Acetaminophen (paracetamol) pharmacokinetics in contraceptive pill–using Myanmar Women

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Acetaminophen(paracetamol) pharmacokinetic study was made on a total of 16 healthy adult Myanmar women of reproductive age, half of whom were pretreated chronically for 6 months with an oral contraceptive steroid (OCS), namely, Combination 5. Single oral dose (930 mg) of acetaminophen showed similar extent of maximum plasma acetaminophen concentration in either group. However, the OCS causes significant effect ($p<0.05$) on plasma acetaminophen resulting in shortening of half-life by 21.6% and augmentation of clearance by 5.9%. The OCS affected predominantly the sulphate conjugation of acetaminophen. In regimen requiring repeated dosings, acetaminophen should be administered more frequently in the pill-users.

INTRODUCTION

In this country, one of the most commonly used symptomatic medication as analgesic/ antipyretic is the drug acetaminophen (paracetamol), either by general public on an analogous over-the -counter drug or by health personnel on an essential drug concept. Changes in metabolism of this drug in pill users had been reported (1,2). Incidentally oral contraceptive steroid (OCS) has a growing popularity among Myanmar women. The present study therefore investigated an acetaminophen pharmacokinetics in OCS users among the Myanmar women, aiming them to use this drug rationally.

MATERIALS AND METHODS

The study was conducted on a total of 16 healthy adult Myanmar women, at reproductive age being 17-45 years and body weight of 39-60 kg and equally divided into two groups (i.e., one test and one control) with the individual randomly allocated.

Priming phase : Individual subject in the test group was daily administered for a cycle period of at least 6 months with a popularly used brand OCS, namely, Combination 5 (containing norgestrol 0.05 mg, ethinyloestradiol 0.05 mg and ferrous fumarate). No other drug was administered to any control subject during this phase of study.

Intraction phase : At the end of the priming phase, each volunteer fasted overnight, was orally administered with a single dose of paracetamol 930 mg (MPI : Yangon, Myanmar) in the moring and drinking of water allowed ad libitum during the next 4 hours of trial period. Venous blood sample (5ml each) were collected from the median cubital vein using vacutainer tubes (Becton & Dickerson) at various post-drug time intervals, namely, 15, 30, 60, 120 and 240 minutes. Plasma drug concentrations for either the parent compound acetaminophen or its major metabolities, i.e., sulphate and glucuronide were assayed according to the modified method of Howie et al (3) and Mitchell et al (1) using the Water Associates High Performance Liquid Chromatography system composed of components with Models 204 W/510, U6K and 440 (Millipore; Milford, Massachusetts, USA).

Evaluation : Pharmacokinetic parameters were calculated namely, plasma half-life ($t_{\frac{1}{2}}$), concentration at zero time (C_o),

Table . Plasma pharmacokinetic arameters of acetaminophen and its metabolities of sulprate and glucuronide following single oral dose of acetaminophen 930 mg in Myanmar women chronically taking oral contraceptive steroid Combination 5.

	$t_{\frac{1}{2}}$ (h)	C_o mg ml^{-1}	C_{max} mg ml^{-1}	T_{max} (h)	K_{el}	aVd L kg^{-1}	Cl ml^{-1} min^{-1} kg^{-1}
Acetaminophen							
Control	2.50	31.9	21.4	1.29	0.29	0.64	3.0
	± 0.20	± 3.5	± 2.9	±0.20	±0.02	±0.05	±0.3
	*	n.s	n.s	n.s	n.s	n.s	n.s
OCS	1.96	44.6	23.9	1.55	0.04	0.59	3.2
	±0.05	±7.5	±4.7	±0.20	±0.05	±0.11	±0.4
Acetaminophen sulphate							
Control	2.12	3.3	2.1	1.18	0.37	5.90	35.6
	±0.26	±0.3	±0.1	±0.3	±0.06	±0.60	±5.3
	n.s	*	*	n.s	n.s	n.s	**
OCS	2.78	13.1	8.0	1.44	0.27	3.49	12.5
	±0.29	±4.5	±2.4	±0.16	±0.03	±1.25	±3.8
Acetaminophen glucuronide							
Control	1.96	37.1	18.8	1.79	0.37	0.77	4.9
	±0.20	±7.4	±4.1	±0.05	±0.06	±0.20	±1.5
	*	n.s	n.s	n.s	n.s	n.s	n.s
OCS	2.9	74.5	32.1	1.97	0.27	0.51	2.2
	±0.50	±33.8	±10.5	±0.12	±0.05	±0.10	±0.4

Each value is the means of 8 subjects with its standard errors. Signigicant level of difference statistically between the two treatments are depicted as (*)= $P<0.05$; (**)= $P<0.01$; (***)= $P<0.0001$ and n.s= not significant at the level of $P<0.05$.

maximum plasma concentration (C_{max}), elimination rate constant (K_{el}), apparent volume of distribution (aVd) and systemic clearance (Cl). Paramount clinical information of any difference in the half-life of acetaminophen between the two groups was scrutinized statistically, using the Student's t test. Metabolising profiles of both the sulphate and gulcuronide conjugations were also vividly portrayed by scanning the time-course concentrations of the metabolites.

