PARACETAMOL ABSORPTION FROM PARAMAX, PANADOL AND SOLPADEINE

J.R. DOUGALL, B. CUNNINGHAM & W.S. NIMMO

University of Glasgow, Department of Anaesthesia,
Western Infirmary, Glasgow G11 6NT

Plasma paracetamol concentrations were measured after oral administration of three pharmaceutical preparations to four healthy volunteers. The formulations were Paramax (paracetamol with metoclopramide), Solpadeine (paracetamol with codeine and caffeine) and Panadol (paracetamol alone). After Solpadeine, concentrations at 15 min were significantly higher than after Panadol. Absorption of paracetamol from Paramax tablets did not differ significantly from Solpadeine or Panadol.

Introduction

The pharmaceutical formulation of paracetamol is known to influence its rate of absorption (Prescott & Nimmo, 1971). For example, absorption from an effervescent formulation is more rapid than from tablets, as shown by earlier and higher peak plasma concentrations (Hedges & Kaye, 1973).

Metoclopramide also increases the rate of paracetamol absorption by accelerating gastric emptying (Nimmo *et al.*, 1973) but it must be given either before the paracetamol or else given intravenously. In patients with migraine there is delayed absorption of aspirin during an attack and metoclopramide 10 mg i.m. reverses this delay (Volans, 1974, 1975). Oral metoclopramide administered at the same time as another drug has not been shown to accelerate drug absorption.

Paramax is a preparation containing paracetamol 500 mg and metoclopramide 5 mg presented either as a tablet or a sachet of effervescent powder. It has been introduced for the symptomatic treatment of migraine with the claim that the inclusion of metoclopramide promotes more rapid absorption of paracetamol by relieving gastric stasis, as well as reducing nausea and vomiting (Data Sheet). However, plasma concentrations of metoclopramide may vary widely after oral administration and the effect of a low oral dose is likely to be unpredictable (Bateman *et al.*, 1979).

In the present study we have compared plasma paracetamol concentrations following oral administration of Paramax, Panadol (1 tablet contains 500 mg paracetamol) and Solpadeine (1 tablet contains 500 mg paracetamol, 8 mg codeine phosphate and 30 mg caffeine which is dissolved in water before administration).

Methods

Four normal male volunteers with a mean ($\pm$ s.d.) age of 31 ± 2.5 years and a mean weight of 69 ± 5 kg, took part in the study. They were currently receiving no other drug therapy. Subjects were studied on three occasions separated by a minimum of 7 days, and in random order, were allocated each preparation once. They were fasted for at least 4 h before drug administration and were ambulant throughout the procedure. No food, fluid or tobacco was allowed throughout.

Drugs were administered with 100 ml of water as:

- (a) Paramax (Beechams) 2 tablets (1 g paracetamol + 10 mg metoclopramide).
- (b) Panadol (Winthrop) 2 tablets (1 g paracetamol).
- (c) Solpadeine (Winthrop) 2 tablets (1 g paracetamol, 16 mg codeine phosphate and 16 mg caffeine).

The Paramax and Panadol tablets were swallowed whole while the Solpadeine tablets were dissolved in water and the solution was swallowed.

Venous blood samples were taken at 15, 30, 45, 60, 75, 90 and 120 min after drug administration. Following separation of the plasma and storage at -20°C , plasma paracetamol concentrations were measured by high performance liquid chromatography (Howie *et al.*, 1977). Paracetamol absorption was assessed from peak concentration, time to peak, concentration at 15 min, and the area under the curve of plasma concentration against time (AUC) at 30 and 120 min. Statistical analysis was by the Wilcoxon rank sum test.

Results

The results are shown in Figure 1 and Table 1. Fifteen minutes after administration of Solpadeine, plasma concentrations of paracetamol were significantly

Figure 1 Mean ($\pm$ s.e. mean) plasma paracetamol concentration in four normal individuals following oral Solpadeine ($\blacktriangle$), Paramax ($\circ$), and Panadol ($\bullet$). Each subject received paracetamol 1 g with 100 ml water.

higher than those achieved after Panadol. The mean $\pm$ s.d. concentrations were $20.4 \pm 3.8 \mu\text{g ml}^{-1}$ and $9.1 \pm 6.5 \mu\text{g ml}^{-1}$ respectively. In addition the AUC at 30 min was significantly greater with Solpadeine compared to Panadol. Results for Paramax did not differ significantly from Solpadeine or Panadol. Of the three preparations the highest mean peak plasma concentration and the shortest mean time to peak were observed after Solpadeine, but the differences did not reach statistical significance. In all subjects the peak plasma paracetamol concentrations after Solpadeine occurred at 15 min but after Panadol

ranged from 15–45 min and after Paramax ranged from 15–60 min. There were no significant differences in AUC at 120 min.

Discussion

Absorption of paracetamol from Solpadeine is significantly faster than from Panadol as shown by the higher plasma concentration at 15 min and greater AUC at 30 min.

The absorption of paracetamol from Paramax

Table 1 Paracetamol absorption from three proprietary preparations in four subjects

Drug	Peak plasma concentration ($\mu\text{g ml}^{-1}$)	P*	Mean time to peak (min)	P*	Plasma concentration at 15 min ($\mu\text{g ml}^{-1}$)		AUC ² 0–30 min		AUC P–120 min	
						P*		P*		P*
Solpadeine	20.4 ± 3.8	NS	15	NS	20.4 ± 3.8	< 0.05	421 ± 70	< 0.05	1441 ± 163	NS
Paramax	17.3 ± 2.8	NS	22.5 ± 8.6	NS	14.3 ± 5.5	NS	341 ± 98	NS	1336 ± 221	NS
Panadol	16.6 ± 4.3	—	37.5 ± 19.4	—	9.1 ± 6.5	—	245 ± 112	—	1225 ± 212	—

¹ Values are mean $\pm$ s.d.

² AUC – area under curve of plasma concentration against time ($\mu\text{g ml}^{-1} \text{ min}$)

P* Solpadeine and Paramax compared with Panadol (Wilcoxon rank sum test)

tablets is not significantly different from Panadol in normal subjects. The rate in patients with gastric stasis, as may occur in migraine, is still unknown but since metoclopramide is itself absorbed from the upper small intestine the absorption is not likely to be accelerated.

The effervescent form of Paramax has not been studied, but our findings in this small group of volunteers are compatible with the statement (Drugs

and Therapeutic Bulletin, 1980) that Paramax was licensed without convincing published evidence that it is more effective than paracetamol alone in relieving migrainous headache.

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