynecomastia, reduced libido and impotence, particularly in high doses for 12 to 79 months (mean 38 months) (Sewester et al. 1991 : 1457).

Central Nervous System Effects. Effects on the CNS are most likely in elderly patients who have renal or hepatic impairment (Jacob, 1992 : 170). Possible reactions include confusion, hallucinations, CNS depression (lethargy, somnolence) and CNS excitation (restlessness, seizures) (Lehne et al. 1990).

TOXICITY

Cimetidine doses up to 15 g have not been associated with untoward effects.

There is no experience with deliberate overdosage. Toxic doses in animals are associated with rapid respiration

or respiratory failure, tachycardia, muscular tremors, vomiting, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, collapse and cholinergic-type effects including lacrimation, salivation, emesis, miosis and diarrhea (Sewester et al. 1991 : 1458).

DRUG INTERACTIONS

Pharmacokinetic drug interactions with cimetidine occur at the sites of gastrointestinal absorption and elimination including metabolism and excretion. Cimetidine reduces the absorption of ketoconazole, indomethacin, ferrous salts and tetracyclines (Somogyi et al. 1987 : 322; Sewester et al. 1991 : 1456). Antacids, anticholinergics and metoclopramide may decrease the absorption of cimetidine. Cimetidine does not alter plasma protein binding of other drugs, but reduces the volumes of distribution of imipramine, labetolol, lidocaine and pethidine by unknown mechanisms. Cimetidine increases the plasma concentrations of drugs in a wide range of therapeutic classes (Somogyi et al. 1987 : 322). Further, cimetidine acts through binding to the haem portion of cytochrome P450 or through inhibition of its synthesis as an inhibitor of phase I drug metabolism (i.e. hydroxylation, dealkylation) with some degree of specificity (Somogyi et al. 1987 : 322).

Cimetidine reduces the hepatic metabolism of drugs metabolized via the cytochrome P450 pathway, delaying elimination and increasing serum levels. Drugs metabolized

by hepatic microsomal enzymes, particularly those of low therapeutic ratio or in patients with renal or hepatic impairment, may require dosage adjustment. This applies to the following drugs administered of concomitantly with cimetidine : benzodiazepines (does not include agents metabolized by glucuronidation, lorazepam, oxazepam, temazepam), caffeine, calcium channel blockers, carbamazepine, labetalol, lidocaine, metoprolol, metronidazole, pentoxifyline, phenytoin, propranolol, sulfonylureas, theophyllines, triamterene, tricyclic antidepressants, warfarin and antimalarial drug (i.e. chloroquine, quinine, quinidine) (Sewester et al. 1991 : 1456).

Cimetidine does not inhibit conjugation mechanisms including glucuronidation, sulphation and acetylation or deacetylation (Somogyi, et al. 1987 : 322).

Cigarette-smoking reverses cimetidine-induced inhibition of nocturnal gastric secretion, hindering ulcer healing. Cigarette smoking is closely related to ulcer recurrence (Sewester et al. 1991 : 1456; Govoni et al. 1990 : 192).

MATERIALS AND METHODS

CHEMICALS AND REAGENTS

Mefloquine (Lariam(R); F. Hoffmann-La Roche Ltd Basel Switzerland Lot No. B0800) was obtained from the Malaria Division (Ministry of Public Health, Devavesm Palace, Bangkok, Thailand). Cimetidine (Tagamet(R), Smith Kline & French Co, Lot No. 1A943/27) was purchased from Songklanagarind Hospital, Thailand. Standard mefloquine, pyrimethamine and aquasil were obtained from the Department of Immunology and Biochemistry, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand. Methanol (HPLC grade) was purchased from J.T. Baker Inc. (Phillipsburg, NJ. 08865 USA), dichloromethane from Farmitalia Carlo Erba (via C. Imbonati 24-20159 Milano) and 1-octane sulfonic acid sodium salt 98% (Lot No. 40H5614) from Sigma Chemical Company (St. Louis, USA). Analytical grade phosphoric acid 85% (Mallinckrodt) and sodium hydroxide were purchased from May & Baker Ltd (Dagenham, England)

INSTRUMENTATION AND CHROMATOGRAPHIC CONDITIONS

The HPLC system consisted of a liquid chromatograph (Milton Roy, Model CM 4000, Riviera Beach, Florida, U.S.A), an ultraviolet detector (Model Spectromonitor 3100) and an injector (Rheodyne, Model 7125, Cotati, CA. U.S.A) with a 50 ul sample loop. Detection was made with the variable-

wavelength UV detector set at 222 nm and peak height was measured with a Milton Roy Model CL-108 integrator. A Model LDC/Milton Roy recorder was used with attenuation set at 4 and chart speed at 2 $ml.min^{-1}$.

Chromatographic separation was performed on a Partisil 10 ODS-3 column, particle size 10 um, 25 cm x 4.6 mm I.D. (Phenomenex Torrance, CA, U.S.A.). A guard-pak precolumn module was used to obviate the effect of rapid column degeneration.

METHODS

1. Subject and protocol

1.1 Subjects

The subjects were ten Thai male volunteers, aged between 20 and 40 years (weight 45-68 kg, mean weight 59 kg), who were healthy as determined by medical history, physical examination and laboratory testing. Laboratory analyses included an evaluation of haematological parameters (haemoglobin, haematocrit, white blood cell count and differential white blood cell), liver function (albumin globulin, bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase) and renal function (BUN, creatinine, urinalysis) were performed. Two of the volunteers were Thai Muslim and eight were Thai according to their family history. No other concurrent drugs were taken in the month preceding the study or during the study itself. Five subjects

smoke 2-20 cigarettes daily and six subjects drank an average of 250 ml of Thai whisky per month. Each volunteer was given a detailed explanation of the purpose and protocol of this study and each gave written consent. All subjects were asked to abstain from smoking and drinking alcoholic beverages during the course of the study. The study was approved by the Faculty of Science Ethics Committee, Prince of Songkla University.

1.2 Protocol

In the morning after an overnight fast, each subject took a single oral dose of 500 mg of mefloquine. The drug was administered with a glass of water under supervision. No food was taken until at least 1 1/2 hours after ingestion of the drug. Caffeine was abstained from for 12 hours after mefloquine ingestion.

Five ml of blood was collected from an antecubital vein into heparinized plastic tubes (50 units heparin sodium per ml of blood) and the plasma separated within 30 min. The plasma was stored in plain plastic tubes at -20 °C until analysis. Samples were collected before, then at 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h, and on days 2, 3, 4, 7, 14, 21 and 28 after the end of oral dosing. The subjects remained in the research room for 12 hours and returned for blood sampling as scheduled.

