Acta Medica et Biologica
Vol. 42, No. 2, 51-55, 1994

Effects of Caffeine on the Pharmacokinetics of Paracetamol

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Received July 30, 1993

Summary. **This study was undertaken to determine the effect of caffeine on paracetamol pharmacokinetics in normal subjects. Each person was examined two times (two phases) at one week intervals after the administration of two tablets (0.5 g of paracetamol +0.05 g of caffeine in one tablet) of Finimal (Roche-Nicholas B.V., Bladel, Netherlands) or two tablets (0.5 g of paracetamol in one tablet) of Paracetamol (Roche-Nicholas B. V., Bladel). The study was performed on two randomly assigned subgroups (cross-over). The blood was sampled before (0), and 0.25-0.5-1.0-1.25-1.5-2.0-4.0-6.0-8.0 h after drug administration. Plasma paracetamol was determined by an improved gas chromatographic method, as described by Thoma et al. The course of the changes in the drug concentrations in plasma was described with a one-compartment open model for extravascular administration. A comparison of paracetamol concentrations in the blood plasma after application of both paracetamol alone and paracetamol in combination with caffeine (Finimal) showed slightly depressed drug levels after the administration of Finimal. Significantly lower levels were observed after 0.5, 1.0 and 1.25 h. A comparison of pharmacokinetic parameters also indicated mild differences between Finimal and paracetamol alone. In subjects receiving Finimal, a decrease in C_{max}, k_a, k_{el}, AUC and an increase in V_D, t_{max}, $t_{0.5}$ and Cl_T, was observed. The obtained results may be summarized as follows: 1) There is a pharmacokinetic interaction between caffeine and paracetamol applied as a single therapeutic dose; 2) Such an interaction may attenuate liver toxicity.**

INTRODUCTION

Clinical studies have been conducted in recent years to explore the analgesic effects of caffeine as an adjuvant to paracetamol in patients with postpartum pain,[1)] idiopathic headache, and postoperative orthopedic pain.[2)] These have proved that caffeine enhances the analgesic efficacy of paracetamol.

Siegers studied the effect of oral doses to rats of caffeine given together with paracetamol, and found that caffeine inhibited its absorption and lowered its serum concentration.[3)] He suggested that the delayed stomach emptying as a result of the relaxing effect of caffeine on the gastric muscle was probably the cause of the diminished absorption of orally administered drugs in the presence of caffeine. However, it was proved that the addition of caffeine to paracetamol significantly shortened the mean time until onset, over that after paracetamol alone. Substantial evidence was provided in support of the proposition that caffeine contributes to the effectiveness of paracetamol.[1,2)]

Finimal is composed of paracetamol and caffeine. Comparative pharmacokinetics of Finimal and paracetamol allow one to deduce the effect of caffeine on the kinetics of paracetamol with caffeine as opposed to paracetamol alone. In marked contrast to the safety of paracetamol used in proper doses is the very serious hepatoxicity associated with overdosage of the drug.[4)]

This study was undertaken to determine the effect of caffeine on paracetamol pharmacokinetics in normal human subjects.

MATERIALS AND METHODS

The study was carried out on 9 male persons, aged 24-48 (mean 35.2) years, body weight 62.5-91 (mean 75.6) kg (Table 1). All volunteers were in good health: subjective and objective tests revealed no abnormality. Additional examinations, blood sedimentation rate, blood cytology, aminotransferases (AspAT, AlAT), alkaline phosphatase, blood urea nitrogen, creatinine, protein, glucose, bilirubin, total cholesterol, triglycer-

Table 1. List of subjects.

Nr	Initials	Age (years)	Body weight (kg)
1.	G. C.	24	71
2.	S. M.	38	70
3.	P. R.	24	62.5
4.	S. H.	48	67
5.	B. H.	39	88.4
6.	N. R.	48	91
7.	S. G.	24	76.5
8.	G. J.	47	74
9.	W. D.	25	79.8

Nr: Subject number.

Table 2. Treatment schedule.

Study	Subject Nr	Subgroup	Phase	
			I	II
Paracetamol (p)	1, 2, 3, 7, 9	1	P	F
Finimal (F)	4, 5, 6, 8	2	F	P

Nr: Subject number.

ide, urine analysis, chest x-ray and electrocardiogram (ECG) did not show any deviation from normal values. All subjects abstained from alcoholic beverages and from taking any medication at least 2 weeks before and 24 h after the study. They did not smoke. All subjects agreed voluntarily to take part in the study and signed a volunteer contract.

Each person was examined two times (two phases) at one week intervals after the administration of two tablets (0.5 g of paracetamol +0.05 g of caffeine in one tablet) of Finimal (Roche-Nicholas B.V., Bladel, Netherlands) or two tablets (0.5 g of paracetamol in one tablet) of Paracetamol (Roche-Nicholas B.V., Bladel). The subjects fasted for 18 h before and 4 h after the administration of the tablets. Two tablets of Finimal or Paracetamol were given with 200 ml of water. In each phase of the two-way cross-over study, each subject swallowed the preparations intact. The study was performed on two randomly assigned subgroups. The blood was sampled from the cubital vein into heparinized tubes both before (0), and 0.25-0.5-1.0-1.25-1.5-2.0-4.0-6.0-8.0 h after the drug administration, and frozen at −20°C until analysis.

