

## Effects of migraine attack and metoclopramide on the absorption of tolfenamic acid

RIITTA A. TOKOLA & PERTTI J. NEUVONEN

Department of Clinical Pharmacology, University of Helsinki, Paasikivenkatu 4, SF-00250 Helsinki 25, Finland

1 The effect of acute migraine attack and rectally given metoclopramide on the absorption of orally given tolfenamic acid (300 mg) was investigated in seven female patients in a crossover study consisting of four phases, two without migraine and two during migraine. Metoclopramide hydrochloride (20 mg) or placebo was given double-blind.

2 Migraine attacks delayed the absorption of tolfenamic acid. Serum concentrations of tolfenamic acid 1.5 and 2 h after drug administration remained smaller, the peak serum concentration ( $t_{\max}$ ) occurred later and the area under the serum concentration-time curve between zero and 2 h ( $AUC_{0-2\text{h}}$ ) remained decreased during migraine.

3 Metoclopramide pretreatment in migraine attacks increased the serum concentration of tolfenamic acid at 1.5 h, but its peak concentration, time to peak concentration and the  $AUC_{0-5\text{h}}$  remained unchanged as compared with the values obtained with tolfenamic acid alone.

4 Between the absorption of tolfenamic acid without migraine and after metoclopramide pretreatment during migraine no significant differences existed.

5 When the patients were studied without migraine the serum concentrations of tolfenamic acid 45 min and 60 min after its administration were higher after metoclopramide than after placebo pretreatment.

6 During migraine attacks the serum concentrations and the  $AUC_{0-5.5\text{h}}$  of metoclopramide were slightly lowered.

7 The impairment of drug absorption by migraine was not related to the duration or severity of the attack.

8 The observed changes in drug absorption during migraine attacks are obviously due to the delay in gastric emptying. Rectally administered metoclopramide accelerates the absorption of orally given tolfenamic acid.

**Keywords** metoclopramide tolfenamic acid migraine

### Introduction

Drug absorption is greatly influenced by gastrointestinal motility, the gastric emptying time being the rate limiting factor, except for very slowly absorbed drug formulae (Prescott, 1974; Nimmo, 1981). The majority of migraine attacks is associated with gastrointestinal symptoms. Accordingly, migraine may delay drug absorption (Volans, 1974, 1978). During migraine

attacks plasma drug concentrations after effervescent aspirin (Volans, 1974), and paracetamol (Tokola & Neuvonen, 1981), have been lower than normal.

Pharmacological alteration of the gastric emptying rate has been shown to produce changes in drug absorption in normal conditions as well as in some pathological states, as acute

migraine, where the gastric emptying is delayed (Nimmo, 1976). During migraine attacks plasma concentrations of salicylate 30 and 60 min after ingestion of aspirin were higher when metoclopramide was given intramuscularly prior to it than after aspirin alone (Volans, 1975). Higher maximum aspirin and salicylate concentrations in serum occurred in patients treated previously with oral or intramuscular metoclopramide than in others without metoclopramide (Ross-Lee *et al.*, 1982).

Tolfenamic acid, *N*-(2-methyl-3-chlorophenyl)-anthranilic acid, is a nonsteroidal anti-inflammatory agent. Chemically it closely resembles mefenamic and flufenamic acids and diclofenac. Tolfenamic acid inhibits the biosynthesis of prostaglandins (PG) and has inhibitory actions on PG receptors, too (Lindén *et al.*, 1976; Vapaatalo *et al.*, 1977). The clinical efficacy of tolfenamic acid in the treatment of migraine attacks has been demonstrated (Vapaatalo *et al.*, 1977; Hakkarainen *et al.*, 1979, 1982; Ala-Hurula *et al.*, 1981).

Metoclopramide is a *p*-aminobenzamide derivative that increases gastric motility and gastric emptying rate by increased peristalsis and dilatation of pylorus and duodenum. It acts on the brain by blocking dopamine receptors. It blocks the stimulation of the chemoreceptor trigger zone by apomorphine and thereby is thought to prevent nausea and vomiting. It also abolishes the slowing of gastric emptying caused by apomorphine. Peripherally, metoclopramide stimulates the release of acetylcholine and sensitizes gastric smooth muscle to acetylcholine stimulation. Its gastrointestinal functions may be abolished by atropine, thereby indicating that they are dependent on cholinergic neuro-transmission. Metoclopramide has been reviewed by Pinder *et al.* (1976), Schulze-Delrieu (1981) and Harrington *et al.* (1983).