After 2 months of being drug free, subjects received cimetidine tablet at an oral dose of 400 mg twice a day (after breakfast and at bedtime) for 7 days

prior to mefloquine administration. In the morning of day 8 after an overnight fast all subjects ingested a 400 mg tablet of cimetidine 2 hours before mefloquine administration. Blood samples were collected before cimetidine and after mefloquine administration according to the bloodletting schedule above. Cimetidine was administered at bedtime on this day and the regimen continued as described above until the last blood sample was obtained.

2. Analytical methods

Mefloquine concentration in the plasma was assayed by a high performance liquid chromatographic (HPLC) method (Edstein et al. 1991).

2.1 Mobile phase

The mobile phase consisted of 65% methanol and 35% water containing 15 mM octanesulfonic acid sodium salt (adjusted to pH 3.8 with 1.5 M phosphoric acid). The mobile phase was freshly prepared each day and was filtered through 0.45 u filter paper (Pierce, Rock ford, IL, U.S.A) and degassed before use. The flow rate was 2.0 $ml.min^{-1}$ which gave a pressure of 1,700-1,900 psi. All analyses were performed at room temperature (23-27 °C).

2.2 Stock standard solution

Stock solution of mefloquine was prepared by dissolving 4 mg standard mefloquine in methanol and adjusting the volume to 10 ml (400 $ug.ml^{-1}$) in a 10 ml volumetric flask. Working standard solutions were prepared by appropriate dilution of the stock standard solution with

distilled water (Appendix-1). The stock solution could be stored at 4 °C. for at least 6 months (Edstein, 1991)

2.3 Stock internal standard solution

Pyrimethamine was used as the internal standard. It was prepared by dissolving 2.5 mg of pyrimethamine in methanol and adjusting the volume to 10 ml (250 $ug.ml^{-1}$) in a 10 ml volumetric flask. Working solution A was prepared by dilution of 0.1 ml stock solution with 4.9 ml of distilled water (5.0 $ug.ml^{-1}$). Working solution B was obtained by mixing 1.0 ml of solution A and diluting to 5.0 ml with distilled water (1.0 $ug.ml^{-1}$). The stock solution was stored at 4 °C.

2.4 Direct injection of an aqueous solution

50 ul of working internal standard solution (1.0 $ug.ml^{-1}$) and 50 ul of working standard solution (Appendix-1) were injected onto the column.

2.5 Extraction procedure

Extraction of drugs from plasma was carried out in 16 x 125 mm glass culture tubes with polytetrafluoro-ethylenelined screw caps (Corning, NY, U.S.A.) pretreated with 0.2% Aquasil to minimize drug adsorption.

Mefloquine extraction was performed by : adding 100 ul of internal standards, 1 ml of 1 N sodium hydroxide and 8 ml of dichloromethane into 0.5 ml of plasma. The contents of the tube were mixed on a rotator at 30 rpm for 15 min. After centrifugation at 1,000 g for 10 min, the aqueous phase was discarded. Five ml of organic phase was

transferred to a clean glass tube and evaporated to dryness at 40 °C under a steady stream of nitrogen. The residue was reconstituted in 200 ul of mobile phase and the contents were transferred to a polypropylene microcentrifuge tube. After centrifugation at 1,000 g for 10 min, 50 ul of the supernatant was injected onto the column.

2.6 Calibration Procedure

Calibration samples were obtained by adding 100 ul of working standard solution and 100 ul of working internal standard solution (1.0 $ug.ml^{-1}$) to 0.5 ml drug-free plasma. The spiked plasma samples were extracted as described above, and peak height ratios of mefloquine to internal standards were plotted against concentrations (Figure 4.). Calibration standards were run on each day of analysis.

2.7 Detection Limit

The limit of detection of mefloquine in plasma was 31.256 $ng.ml^{-1}$.

2.8 Extraction Recovery

The extraction recovery was determined by comparing peak height obtained from an extracted sample containing a known amount of compound with the peak height obtained from a direct injection of an aqueous solution containing the same concentration of each compound. The extraction recovery of mefloquine from plasma was approximately 91% (Table 2).

2.9 Assay Precision

The interassay and intraassay precision was determined by analysis of spiked plasma at different concentrations within the linear range of the calibration curve (Table 3).

2.10 Accuracy

Accuracy was determined as the percentage difference of the amount of drug added to drug-free plasma versus the amount of drug measured (Table 4).

3. Pharmacokinetic Calculations

The pharmacokinetic parameters were calculated from a nonlinear least-squares regression program NONLIN (Metzler and Weiner, 1984), using a one compartment model.

Student t-test (Rimm et al. 1980) was used to determine statistical significance of the data and level of minimal was set at $p < 0.05$. Data are expressed as mean $\pm$ s.d. unless otherwise indicated.

TABLE 2 The percentage recovery of mefloquine from plasma.

Amounts of MQ in 1.0 ml plasma (ng)	n	Peak Height Obtained From		Recovery (%)
		Direct Injection	Extraction	mean ± SD
250	2	1700.00	1595.20	93.10±1.05
		1632.00	1507.20	
500	2	3091.00	2700.00	89.41±2.91
		3157.50	2888.00	
1500	2	9600.00	9000.80	92.07±2.40
		10557.50	9540.80	
			mean =	91.53%

MQ, mefloquine; n, number of observations.

TABLE 3 Assay precision

Amounts of MQ in 1.0 ml plasma (ng)	n	Precision	
		Interassay CV (%)	Intraassay CV (%)
250	2	8.78	2.89
500	2	3.84	1.51
1500	2	2.03	6.41
	mean	5.81	4.90

MQ, mefloquine; CV, coefficient of variation; n, number of observations.