RESULTS

Effects of chronic administratiion of the OCS on major pharmacokinetic parameters of acetaminophen and its metabolites of sulphate and glucuronide in Myanmar women are shown in TAble . Whilst the OCS did not alter the plasma acetaminophen maximum concentration,it stimulated the metabolism signi icantly, thereby shortening the half-life of acetaminophen (Fig 1) as much as 21.6 % while augmenting the clearance by as much as 5.9% and thereby delaying the time for the occurence of maximum acetaminophen plasma concentration.

Simultaneous pharmacokinetic determinations of the metabolites denoted the OCS caused the sulphate conjugation to be markedly affected, resulting in high concentration of plasma acetaminophen

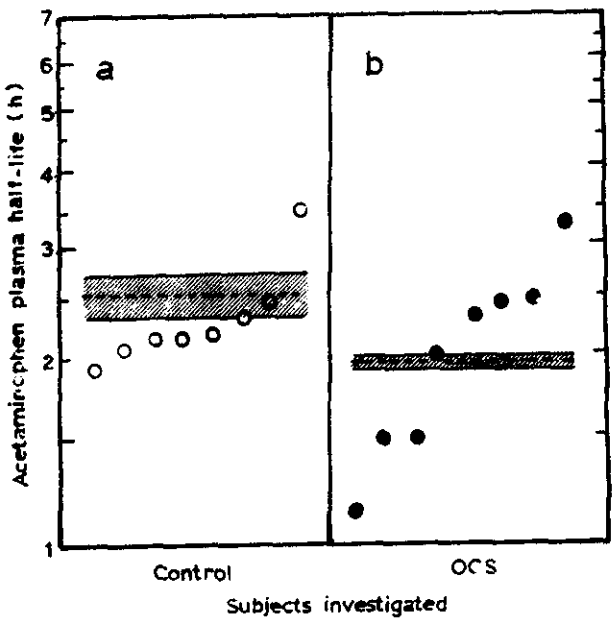

Fig 1. Distribution diagram of subjects in relation to acetaminophen plasma half-life in Myanmar women.

Groups means is denoted as dotted lines, with the respective standard errors of the means coverage as hatched areas.

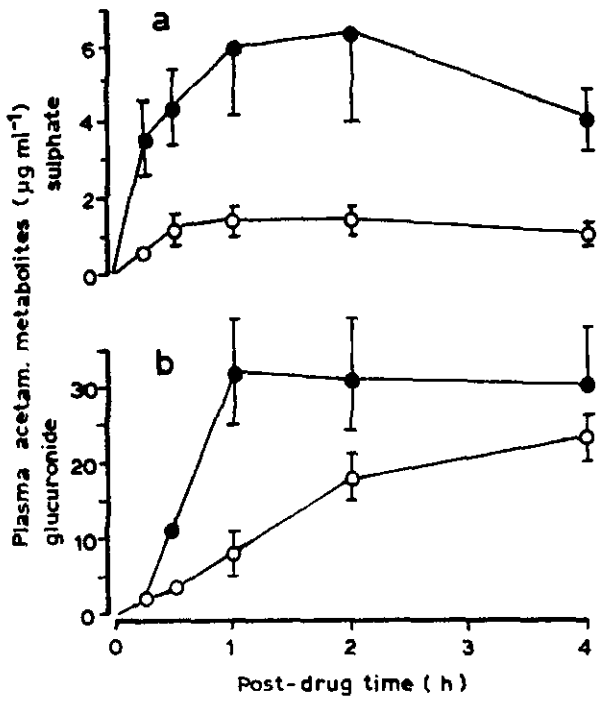

Figure 2. Time course response of acetaminophen metabolites of sulphate and glucuro- following acteaminophen 930 mg oraliy administered to Myanmar women.

Upper panel (a) and lower panel (b) illustrate the responses of the acetaminophen metabolites sulphate and glucuronide, respectively. Each *point represents* the means of 8 observations, together with the standard errors of the means indicated as vertical bars, for the control (o) and the test (o) groups.

sulphate (Fig 2) and reciprocal reduction in both conjugation processes (Table), with respective to *diminished* clearance and prolonged half-life.

DISCUSSION

Acetaminophen, a low intrinsic clearance and binding insensitive drug, showed a pharmacokinetic profile of Myanmar women similar to those of Westerners (4). Chronic administration of the OCS Combination 5 did not alter the maximum plasma acetaminophen concentration in Myanmar women, a finding similar to the Westerners (1). Therefore, the analgesic/ antipyretic activities of acetaminophen will be attained with the usual recommended therapeutic dosage. However, the OCS *delayed the onset* and shortened the duration of pharmacological activities of acetaminophen resulting in shortening the half-life and augmenting the clearance. The increase clearance of 5.9% in Myanmar women was not to the extent seen in those of the Westerners, where Abernathy et al (2) and Mitchell et al (1) reported to be 41% and 64% respectively. In Myanmar women, the OCS mainly affected the sulphation of acetaminophen which is the principal process of metabolism of this drug (5). Decreease in excretion of the metabolites might probably act as 'feed-back' to cause *stimulation of metabolism* of the parent compound acetaminophen.

For the once-off use of acetaminophen, the usual *recommended dose could* produce a full therapeutic effect. In ailment where repeated administrations *of the acetaminophen* is indicated, those pill-using Myanmar women should require more frequent dosings.

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