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Chronopharmacokinetics of paracetamol in normal subjects

J. MALAN, J. MONCRIEFF & E. BOSCH
Department of Pharmacology, University of Pretoria, Pretoria, Republic of South Africa

The chronopharmacokinetics of paracetamol was studied in six male volunteers. Serum concentrations of paracetamol were determined after a single oral dose of 1 g, on three occasions, spaced at least 1 week apart. Plasma drug concentration *vs* time curves were obtained after dosage at 08.00 h (Day 1), 14.00 h (Day 2) and 20.00 h (Day 3), under standardized conditions. Pharmacokinetic parameters compared were $t_{½,\alpha}$, $t_{½,z}$, t_{max}, C_{max} and AUC_{po}. No statistically significant differences were found.

Keywords paracetamol pharmacokinetics chronopharmacology

Introduction

Circadian rhythmic changes in the pharmacokinetics of several drugs have been documented and reviewed (Reinberg & Smolensky, 1982).

In the case of paracetamol, it has been noted that the elimination half-life was slightly (15%), but significantly ($P < 0.025$) longer in healthy males at 06.00 h than at 14.00 h (Shively & Vesell, 1975).

We decided to investigate and compare possible differences in pharmacokinetic parameters ($t_{½,\alpha}$, $t_{½,z}$, t_{max}, C_{max} and AUC_{po}) after a single dose of paracetamol, when taken at 08.00 h, 14.00 h and 20.00 h.

Methods

Six healthy non-smoking adult male volunteers participated in the study. An open cross-over trial design was used, i.e. each volunteer served as his own control. Written informed consent was obtained and the study approved by the local Ethics Committee.

On three occasions, spaced at least 1 week apart, the subjects took 1 g of paracetamol (2 × 500 mg tablets: Panadol®) as a single dose *per os*, with 250 ml tap water. On the first trial day, medication was taken at 08.00 h, on the second at 14.00 h and on the third, at 20.00 h.

The volunteers were fasting for at least 8 h when dosing took place. A standardized meal was ingested 2 h after medication. For these first 2 h of each study, the subjects were supine. No other medication was permitted for the duration of the project. Blood samples were drawn via an indwelling intravenous cannula, before and at the following intervals after medication: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6 and 8 h.

The samples were assayed by h.p.l.c. using a rapid micro method developed in the department, utilizing reverse phase separation and u.v./VIS spectrophotometric detection at 247 nm, with aminophylline as internal standard.

Internal standard was added to 100 μl serum in a centrifuge tube to give a concentration of 20 μg/ml. The protein was then precipitated with 10% perchloric acid and, after shaking, the tube was spun at 3000 rev/min for 3 min and 100 μl of the clear supernatant was injected onto the C18 reverse phase column and eluted with 6% acetonitrile in pH3 phosphate buffer at a flow rate of 2.5 ml/min and a column temperature of 37°C. The drug was detected at 247 nm and quantified from the standards curve on the basis of peak height ratio. The detection limit was 0.1 μg/ml and the deviation was ± 0.1 at the 5 μg/ml level. The response was linear from 0.5 μg/ml–50 μg/ml with a correlation coefficient of 1.000.

Data were processed by 'CSTRIP', a computer program for obtaining initial polyexponential parameter estimates (Sedman & Wagner, 1976).

The Friedman test was used to determine statistically significant differences. A *P*-value of ≤ 0.05 was regarded as indicative of significance.

Results

The mean values ($n = 6$) of the following pharmacokinetic parameters are summarized in Table 1 and illustrated graphically in Figure 1: $t_{½,\alpha}$, $t_{½,z}$, t_{max}, C_{max} and AUC_{po}.

Table 1 Results (mean values and s.d.) of pharmacokinetic data evaluated

Parameter	*Day*	*Mean (n = 6)*	*s.d.*
$t_{½,\alpha}$ (h)	1	0.2	0.1
	2	0.2	0.0
	3	0.2	0.1
$t_{½,z}$ (h)	1	2.4	0.4
	2	2.3	0.5
	3	2.5	0.2
t_{max} (h)	1	0.8	0.2
	2	0.9	0.3
	3	1.0	0.1
C_{max} (μg/ml)	1	9.0	2.8
	2	9.4	3.4
	3	8.7	1.6
AUC_{po} (mg ml^{-1} h)	1	33.0	10.4
	2	34.8	14.9
	3	35.2	8.3

Day 1 = medication given at 08.00 h,
Day 2 = medication given at 14.00 h and
Day 3 = medication given at 20.00 h

Discussion

It has been established that there are circadian changes of drug disposition in man (Reinberg & Smolensky, 1982). These chronopharmacokinetic differences may be of therapeutic importance in some cases, e.g. for indomethacin (Clench *et al.*, 1981; Guissou *et al.*, 1983) and theophylline (Lesko *et al.*, 1980).

It was previously reported that the terminal elimination half-life ($t_{½,z}$) of paracetamol was significantly longer in normal volunteers when given at 06.00 h than at 14.00 h (131.1 ± 8 min at 06.00 h; 114 ± 9.8 min at 14.00 h; decrease equal to ± 15%, $P < 0.025$) (Shively & Vesell, 1975). This was presumed to be due to a change in the volume of distribution. It has also been claimed that paracetamol absorption was five times more rapid after an overnight fast than after concomitant ingestion of a high carbohydrate breakfast (McGilveray & Mattok, 1972).

Our study was done under rigidly controlled and standardized conditions. It is clear that no statistically significant differences were found between the pharmacokinetic parameters studied, and that time of dosing did not seem to cause influential changes in the absorption and disposition pattern of paracetamol.

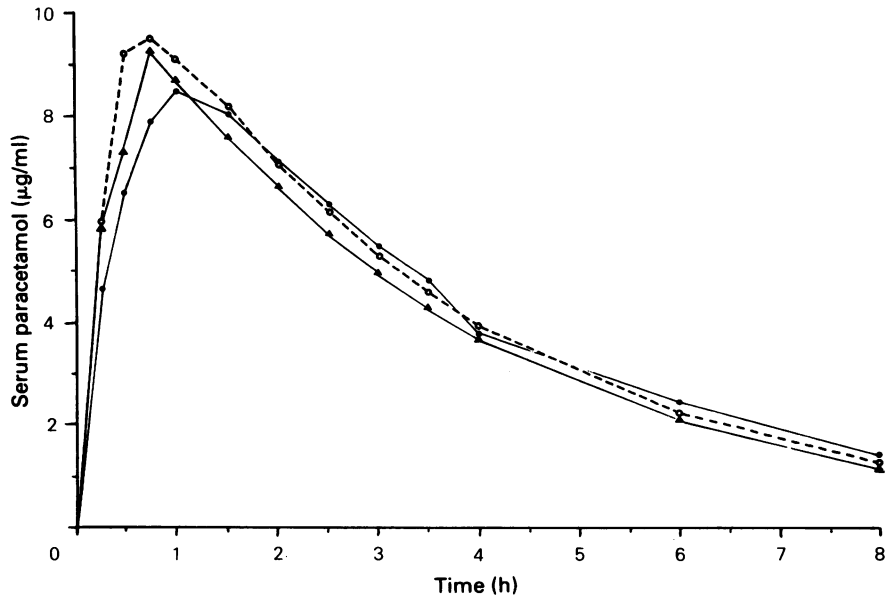

Figure 1 Mean serum concentrations of paracetamol after administration at 08.00 h (▲), 14.00 h (○) and 20.00 h (●).

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