TABLE 4 Accuracy determination

Amounts of MQ in 1.0 ml plasma (ng)	n	Expected values (ng)	Measured values (ng)	%Deviation
250	2	250	245	2.0
			230	8.0
500	2	500	450	10.0
			470	6.0
1500	2	1500	1405	6.33
			1420	5.33
				mean = 6.28%

MQ, mefloquine; n, number of observations

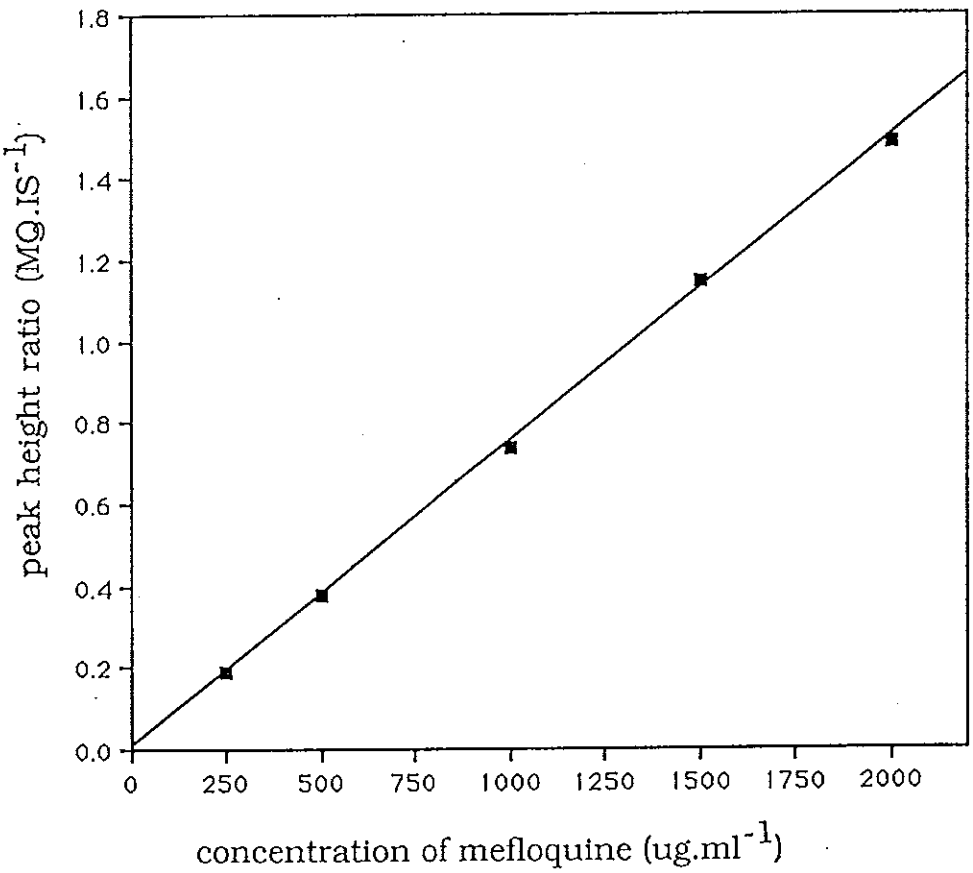

Figure 4 Calibration curve of mefloquine, correlation coefficient (r) = 0.999

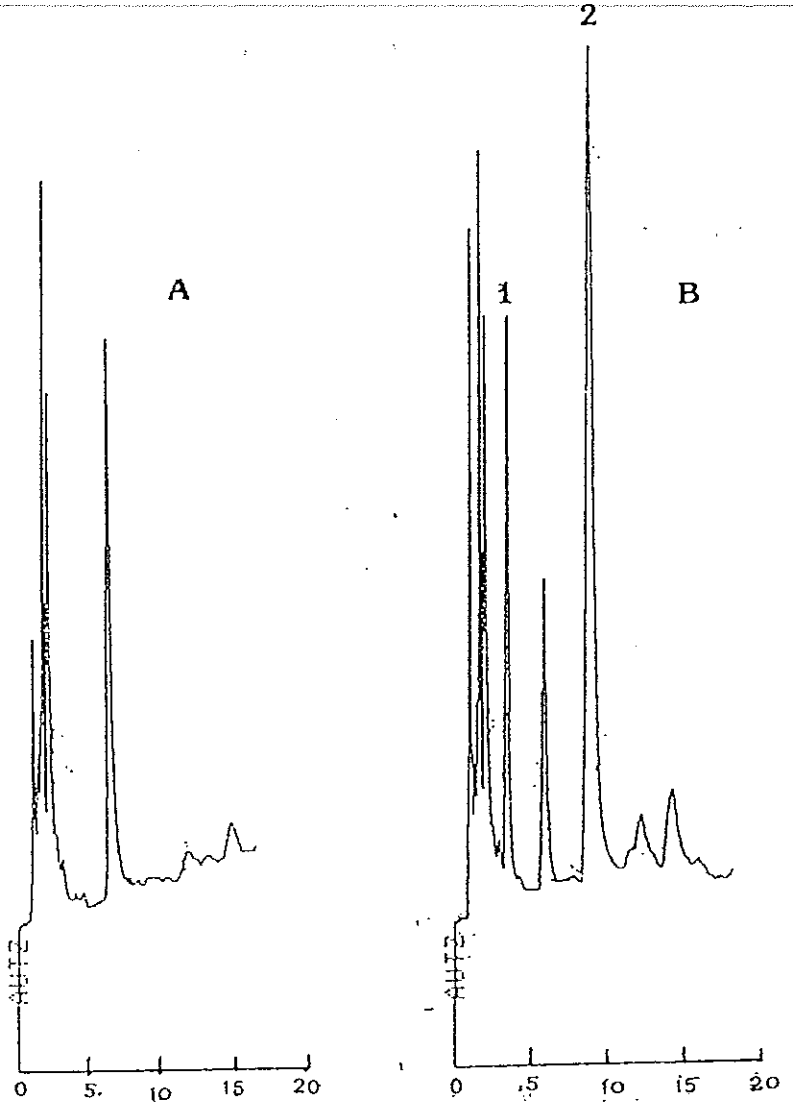

Figure 5 Chromatograms of extracted human plasma sample (0.5 ml) of (A) blank, (B) spiked with 100 ng pyrimethamine (1) and 1500 ng standard mefloquine (2).