Plasma paracetamol was determined by an improved gas chromatographic method (gas chromatograph Perkin-Elmer 8410) described by Thoma et al.[5] The glass column (1.8 m×2 mm i.d.) was packed with 3% OV_{17} on Gas Chrom Q on 100/120 mesh. Operating parameters were as follows: flame ionization detector (FID) temperature, 275°C; injection port, 300°C; oven, 180°C; carrier gas, nitrogen at 40 ml/min; amplifier $\times 10^{-10}$; attenuation ×4.

The course of the changes of the drug in plasma was described with a one-compartment open model for extravascular administration.[6] The treatment schedule is outlined in Table 2.

In order to estimate the pharmacokinetics of paracetamol, the following parameters were calculated: rate constant for absorption (k_a); area under the plasma concentration vs time curve (AUC); peak concentration (C_{max}); time to the peak concentration (t_{max}); the elimination half-life ($t_{0.5}$); the apparent volume of distribution (V_D) and the apparent volume of distribution in relation to one kg body weight ($\triangle V_D$); rate constant for elimination (k_{el}); total body clearance (Cl_T) and total body clearance in relation to one kg body weight ($\triangle Cl_T$).

The area under the plasma concentration vs the time curve (AUC) of paracetamol was calculated according to the linear trapezoidal rule with extrapolation to the infinity. Total body clearance (Cl_T) was calculated as the ratio of the dose to the AUC. The absorption of oral paracetamol was considered to be complete. The elimination half-life ($t_{0.5}$) and the apparent volume of distribution (V_D) were calculated from the slope of the terminal log drug concentration vs the time curve.

Statistical analyses were performed with the Student paired t-test, with each subject acting as his own control. All aspects of this investigation were approved by the Academic Ethical Committee for the Protection of Human Subjects.

RESULTS

The comparison of paracetamol concentrations in the blood plasma after the application of paracetamol alone and paracetamol in combination with caffeine (Finimal) shows a slight decrease in the drug level after the administration of Finimal (Fig. 1). Significantly lower levels were observed at 0.5 h, 1.0 h and 1.25 h after the drug application.

A comparison of pharmacokinetic parameters also indicated mild differences between Finimal and paracetamol alone (Table 3). In subjects receiving Finimal,

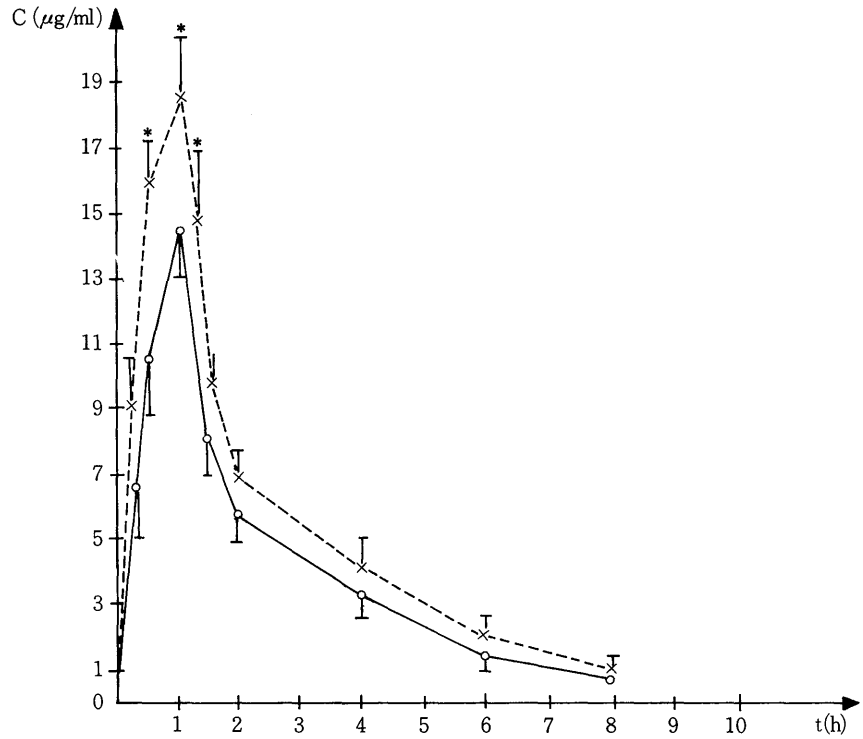

Fig. 1. Mean plasma concentration time profiles of paracetamol following the administration of paracetamol without (×·····×) and with (○——○) caffeine. C: drug concentration. t (h): time in hours. * Significant difference.

Table 3. Pharmacokinetic parameters of paracetamol.

