Effect of migraine attacks on paracetamol absorption

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- 1 The absorption of effervescent paracetamol (1000 mg) was investigated in nine female patients during a migraine attack and in the same patients when headache free.
- 2 Migraine attack decreased ($P < 0.05$) the areas under the serum paracetamol concentration–time curves (AUC) of 0–2 h, 0–4 h and 0–6 h and the peak serum concentration.
- 3 The severity of nausea correlated significantly with the decrease in the AUC values.
- 4 Our results support findings of delayed gastric emptying in migraine attacks. Both a delay and an impairment of drug absorption may follow.

Keywords migraine paracetamol absorption bioavailability

Introduction

Acute migraine may delay gastric emptying (Volans, 1978). Absorption of aspirin (Volans, 1974), aspirin and metoclopramide (Ross-Lee *et al.*, 1983) and tolafenamic acid (Tokola & Neuvonen, 1984) has been shown to change during migraine. The rate of absorption of oral paracetamol depends on the rate of gastric emptying (Heading *et al.*, 1973; Clements *et al.*, 1978). In fasting healthy subjects, absorption of effervescent paracetamol in solution is very rapid with peak serum concentrations mostly occurring within 30 min of ingestion (Perucca & Richens, 1979). We have investigated the absorption of effervescent paracetamol in migraine patients during a migraine attack and in headache free interval.

Methods

Patients

Nine female out-patients with diagnosis of common migraine as defined by the Ad Hoc Committee (1962), mean age 45 years, range 31–51 years, and mean weight 66 kg, range 54–70 kg, volunteered for the crossover study.

They were all non-smokers and had no daily drug treatments. Besides migraine, they had no other diseases.

Study design and drugs

The study was approved by the Local Ethical Committee and the purpose and nature of the study were explained to each patient. The interval to the previous migraine attack was at least 1 week. No drugs or ethanol were allowed within 24 h prior to the investigation.

The patients came to the clinic as soon as they could in the initial phase of a migraine attack, and later without attack. The study was performed after an overnight fast in all but two cases (migraine attacks in patients number 5 and 8). Over 4 h had elapsed from the last food ingestion. In two patients vomiting interrupted the study at the first call, but they came later during another migraine attack, and these data were used.

On arrival at the clinic an i.v. cannula was inserted into the forearm for blood sampling. Immediately after cannulation and the first blood sample each patient drank a water solution of paracetamol (Panadol effervescent,

Table 1 Effect of a migraine attack on some pharmacokinetic parameters of effervescent paracetamol derived from serum concentrations following a single oral dose of paracetamol (1000 mg) in a cross-over study ($n = 9$).

Patient*	Age (years)	Weight (kg)	Peak serum concentration ($\mu\text{mol l}^{-1}$)		Peak time (h)		Serum half-life (h)	
			Migraine	Without migraine	Migraine	Without migraine	Migraine	Without migraine
1	50	65	142	195	0.5	0.5	1.7	1.9
2	48	65	93	85	0.5	1.0	2.0	1.9
3	51	68	71	159	1.0	0.5	2.4	1.9
4	50	54	207	213	0.25	0.25	1.7	1.7
5	31	69	70	187	1.0	0.5	2.1	2.3
6	36	69	103	130	0.5	0.5	2.0	1.9
7	45	69	91	131	0.5	0.5	1.9	1.8
8	49	68	101	89	1.5	0.5	2.1	1.8
9	49	70	99	105	0.5	0.5	1.9	1.9
Mean	45	66	109	144	0.7	0.5	2.0	1.9
$\pm$ s.e. mean	2	2	14	16	0.1	0.1	0.1	0.1
Paired <i>t</i> -test (2-tailed)			$P < 0.05$		NS		NS	

*Additional drugs needed and the time of their administration:

Patient 1. 5 ml Litalgin® (pitofenone + dipyrone) i.m. at 3.5 h

Patient 3. 1 supp. Litalgin® p.r. at 3 h

Patient 6. 3 caps Clotam 100 mg® (tolfenamic acid) p.o. at 3.5 h

Winthrop), 1000 mg in 150 ml. Because posture affects the rate of paracetamol absorption (Nimmo & Prescott, 1978), the patients were supine for 2 h after drug ingestion. Fluids and food were withheld for 3 h. On both occasions blood samples were taken at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 h. The serum was separated and stored deep frozen until analysed.