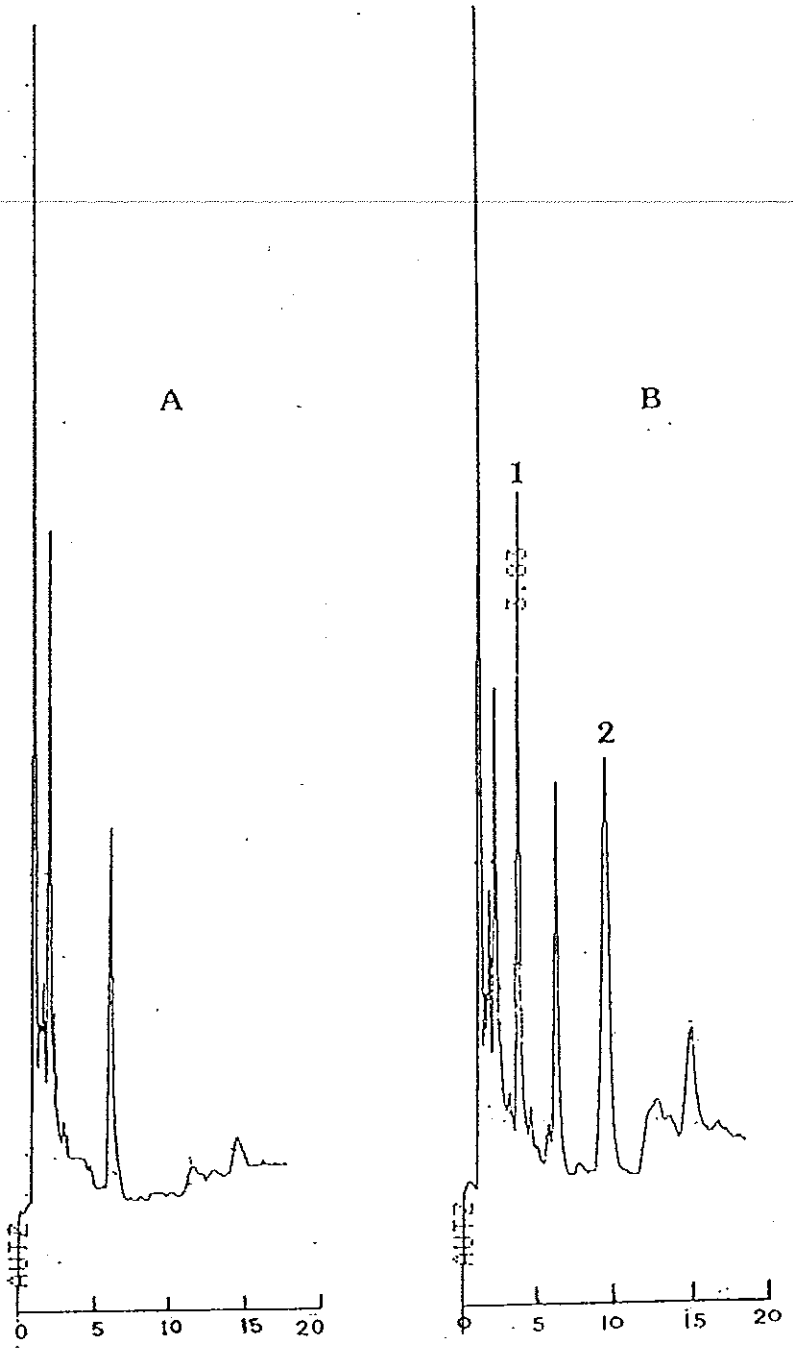

Figure 6 Chromatograms of extracted samples (0.5 ml) of (A) predose plasma, and (B) plasma obtained at 4 hours following the administration of mefloquine 500 mg to volunteer and spiked with 100 ng pyrimethamine (1) (mefloquine concentration is 690 $ng.ml^{-1}$) (2)

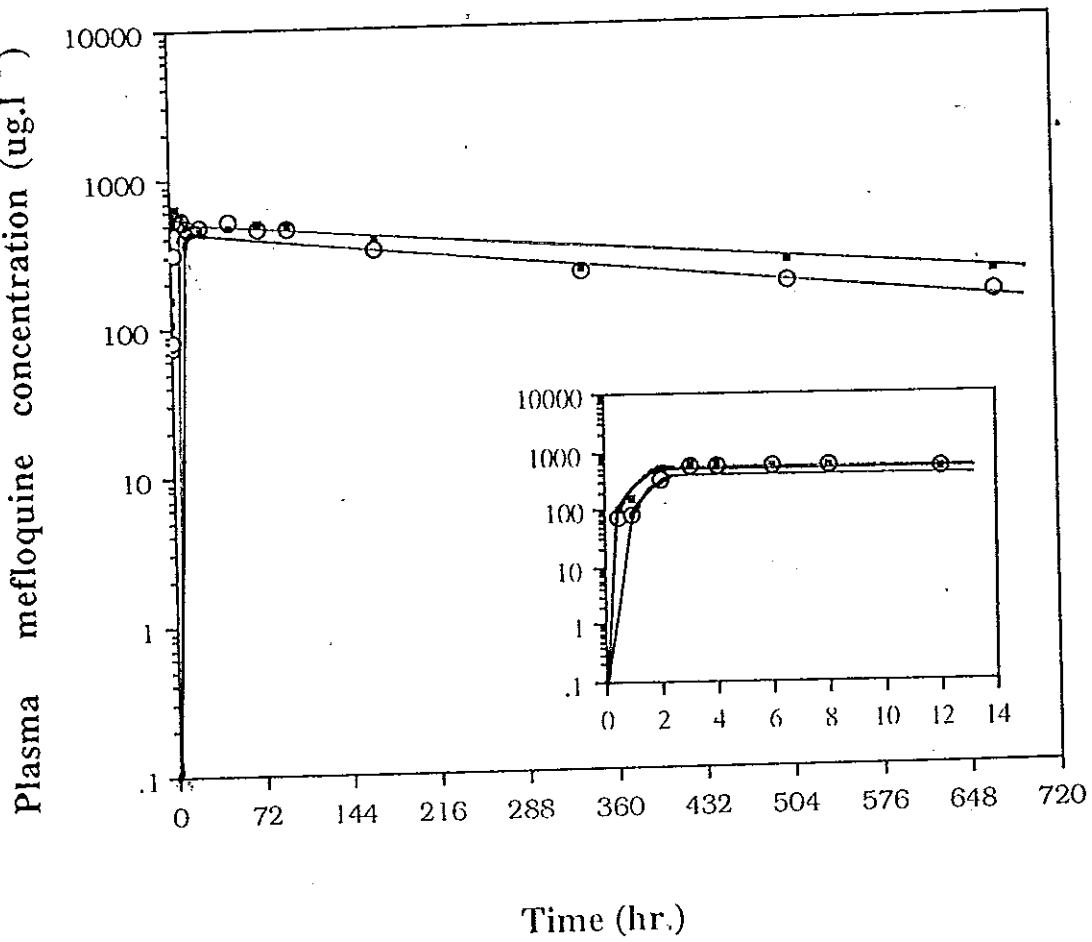

Figure 7 Semi-logarithmic plasma mefloquine concentration time profile following a single oral dose of 500 mg. of Lariam$^{(R)}$ (○), and after concomitant administration of cimetidine 800 mg daily for 28 days (■) in ten volunteers. *Inset* shows plasma mefloquine concentration with time scale expanded for the first 12 hr after administration.

RESULTS

The values of laboratory tests of all volunteers were comparable in both before and after drug administration. No changes were observed on routine testing of urine for glucose, blood and albumin. Table 5 gives details of the haematological and biochemical data before and after the study. There were no changes in liver function, renal function or haematological parameters after the study.