The effect of rectally given metoclopramide on the absorption of tolfenamic acid has been recently demonstrated (Tokola *et al.*, 1982). This paper describes a 4-phase study of the effects of acute migraine and rectal metoclopramide on the absorption of tolfenamic acid in migraine patients.

## Methods

### Patients

Originally eleven patients with diagnosis of migraine according to the Ad Hoc Committee (1962) volunteered for the study. However, four patients came for the tests only once or twice without migraine but not, as they were supposed

to do, during two migraine attacks in the course of 3 years. Thus, seven female patients, mean age 38 years and mean weight 60 kg were included in the crossover study (Table 1). None of the patients had either evidence of other disease or regular drug treatment. One of them was a smoker. All suffered from common migraine with 1–4 monthly attacks (mean duration 12; range 3–48 h). The reasons for the dropouts were: one patient became pregnant, one got a duodenal ulcer, and two patients could not leave their duties.

### Study design and drugs

The study protocol was approved by the Local Ethical Committee. The patients came to the laboratory in the Department of Clinical Pharmacology for absorption studies twice without migraine and twice as soon as possible after the beginning of a migraine attack, when at least 1 week had passed since the previous attack or drug absorption study. Pretreatment with placebo or metoclopramide was given double-blind in a randomized order. The patients were forbidden to take any drugs or alcohol within 24 h prior to the investigation. The phases without migraine were always started after an overnight fast and with migraine attack at least 4 h after the last food ingestion. For 2.5 h after starting drug therapy the patients lay on a couch and were forbidden to turn in the left lateral position, because it may influence the rate of drug absorption. Fluids and food were withheld for 3.5 h.

First a single rectal dose of metoclopramide hydrochloride (20 mg, Metopram<sup>®</sup> supp., Leiras Pharmaceutical Plant, Finland) or placebo was given, and 30 min later a single oral dose of three capsules of tolfenamic acid (a total of 300 mg, Clotam<sup>®</sup> capsules, Medica Pharmaceutical Company Ltd, Finland) with 150 ml of water.

Venous blood samples were obtained through a teflon cannula from a forearm vein prior to rectal drug administration, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4 and 5 h after administration of tolfenamic acid. The serum was separated and stored deep-frozen until analyzed.

The assessment of subjective responses, pain and gastrointestinal symptoms, was made using the visual analogue scale rated from 0 to 100 (VAS<sub>0-100</sub>). Each patient was given an assessment sheet with two 10 cm lines on it, and placed a mark somewhere on the line to record her assessment of her own state at every hour. In the pain rating scale 100 means pain which in the patient's migraine could not be more severe. In the gastrointestinal symptom scale 100 means vomiting and severe nausea before the beginning

**Table 1** Characterization of the patients and some pharmacokinetic parameters of tolfenamic acid derived from serum concentrations following a single oral dose of tolfenamic acid (300 mg) to seven patients. The crossover study consisted of four phases, two during a migraine attack and two without it.

Patient	Age (years)	Weight (kg)	Placebo pretreatment				Metoclopramide pretreatment							
			AUC <sub>0-2h</sub> (mg l <sup>-1</sup> h)		t <sub>max</sub> (h)		C <sub>max</sub> (mg l <sup>-1</sup> )		AUC <sub>0-2h</sub> (mg l <sup>-1</sup> h)		t <sub>max</sub> (h)		C <sub>max</sub> (mg l <sup>-1</sup> )	
			Migraine	Without migraine	Migraine	Without migraine	Migraine	Without migraine	Migraine	Without migraine	Migraine	Without migraine	Migraine	Without migraine
1	36	68	0.62	5.07	3	1	3.82	3.41	4.09	4.32	1.5	1.0	4.44	3.44
2	34	51	5.16	6.01	1.5	2	3.45	9.10	3.64	7.68	1.5	0.5	3.72	6.60
3	31	70	3.00	2.47	2.5	2	2.18	2.20	4.63	5.80	1.5	1.5	3.60	4.56
4	41	54	2.80	3.61	3	2	4.45	3.65	1.80	3.60	5.0	2.0	3.65	3.31
5	42	53	0.36	3.51	4	2	6.90	3.61	2.75	7.67	4.0	2.0	4.50	5.90
6	42	58	1.21	1.95	2	0.8	1.30	1.48	4.14	2.37	0.75	1.0	3.15	1.76
7	37	65	0.85	5.89	4	2	3.46	6.90	2.69	11.15	2.0	1.0	2.76	8.97
Mean	38	60	2.00	4.07	2.86	1.69	3.65	4.34	3.39	6.08	2.32	1.29	3.69	4.93
s.e. mean	2	3	0.66	0.61	0.36	0.20	0.67	1.02	0.38	1.13	0.59	0.21	0.24	0.91
			*			*	NS	NS	NS	NS	NS	NS	NS	NS