Parameter	Paracetamol	Finimal	Statistical P-value
k_a (h^{-1})	2.320±0.142	2.120±0.295	>0.1
C_{max}(μg/ml)	15.98 ±1.15	11.73 ±1.58	<0.02
t_{max}(h)	0.74 ±0.06	0.89 ±0.10	>0.1
AUC (μg/ml ×h)	40.00 ±4.54	31.15 ±2.04	>0.1
$\triangle V_D$(l)	35.37 ±2.54	52.79 ±6.55	<0.05
V_D(l/kg)	0.47 ±0.03	0.70 ±0.09	<0.05
$t_{0.5}$ (h)	0.99 ±0.15	1.11 ±0.13	>0.1
k_{el}(h^{-1})	0.82 ±0.11	0.72 ±0.11	>0.1
Cl_T(l/h)	27.72 ±3.15	33.44 ±2.57	>0.1
$\triangle Cl_T$(l/kh/h)	0.37 ±0.04	0.45 ±0.04	>0.1

Mean (± SE)

a statistically significant decrease in the peak concentration (by 27%) and a 49% increase in the apparent volume of distribution was observed. Also there was demonstrated a non-significant 22% decrease in the area under the plasma concentration vs the time curve, a 9% decrease in the rate constant for absorption, and a 12% one for the rate constant for elimination, as well as an increase in time to the peak concentration by 28%, prolongation of the elimination half-life by 12%, and an increase in the total body clearance by 20%.

DISCUSSION

Paracetamol is rapidly and completely absorbed from the gastrointestinal tract; its bioavailability is about 90%.[7] Peak plasma levels from tablet forms are reached within 40 to 60 min of ingestion. Protein binding of paracetamol in plasma is low, ranging from 15% to 20%. The volume of distribution is estimated to be 0.5 to 1.3 L/kg, and does not change with advanced age. The half-life ranges from 1.5 to 3.3 h, and total body clearance estimates vary from 2.4 to 6.9 ml/min/kg.[7,8] The pharmacokinetic parameters that we have obtained in our study (especially

C_{max}, t_{max}, $\triangle V_D$, $t_{0.5}$ and $\triangle Cl_T$) accord with those described in the literature.

Studies in mice of interactions between paracetamol and caffeine revealed that caffeine given immediately after paracetamol antagonized the acute toxicity of paracetamol and reduced the severity of paracetamol-induced hepatic necrosis, as assessed both grossly and microscopically.[9] On the other hand, Onrot et al. demonstrated that caffeine and theophylline reduced an apparent liver plasma flow in normal subjects.[10] The methylxanthine-induced declines in liver plasma flow may alter the disposition of concomitantly administered drugs. They may prolong the half-life and increase steady-state levels of hepatically eliminated drugs.

Aspects of an paracetamol-caffeine interaction which deserve investigation include a determination as to whether or not there is any interaction between the two drugs in humans, in terms of potentially enhanced or attenuated liver toxicity. Paracetamol is largely cleared from the blood through biotransformation by hepatic cytochrome P-450 mixed function oxidases. Minor metabolites are formed by hydroxylation and deacetylation. Caffeine may induce the activity of cytochrome P-448 and P-450 mixed function oxidases changing the rate of drug metabolism.[11,12] The data obtained by us seem to prove that an interaction between paracetamol and caffeine does occur. The effect of caffeine on paracetamol pharmacokinetics is expressed by a lower concentration of the drug in the plasma, by diminution of the area under the plasma concentration vs the time curve, and by an increase in total body clearance. Despite these findings, paracetamol analgesia is not decreased by caffeine. Moreover, it is even significantly increased.[10] Our observations are in agreement with Siegers,[3] who found that caffeine given orally to rats together with paracetamol lowered its serum concentration. Siegers et al. demonstrated an analgesic effect of caffeine in rats.[13] He also showed that the combination of paracetamol and caffeine at low doses induced analgesic effects that are comparable to those expected at higher doses, and the results suggested a potentiation.

Considering the comparative bioavailability of different preparations of paracetamol administered in single doses orally, the superiority of Finimal to Panadol (Winthrop) has been demonstrated.[14] The reasons for such a difference, and generally for differences in biological availability may be numerous: particle size; the drug form (crystalline or salt); tablet compression and excipient. Our present study compared the pharmacokinetics of the tablets of paracetamol alone with those containing additional small doses of caffeine prepared identically by the same producer. The earlier study indicated that caffeine strikingly increased the survival rate of mice after a toxic dose of paracetamol, prevented the depletion of reduced glutathione, and diminished histological changes in the liver.[15] Taking into account this observation and our present results, it is to be noted that a combination of paracetamol with caffeine in one preparation (Finimal) may be less toxic than paracetamol alone, especially in the case of overdosage.

CONCLUSIONS

1. There is pharmacokinetic interaction between caffeine and paracetamol applied as single therapeutic dose.
2. Such an interaction may attenuate liver toxicity.

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