No side effects were observed after 500 mg of mefloquine. One volunteer had dizziness after taking the third dose of cimetidine following a 24-hour mefloquine administration. This symptom occurred for a few days and required no specific treatment. Two other volunteers had transient headache after taking cimetidine alone in the first week. No other adverse effects were observed.

PHARMACOKINETIC STUDY

The profiles of plasma mefloquine concentrations with and without cimetidine in the ten subjects are shown in Figure 7. It was found that measurable concentrations of mefloquine were present in all samples taken up to 28 days after drug administration, the mean concentration being 143 $ug.l^{-1}$ with a range of 45 to 225 $ug.l^{-1}$

There was considerable inter-individual variation in the peak plasma concentration of mefloquine (C_{max}), which ranged from 354.76 $ug.l^{-1}$ to 705.82 $ug.l^{-1}$ (556.46 $\pm$ 117.41 $ug.l^{-1}$; mean $\pm$ s.d.) for the mefloquine users, and from 393.38 $ug.l^{-1}$ to 788.44 $ug.l^{-1}$ (569.14 $\pm$ 120.12 $ug.l^{-1}$; mean $\pm$ s.d.) for mefloquine with cimetidine users. A large variation also occurred in the time to peak concentration (T_{max}), ranging from 7.62 hours to 30.95 hours (12.54 $\pm$ 7.35 hr.; mean $\pm$ s.d.) for the mefloquine users, and from 5.073 hours to 12.47 hours (7.46 $\pm$ 2.41 hr.; mean $\pm$ s.d.) for the mefloquine with cimetidine users. The differences between the peak plasma concentrations and times to peak concentration were not significantly different for the two conditions. The pharmacokinetic data are summarized in Table 6. There were significant differences between the parameters for the mefloquine user and those for the mefloquine with cimetidine users : the mefloquine with cimetidine users had a significantly longer elimination half-life ($t_{1/2}$) (14.44 days versus 9.63 days; $p < 0.05$). The body clearance (Cl) of mefloquine were significantly lower (0.03 $\pm$ 0.02 $l.hr^{-1}.kg^{-1}$; mean $\pm$ s.d.) in the mefloquine-cimetidine volunteers compared with 0.05 $\pm$ 0.03 $l.hr^{-1}.kg^{-1}$ (mean $\pm$ s.d.) in the mefloquine volunteers ($p < 0.05$). The mean absorption rate constant (K_a) of mefloquine were significantly greater in the mefloquine-cimetidine volunteers (0.89 $\pm$ 0.28 hr^{-1} versus 0.49 $\pm$ 0.17 hr^{-1}; mean $\pm$

s.d., $p < 0.05$) but the mean elimination rate constant (K_e) was significantly lower (0.002 ± 0.001 hr^{-1} versus 0.003 ± 0.001 hr^{-1}; mean $\pm$ s.d., $p < 0.05$).

The area under the curve of mefloquine was greater after concomitant administration with cimetidine (308.751 ± 144.933 $mg.hr.l^{-1}$ versus 225.182 ± 109.760 $mg.hr.l^{-1}$; mean $\pm$ s.d.) but this difference was not statistically significant.

The volume of distribution (Vd) of mefloquine appeared to be similar in the volunteers who received mefloquine alone and co-administration with cimetidine (15.58 ± 3.56 $l.kg^{-1}$ and 15.45 ± 3.44 $l.kg^{-1}$; mean $\pm$ s.d.)

Table 5 Safety data

Routine testing	Normal range	Initial value (mean±s.d)	After study value (mean±s.d)	Paired student's t-test
Haemoglobin (g/dl)	12-18	14.85±0.52	15.12±0.71	NS
White blood cell (cells/mm^3)	4,000 -11,000	8930±1517.34	8510±1386.80	NS
Neutrophils (%)	24-77	47±8.77	44.89±14.44	NS
Alkaline phosphatase (u/L)	39-117	90.4±23.06	88.10±13.03	NS
Blood Urea Nitrogen (mg %)	5.6-16.6	11.05±1.45	11.19±3.65	NS
Serum creatinine (mg %)	0.8-1.4	1.06±0.10	1.09±0.08	NS
SGOT. (u/L)	up to 37	32.10±19.27	28.80±11.47	NS
SGPT. (u/L)	up to 40	35.90±33.66	30.00±18.23	NS

Table 6 Pharmacokinetic parameters of mefloquine in ten volunteers before and after cimetidine (mean ± s.d.)

Parameters	Mefloquine alone	Mefloquine + Cimetidine	Paired student's t-test
C_{max} ($ug.l^{-1}$)	556.457±117.411	569.135±120.115	NS
T_{max} (hr)	12.541±7.346	7.456±2.414	NS
*$T_{1/2}$ (day)	9.625	14.438	$p < 0.05$
*$T_{1/2}$ abs (hr)	1.406	0.782	$p < 0.05$
K_a(hr^{-1})	0.493±0.171	0.886±0.281	$p < 0.05$
K_e(hr^{-1})	0.003±0.001	0.002±0.001	$p < 0.05$
Vd($l.kg^{-1}$)	15.579±3.563	15.453±3.441	NS
AUC($mg.hr.l^{-1}$)	225.182±109.760	308.751±144.933	NS
Cl($l.hr^{-1}.kg^{-1}$)	0.051±0.026	0.031±0.015	$p < 0.05$

* Harmonic mean

DISCUSSION

The results of this study show a rapid absorption of mefloquine in Thai volunteers (Figure 7). Cimetidine significantly decreased the clearance (Cl) and the elimination rate constant (K_e) and prolonged the elimination half-life ($t_{1/2}$) of mefloquine. These effects of cimetidine on the pharmacokinetic properties of mefloquine may be mediated by inhibition of the hepatic mixed function oxidase system by cimetidine and might be similar to those occurring with quinine (Wanwimolruk et al. 1986).