The assessment of pain and nausea was done using four point scales. The score was: 0 = no symptoms, 1 = slight, 2 = moderate, 3 = severe symptoms. The evaluation was done by the patients at the beginning and the end of the study. After 3 h the patients were allowed to take additional drugs if needed for attack relief (Table 1).

Drug analysis

Unchanged paracetamol in serum was measured by h.p.l.c. (Miceli *et al.*, 1979). Conversion to mass units: $1 \mu\text{mol/l} = 0.151 \text{ mg/l}$.

Pharmacokinetic analyses

The absorption of paracetamol was characterized by the time to peak serum concentration (t_{max}), the peak serum concentration (C_{max}), and the areas under the serum drug concentration-time curves (AUC) between zero and 2 h, 3 h, 4 h and 6 h calculated by the trapezoidal rule. The serum half-life ($t_{1/2}$) of paracetamol was calculated from the regression of the linear terminal phase.

Statistical analysis

The observations were analysed statistically using a paired *t*-test. Possible correlation between the parameters was estimated using the Spearman two rank correlation test. Means $\pm$ s.e. mean are given. The level of significance was set at 95%.

Results

Clinical data

The mean duration of a migraine attack at the time of drug ingestion was 3.1 ± 0.7 h. The severity of headache was moderate in seven patients, slight in two. Three patients had no nausea, three had slight, two moderate and one patient severe nausea when taking the drug. One patient (number 3) with only 1.0 h duration of her migraine attack had already severe nausea and moderate headache, and another patient (number 8) with 6.6 h duration had no nausea but moderate headache. Three patients needed additional drugs for their migraine attacks after 3 h (Table 1), and two patients after 6 h. The duration of the migraine attack after paracetamol administration was over 6 h in all patients.

Pharmacokinetic data

After oral administration of effervescent paracetamol serum concentrations rose rapidly both

Figure 1 Effect of a migraine attack on the absorption of a single 1000 mg oral dose of effervescent paracetamol in a cross-over study ($n = 9$). Mean $\pm$ s.e. * $P < 0.05$. ● without migraine, ○ during migraine.

during a migraine attack and without it. The mean serum concentrations as a function of time are shown in Figure 1. The levels were lower up to 1.5 h during a migraine attack than without migraine, the difference being significant ($P < 0.05$) at 0.5 h and 1 h. The serum drug concentrations of two patients with

Figure 3 Areas under the serum paracetamol concentration-time curves following a single 1000 mg oral dose in a cross-over study ($n = 9$). Mean $\pm$ s.e. ▨ = during migraine, □ = without migraine. * $P < 0.05$.

migraine attacks of different severity are presented in Figure 2.

The peak serum concentration was lower ($P < 0.05$) during migraine than without it but the peak time was not significantly changed (Table 1).

Migraine attack decreased the $AUC_{0-2\text{ h}}$ by 17%, the $AUC_{0-4\text{ h}}$ by 14% and the $AUC_{0-6\text{ h}}$ by 12% ($P < 0.05$; Figure 3). The $t_{1/2}$ of paracetamol was not influenced by a migraine attack (Table 1).

Figure 2 Effect of a mild migraine attack (patient 4) and of a severe attack (patient 3) on absorption of orally administered effervescent paracetamol (1000 mg). ● = without migraine, ○ = during migraine.

Figure 4 Correlation between the degree of nausea at the time of drug ingestion and the migraine related decrease of the $AUC_{0-4\text{ h}}$ ($\Delta AUC_{0-4\text{ h}}$) of paracetamol ($n = 9$). Spearman two rank correlation test, $P < 0.01$.