\* P < 0.05 (Wilcoxon matched pairs signed ranks test, two-tailed)

of the study. In both scales, 0 means that the patient was free from the respective symptom.

*Drug analyses*

Tolfenamic acid was measured by high pressure liquid chromatography (h.p.l.c.). Serum tolfenamic acid (sample 0.2-0.5 ml) was extracted with dichloromethane at pH 4.5. Flufenamic acid (0.5 mg) was used as internal standard. The organic layer was evaporated under a stream of nitrogen and the residue was dissolved in methanol and injected into the chromatograph, which consisted of a Model U6K universal injector, a reversed phase column (μBondapak C<sub>18</sub>), a Model 6000 A solvent delivery pump system (Water Associates, Milford, Mass.) and a 1030 B variable wavelength (UV) absorbance detector (Hewlett-Packard) operating at 289 nm. The mobile phase was 0.02 M orthophosphoric acid (pH 4.0) in methanol, 3/7 by volume, with a flow-rate of 2 ml/min. Metoclopramide did not interfere with the assay. The practical detection limit for tolfenamic acid in serum was 0.2 mg/l (1 mg/l = 3.82 mmol/l). The coefficient of variation (n = 8) at 0.5 mg/l was 6% and at 5 mg/l 5%.

Metoclopramide was determined by a modified h.p.l.c. method described by Graffner *et al.* (1979). Analyses were performed with the same equipment as in tolfenamic acid assay with the exception that now the column was μPorasil 10 (Waters Associates, Milford, Mass.). Tolfenamic acid did not interfere with the assay. The practical detection limit for metoclopramide in serum was 5 μg/l. The coefficient of variation (n = 8) at 25 μg/l was 7% and at 100 μg/l 4%.

*Pharmacokinetic analyses*

The absorption of tolfenamic acid was characterized by the time to peak serum concentration (t<sub>max</sub>), the peak serum concentration (C<sub>max</sub>) and the area under the serum drug concentration-time curve between zero and 2 h (AUC<sub>0-2h</sub>) and between zero and 5 h (AUC<sub>0-5h</sub>), which were calculated by the trapezoidal rule. The same parameters were determined for metoclopramide.

*Statistical analysis*

For each of the parameters, differences between the four cross-over studies were first examined by a two-way analysis of variance (ANOVA) applied to complete block design. The ordinal Wilcoxon matched pairs signed ranks test (two-tailed) was used to test for any significant differences between the paired observations. Possible correlation between the parameters was estimated using the Spearman two rank correlation test. Means ± s.e. mean are given.

## Results

### Pharmacokinetic data

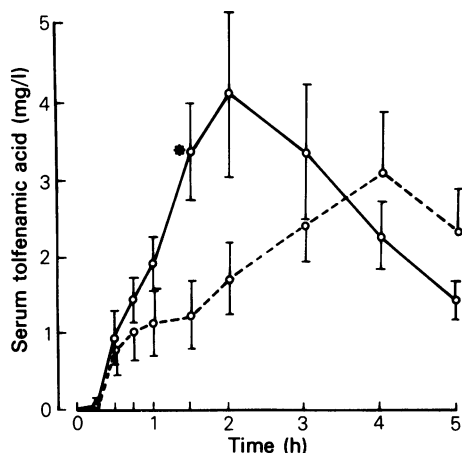
The results of the analysis of variance showed significant differences both between the four different phases and between the seven patients (Table 2). Migraine attacks delayed the absorption of orally given tolfenamic acid (Table 1, Figures 1 and 2). A significant decrease in the serum concentration at 1.5 h ( $T = 2$ ,  $P < 0.05$ ), in the  $AUC_{0-2\text{ h}}$  ( $T = 1$ ,  $P < 0.05$ ) and an increase in the  $t_{\max}$  ( $T = 1.5$ ,  $P < 0.05$ ) were observed during migraine. On the other hand, the bioavailability of tolfenamic acid, measured as the  $AUC_{0-5\text{ h}}$ , remained unchanged in migraine (Figure 2b).