Co-administration of cimetidine had no effect on the peak plasma concentration (C_{max}), area under the time-concentration curve, the time to peak concentration (T_{max}) and the volume of distribution (Vd) of mefloquine. The alterations in the rate of absorption (K_a) and absorption half-life ($t_{1/2}$ abs) of mefloquine might be due to the promotion of gastric emptying and stimulation of intestinal motility. However, previous studies have reported that cimetidine has no effect on gastric emptying and no effect on lower esophageal sphinctor pressure (Sewester et al. 1991). Cimetidine is known to influence the gastro-intestinal absorption of indomethacin and antipyrine, presumably as a result of increase in gastric pH (Somogyi and Muirhead, 1987). This results in an increase in dissolution of weak acids and a decreased in dissolution of

weak bases. Cimetidine, could theoretically have affected the dissolution of mefloquine, but delaying absorption. However, cimetidine did not change gastric pH to a large extent by the time that mefloquine was administered. This is supported by our protocol, volunteers received mefloquine 2 hours after cimetidine and cimetidine is rapidly and well absorbed following oral administration (Brogden et al. 1978; Lauritsen et al. 1990). There is also supported by a previous study that cimetidine increases gastric pH, this effect being maximal after 90 min (Freston, 1982). It is unlikely that cimetidine increased mefloquine absorption peruse through influence on gastric pH. And since mefloquine is a weak base, an elevation in gastric pH by cimetidine would result in a decreased in dissolution of mefloquine, thus lower absorption rate. Cimetidine is known to be an effective inhibitor of the cytochrome P450 enzyme system and thereby reduces the metabolic clearance of drugs undergoing a variety of phase I metabolic transformations (Somogyi and Muirhead, 1987; McEvoy, 1989; Sewester et al. 1991; Murray, 1992). Thus, reduced mefloquine clearance is consistent with what has been noted for numerous other drugs (eg, chloroquine, quinidine and quinine) (Sewester et al. 1991) and indicates that cimetidine might inhibit the metabolic pathways of mefloquine biotransformation. In the present experiment, it is not able to suggest which of the

several metabolic steps associated with mefloquine metabolism has been affected.

The elimination half-life was significantly greater in subjects receiving mefloquine and cimetidine (14 days) compared to subjects receiving mefloquine alone (9 days). The mean plasma mefloquine concentration on day 14 after co-administration was 226 $ug.l^{-1}$. This level is adequate for inhibition of falciparum malaria. Since the *in vitro* minimum inhibitory concentrations of mefloquine were reported as 10^{-7} molar (41.48 $ug.l^{-1}$)in 1982 and $1.7x10^{-7}$ molar (70.51 $ug.l^{-1}$) in 1984 (Suebsang et al. 1986). The longer elimination half-life of mefloquine in the subjects receiving mefloquine and cimetidine might be of prophylactically beneficial in term of frequency of drug admistration. According to WHO recommendation for the prophylaxis of malaria, the doseof 250 mg mefloquine weekly. Thus the frequency of admistration of mefloquine could be reduced to every 2 weeks in the present of cimetidine.However,the problem of tolerance should be taken into account, since there are many reports on increasing of the minimum inhibitory concentrationsof mefloquine. If this is the.case, the prophylactic dose might need adjustment.

The co-administration of cimetidine and mefloquine does not likely to increase toxicity of mefloquine. Since the peak plasma concentration of mefloquine is not altered by cimetidine. According to data obtained from the

haematological parameters and the biochemical investigations, the two drugs do not change these parameters.

Karbwang and White (1990[a]) reported that the peak plasma mefloquine concentrations were higher and elimination half-lives were shorter in subjects with malaria.

Thus the use of cimetidine in the treatment of peptic ulcer in patients with falciparum malaria or cessation should be further investigated.

CONCLUSION

In healthy Thai men, co-administration of mefloquine and cimetidine produces statistically significant increase in the elimination half-life, and the rate of absorption of mefloquine, and decrease in the clearance, the absorption half-life and the rate of mefloquine elimination. No change in the C_{max}, T_{max}, AUC, and apparent volume of distribution were observed in this study. The mean terminal half-life of mefloquine was longer after cimetidine co-administration ($p<0.05$). This difference may be prophylactically beneficial. According to current recommendations, mefloquine is effective when taken a weekly regimen of 250 mg for 4 weeks, followed by 125 mg weekly for another 4 weeks (Karbwang and Harinasuta, 1992 : 117). Because of the longer half-life, the frequency of administration of mefloquine could be reduced in the presentof cimetidine.

In term of toxicity,co-administration of cimetidine and mefloquine does not likely to increase the toxicity of mefloquine. Since peak plasma concentration of mefloquine does not change. According to data obtained from blood count, blood biochemistry, renal and liver function tests, the two drugs do not change these parameters. However, careful clinical observation would be prudent whenever cimetidine and mefloquine are being used at the same time.

Since it was report that C_{max} of mefloquine in patients with malaria infection are generally higher than those in healthy subjects (Karbwang and White, 1990[a] : 277). Future studies in this area should focus on the pharmacokinetic properties of mefloquine in patients with malaria infection who receive cimetidine and mefloquine at a single dose treatment with either 750 or 1250 mg.

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Appendix-1

Preparation of standard mefloquine for calibration curve.

40.0 $ug.ml^{-1}$: 0.5 ml of stock solution (400 $ug.ml^{-1}$) + 4.5 ml distill water

10.0 $ug.ml^{-1}$: 1 mL of 40.0 $ug.ml^{-1}$ + 3 ml distill water.

7.5 $ug.ml^{-1}$: 3 ml of 10.0 $ug.ml^{-1}$ + 1 ml distill water.

5.0 $ug.ml^{-1}$: 2 ml of 7.5 $ug.ml^{-1}$ + 1 ml distill water.

2.5 $ug.ml^{-1}$: 1 ml of 5.0 $ug.ml^{-1}$ + 1 ml distill water.

1.25 $ug.ml^{-1}$: 1 ml of 2.5 $ug.ml^{-1}$ + 1 ml distil water.

ที่ ทม 1209/

คณะวิทยาศาสตร์
มหาวิทยาลัยสงขลานครินทร์
ตู้ ปณ.3 คอหงษ์ 90110

23 สิงหาคม 2534

หนังสือฉบับนี้ให้ไว้เพื่อรับรองว่า

โครงการวิทยานิพนธ์เรื่อง : ผลของ cimetidine ต่อเภสัชจลนศาสตร์ของ mefloquine
(Effects of cimetidine on the pharmacokinetics of mefloquine)

อาจารย์ที่ปรึกษา : ผศ.ดร.เมธี สรรพานิช
ภาควิชาเภสัชวิทยา

ได้ผ่านการพิจารณาและได้รับความเห็นชอบจากคณะกรรมการ Ethics Committee ซึ่งเป็นคณะกรรมการพิจารณาศึกษาวิจัยในมนุษย์ของคณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ แล้ว

ให้ไว้ ณ วันที่ 23 สิงหาคม 2534

.....ประธานกรรมการ
(ผู้ช่วยศาสตราจารย์ ดร.เมธี สรรพานิช)