Correlation between migraine symptoms and serum paracetamol concentrations

There was a significant correlation between nausea at the beginning of the study and the migraine related decrease in the areas under the curves (0–3 h, 0–4 h, 0–6 h; $P < 0.05$ – < 0.01 ; Figure 4). The intensity of headache at the beginning of the study and the change of the areas (ΔAUC) did not correlate significantly but the sum score 'nausea + headache' correlated with the $\Delta AUC_{0-4\text{ h}}$ ($P < 0.01$) and with the $\Delta AUC_{0-6\text{ h}}$ ($P < 0.01$). The duration of the migraine attack before the study seemed not to correlate with serum drug parameters.

Discussion

The present results indicate that a migraine attack delays absorption of oral paracetamol solution and decreases its relative bioavailability. Severity of nausea correlates with the change of the absorption.

A prolongation of the gastric emptying time during migraine attacks has been demonstrated in radiological observations (Hurst & Stewart, 1929; Kaufman & Levine, 1936; Carstairs, 1958; Kreel, 1973). The rate of absorption of paracetamol from both suspensions and tablets has been shown to be related to gastric emptying rate (Heading *et al.*, 1973; Nimmo *et al.*, 1975). The observed decrease in the peak

concentration and in the AUC during the first hours reflects delayed absorption.

Absorption of paracetamol is slowed if gastric emptying is delayed by food, posture, certain diseases or drugs, but the bioavailability is not usually decreased (Jaffe *et al.*, 1971; McGilveray & Mattok, 1972; Nimmo & Prescott, 1978; Forrest *et al.*, 1982; Nimmo *et al.*, 1973, 1975). However, in the present study, where it was tried to minimize the effect of other factors than migraine, a slight decrease also in the relative bioavailability of paracetamol was found. Additional drugs needed by three patients between 3–3.5 h obviously had no significant influence on the pharmacokinetic parameters obtained. The peak times and $t_{1/2}$ were similar and rather short during both phases. Thus the $AUC_{0-6\text{ h}}$ covers more than 80% of the total AUC and can be used as a measure of the relative bioavailability of paracetamol. Interestingly, there were significant differences in the lag time, peak concentration and the amount of aspirin absorbed between normal volunteers and patients during migraine, but the rate of elimination was similar (Ross-Lee *et al.*, 1983).

Paracetamol is completely absorbed but its mean systemic availability, calculated from the areas under the intravenous and oral plasma concentration–time curves, is about 75% (Prescott, 1980), possibly owing to its 'first pass' metabolism (George, 1979; Rawlins *et al.*, 1977). The occurrence of a 'first pass' effect is further suggested by observations of plasma and urinary data in epileptic patients (Perucca & Richens, 1979). The proportion of the dose reaching the systemic circulation appears to depend upon the dose administered, decreasing from nearly 90% after 1–2 g to 63% after 0.5 g (Rawlins *et al.*, 1977). The sulphate conjugation of paracetamol becomes saturated in adults within the therapeutic range (Levy & Yamada, 1971). The dose-dependency of the 'first pass' metabolism at small therapeutic dose levels, together with the delayed gastric emptying could increase the 'first pass' effect during a migraine attack and thus slightly decrease oral bioavailability of paracetamol. The urinary excretion of unchanged paracetamol would not be a reliable parameter of the bioavailability, because it accounts only for 2–5% of the therapeutic dose and because paracetamol has the dose dependent 'first pass' metabolism mentioned.

The results from our study support the conclusions drawn by Volans (1974), that the impairment of drug absorption during a migraine attack correlates with the severity of symptoms. Headache was not as good an indicator as nausea of gastrointestinal disturbance affecting

absorption. The duration of the attack before drug intake did not correlate with the impairment in absorption, because in some patients the severity of the attack increased quickly, in others rather slowly.

The findings of the present study indicate that during the first few hours of a migraine attack

the absorption of oral paracetamol may be delayed and the systemic availability may be decreased if the migrainous symptoms are moderate or severe.

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(Received June 22, 1984,
accepted August 20, 1984)