.....กรรมการ	.....กรรมการ	.....กรรมการ
(อาจารย์รัตนา เจนเจริญธรรม)	(ดร.สุรีย์ ชาติวัยงาม)	(ผศ.ดร.สุทธินี ภูวนาถ)
หัวหน้าภาควิชาชีวเคมี	หัวหน้าภาควิชากายวิภาคศาสตร์	หัวหน้าภาควิชาจุลชีววิทยา
.....กรรมการ	.....กรรมการ	(ลาฝึกอบรม) .....กรรมการ
(ผศ.นายแพทย์วีรวัฒน์ มหิทธนตระกูล)	(ผศ.ประดับ ประสาทแก้ว)	(ผศ.นายแพทย์วิบูลย์ ฤทธิทิศ)
หัวหน้าภาควิชาเภสัชวิทยา	หัวหน้าภาควิชาสรีรวิทยา	ภาควิชาเภสัชวิทยา
.....กรรมการ	.....กรรมการ	.....กรรมการ
(รศ.ถาวร เกียรติทับทิว)	(ผศ.ดร.สุพงษ์ เอกศิริพงษ์)	(ผศ.นายแพทย์กิตติ ลิ่มอภิชาติ)
ภาควิชารัฐประศาสนศาสตร์	ภาควิชาเภสัชกรรม	หัวหน้าภาควิชาอายุรศาสตร์
คณะวิทยาการจัดการ	คณะเภสัชศาสตร์	คณะแพทยศาสตร์

ใบยินยอม

(consent form)

1. **ชื่อโครงการ :** ผลของ cimetidine ต่อเภสัชจลนศาสตร์ของ mefloquine

2. ข้าพเจ้า (นาย, นาง, นางสาว).....นามสกุล..... ยินยอมเข้ารับการศึกษาเกี่ยวกับผลของ cimetidine ต่อเภสัชจลนศาสตร์ของ mefloquine ตามที่ได้รับทราบคำอธิบายดังนี้

3. **วัตถุประสงค์ของการศึกษา :** เพื่อศึกษาถึงปริมาณของ mefloquine ในร่างกายของคนที่ได้รับ cimetidine ร่วมอยู่ด้วยว่าจะมีการเปลี่ยนแปลงไปอย่างไรและสมควรจะปรับขนาดของ mefloquine หรือไม่ในกรณีที่จำเป็นจะต้องใช้ยานี้ร่วมกับ cimetidine

4. **วิธีการศึกษา :** แบ่งออกเป็น 2 ขั้นตอน คือ

ตอนที่ 1 อาสาสมัครทุกคนจะต้องงดรับประทานยาทุกชนิดอย่างน้อย 1 เดือนก่อนทำการศึกษา และอาสาสมัครจะได้รับการตรวจเลือด และตรวจร่างกาย เฉพาะผู้ที่มีสุขภาพดีเท่านั้นที่จะเข้ารับการศึกษาในครั้งนี้ โดยให้อาสาสมัครอดอาหารมา 1 คืน แล้วเจาะเลือด 5 ซีซี หลังจากนั้นให้รับประทาน mefloquine ในขนาด 500 มก 1 ครั้ง และทำการเจาะเลือดครั้งละ 5 ซีซี ที่เวลา 1/2, 1, 2, 3, 4, 6, 8, 12, 24 ชั่วโมง 2, 3, 4, 7, 14, 21 และ 28 วันหลังให้ยาเพื่อนำไปวิเคราะห์หาปริมาณ mefloquine

ตอนที่ 2 อาสาสมัครจะได้รับการพักโดยไม่รับประทานยาใด ๆ เป็นเวลาอย่างน้อย 2 เดือน หลังจากนั้นในวันแรกของขั้นตอนนี้อาสาสมัครทุกคนจะได้รับ cimetidine ขนาด 400 มก วันละ 2 ครั้ง เช้าและก่อนนอน เป็นเวลา 7 วัน ในคืนวันที่ 7 ให้อาสาสมัครอดอาหารหลังเที่ยงคืน และในวันที่ 8 ตอนเช้าหลังรับประทาน cimetidine แล้ว 2 ชั่วโมง อาสาสมัครจะได้รับ mefloquine โดยการรับประทานในขนาดเท่าเดิม จากนั้นเก็บตัวอย่างเลือดเพื่อนำไปวิเคราะห์ในลักษณะเดียวกับที่ทำในตอนที่ 1 และอาสาสมัครจะได้รับ cimetidine ตลอดระยะเวลาที่ทำการทดลอง (28 วัน)

หมายเหตุ : ในระหว่างการศึกษาถ้าอาสาสมัครจำเป็นต้องทานยาอื่นให้ติดต่อขอคำแนะนำจาก นายแพทย์วิบูลย์ ฤทธิทิศ หรือนายแพทย์วีรวัฒน์ มหัทธนตระกูล โทร. 235800-9 ต่อ 2646

5. ผลอันไม่พึงประสงค์ของยา

Mefloquine เป็นยารักษาโรคมาลาเรียชนิด Plasmodium falciparum ที่ดื้อต่อ quinine หรือ chloroquin ในปัจจุบัน mefloquine เป็นยาที่ใช้กันแพร่หลายที่สุดโดยทั่วไปใช้ในขนาด 750 มก. ให้รับประทานครั้งเดียว (ขนาดสูงสุดที่แนะนำให้ใช้คือ 1500 มก.) ซึ่งขนาดยาที่ใช้นี้ไม่พบอาการข้างเคียงที่รุนแรง บางรายอาจพบอาการคลื่นไส้ อาเจียน ท้องเดิน เวียนศีรษะ เป็นต้น ส่วนอาการข้างเคียงที่รุนแรงซึ่งพบได้น้อยมาก เท่าที่เคยมีรายงานไว้ได้แก่ ความดันโลหิตต่ำ หัวใจเต้นช้าลง บางรายหมดสติหรือมีอาการชักซึ่งจะหายไปได้เอง

ส่วน cimetidine เป็นยากลุ่ม H_2-antagonist ที่ใช้ในการรักษาโรคแผลเปปติคที่มีประสิทธิภาพสูงและนิยมใช้กันอย่างแพร่หลายในปัจจุบันโดยใช้ในขนาด 800 มก. ต่อวัน เป็นเวลา 4-8 สัปดาห์ ซึ่งขนาดที่ใช้รักษานี้พบอาการข้างเคียงได้ค่อนข้างน้อย อาการที่พบได้แก่ ท้องเดิน มึนงง เหนื่อยง่าย ปวดศีรษะ การเกิดอาการข้างเคียงที่รุนแรงกว่านี้อาจพบในกรณีที่ใช้ยาในขนาดสูงมากและใช้เป็นระยะเวลานานเกินกว่า 8 สัปดาห์ อาการที่พบได้แก่ หัวใจเต้นช้าลง เกร็ดเลือดต่ำ เม็ดโลหิตขาวลดต่ำ ไตอักเสบ มีความผิดปกติของตับ ในผู้ชายอาจพบอาการเต้านมโต การแพ้ยาพบได้น้อยมากโดยมีอาการทางผิวหนัง มีผื่นขึ้นตามตัว หรือมีอาการทางระบบหายใจ

ผลข้างเคียงของยาทั้งสองชนิดนี้จะหายไปเองได้เมื่อหยุดยา และในระหว่างการศึกษาถ้าเกิดอาการข้างเคียงของยาขึ้นอาสาสมัครจะได้รับการดูแลรักษาจากแพทย์ผู้ร่วมโครงการอย่างใกล้ชิด

6. **โอกาสในการซักถาม :** หากข้าพเจ้ามีข้อสงสัยเกี่ยวกับการศึกษาในครั้งนี้ ข้าพเจ้ามีสิทธิซักถามได้ทุกขั้นตอน

7. **สิทธิการปฏิเสธการร่วมโครงการ :** ในระหว่างการศึกษานี้ข้าพเจ้ามีสิทธิปฏิเสธการเข้าร่วมโครงการได้ทุกเมื่อ

8. **คำยินยอมเข้าร่วมโครงการ :** ข้าพเจ้าได้อ่านและเข้าใจถึงวัตถุประสงค์ของการศึกษาครั้งนี้เป็นอย่างดี และยินดีให้ความร่วมมืออย่างดีที่สุด

....

(ลายเซ็นอาสาสมัคร) วัน เดือน ปี

....

(ลายเซ็นพยาน) วัน เดือน ปี

....

(ลายเซ็นแพทย์) วัน เดือน ปี

คำชี้แจงต่ออาสาสมัครไทย
เกี่ยวกับข้อควรปฏิบัติในระหว่างการทดลอง

1. อาสาสมัครทุกคนจะได้รับการตรวจร่างกายและซักประวัติเกี่ยวกับการเจ็บป่วยตามแบบบันทึกประวัติและการตรวจร่างกาย

2. ในระหว่างการทดลองอาสาสมัครทุกคนจะต้องดำเนินกิจกรรมของตนเองตามปกติ และจะต้องมารับการเจาะเลือดตามที่นัดหมายทุกครั้งอย่างเคร่งครัด (ตามวัน และเวลาที่นัดหมาย)

3. ในระหว่างการทดลองบางครั้งจะต้องคาสายสำหรับการเจาะเลือดไว้ เพื่อสะดวกในการเจาะเลือด และอาสาสมัครจะได้ไม่เจ็บหลายครั้งจากการเจาะเลือด

4. ในระหว่างการทดลองถ้ามีการเจ็บป่วย หรือรับประทานยาอะไรเพิ่มเติมนอกเหนือจากยาที่ได้จากการทดลอง กรุณาแจ้งให้ทราบด้วย

5. ถ้ามีอาการผิดปกติระหว่างการทดลอง เช่น บวมบริเวณเจาะเลือดหรือคาสายเจาะเลือดไว้ หรือหน้ามืด วิงเวียน จะเป็นลม กรุณาแจ้งให้ทราบด้วย

แบบบันทึกประวัติและการตรวจร่างกาย

ของอาสาสมัครไทย

เลขที่.....

วันที่.....

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1. ประวัติส่วนตัว

ชื่อ (นาย, นางสาว, นาง).....

อายุ.....ปี.....เดือน, เพศ.....ชาย, หญิง

อาชีพ.....ที่อยู่.....

ชื่อ ผู้บันทึก.....วันที่.....

แพทย์ผู้ตรวจร่างกาย.....

2. ประวัติการเจ็บป่วย

2.1 <u>ประวัติการเจ็บป่วยในปัจจุบัน</u>

(1).....

(2).....

(3).....

2.2 <u>ประวัติการเจ็บป่วยในอดีต</u>

(1) เคยเจ็บป่วยเป็นอะไรมาก่อน? เมื่อไหร่? รักษาที่ไหน? หมอบอกว่าเป็นโรคอะไร?

.....

.....

(2) ประวัติการผ่าตัด

.....

(3) เคยเป็นโรคภูมิแพ้ (เช่น หืด, หวัดแพ้อากาศ, ลมพิษ, ผื่นคัน) .....

.....

(4) เคยแพ้ยาบ้างไหม? ระบุชื่อยาและอาการของการแพ้ยาเป็นอย่างไรบ้าง..

.....

(5) เคยมีอาการตัวเหลือง ตาเหลือง.....

.....

3. ประวัติการเจ็บป่วยในครอบครัว

3.1 <u>ประวัติโรคกรรมพันธุ์</u>

( ) (1) โรคภูมิแพ้ (หืด, ลมพิษ, หวัดเรื้อรัง, ไซนัสอักเสบ)

( ) (2) โรคเบาหวาน

( ) (3) โรคลมบ้าหมู

( ) (4) โรคเลือด (ธาลัสซีเมีย, ฮีโมฟีเลีย, ขาดเอนไซม์ G-6-PD)

3.2 <u>โรคติดเชื้อ</u> เช่น วัณโรค, หัด, ไข้เลือดออก

4. ประวัติและอุปนิสัยส่วนตัว

( ) (1) ดื่มเหล้า วันละ.....เป็ก, แบน, ขวด/วัน

( ) (2) บุหรี่ วันละ.....มวน, ซอง/วัน

( ) (3) อาหารดิบ ระบุถ้ามี.....

( ) (4) ยา ระบุชื่อยาถ้ามี.....

5. การตรวจร่างกาย

Age.....(yr) Sex.....

Height.....(cm) Body weight.....kgs

GA : .....

Vital Sign : ..BT.....C,.....PR...../min.

..RR...../min,.....BP.....mm.Hg.

Skin : .....

.....

Heart : .....

.....

Lung : .....

.....

Abdomen : .....

.....

.....

.....

Extremities: .....

.....

Neuroexamination :

Conciousness : ( ) poor

( ) fair

( ) good

Eyes : pupil diameter .....

Movement.....

RTL.....

Other.....

Reflexes : .....

.....

Muscle Power : .....

สรุปการตรวจร่างกาย

( ) อยู่ในเกณฑ์ปกติ

( ) ผิดปกติ

6. การตรวจทางห้องปฏิบัติการ

6.1 CBC ผล.....

6.2 FBS ผล.....

6.3 Renal function test (BUN, Creatinine) ผล.....

6.4 Liver function test (SGOT, SGPT, ALP, Direct/indirect bilirubin, Albumin/globulin) ผล.....

7. สรุปผลของการตรวจร่างกายและทางห้องปฏิบัติการ

( ) อยู่ในเกณฑ์ปกติ

( ) ผิดปกติ ระบุ (1).....

(2).....

(3).....

(4).....