When the patients did not have a migraine attack, metoclopramide accelerated the absorption of tolfenamic acid, as reflected in increased serum concentrations at 0.75 h ( $T = 2$ ,  $P < 0.05$ ) and at 1 h ( $T = 0$ ,  $P < 0.02$ ; Figure 3a).

In migraine the serum concentration of tolfenamic acid after metoclopramide pretreatment was higher than after placebo pretreatment ( $T = 0$ ,  $P < 0.02$ ; Figure 3b) at 1.5 h, but lower ( $T = 0$ ,  $P < 0.02$ ) at 4 h.

No significant differences in the absorption of tolfenamic acid were found, when the migraine phase on metoclopramide pretreatment was compared to the phase without migraine on placebo pretreatment. Profiles of the serum concentrations of tolfenamic acid in all four phases in two single patients (no 7 and no 5) are presented in Figures 4a and 4b.

The bioavailability ( $AUC_{0-5\text{ h}}$ ) of tolfenamic acid was not significantly different in the four phases of the study (Figure 2b, Table 2).



**Figure 1** Effect of migraine attack on the absorption of a single 300 mg oral dose of tolfenamic acid ( $n = 7$ ) without migraine  $\circ$ — $\circ$ , during migraine  $\circ$ --- $\circ$ . The serum concentrations are expressed as mean values  $\pm$  s.e. mean. \* $P < 0.05$  in Wilcoxon matched pairs signed ranks test.

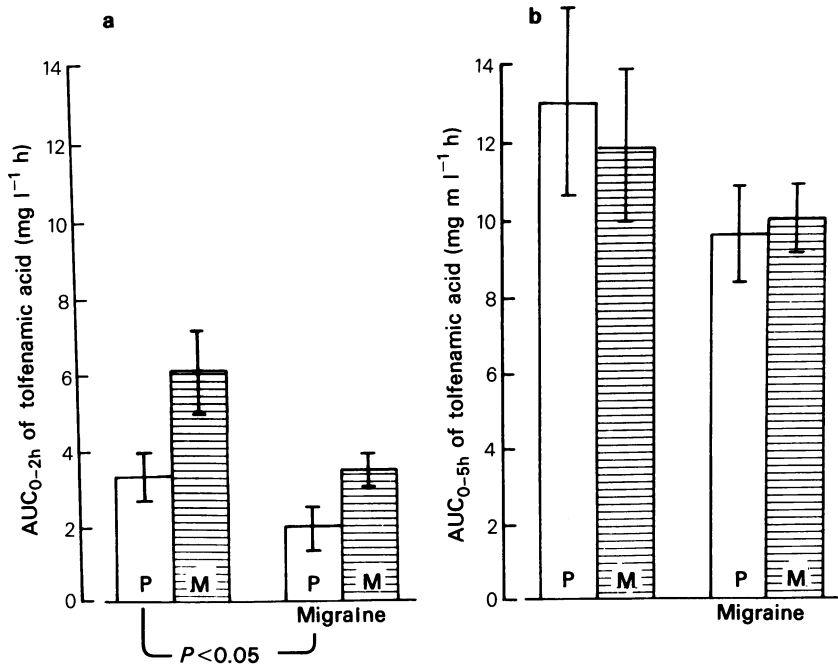
Migraine seemed to decrease the absorption of metoclopramide from suppositories as reflected in the serum concentrations,  $C_{\max}$  ( $67 \pm 6 \mu\text{g/l}$  without migraine and  $39 \pm 6 \mu\text{g/l}$  in migraine) and the  $AUC_{0-5.5\text{ h}}$  ( $278 \pm 27 \mu\text{g l}^{-1}\text{ h}$  without migraine and  $159 \mu\text{g l}^{-1}\text{ h}$  in migraine;  $T = 0$ ,  $P < 0.05$ ; Figure 5).

### Clinical data

The duration of migraine attacks before the beginning of the kinetic study was  $3.4 \pm 0.2$  (range 2.5–5.0) h. During migraine, two patients had vomited both before the administration of

**Table 2** Analysis of variance of some pharmacokinetic parameters of tolfenamic acid.  $F$  and  $P$  values for the differences between four phases and between seven patients are given.

Parameter		Between phases (d.f. 3,18)		Between patients (d.f. 6,18)	
		F	P value	F	P value
Serum concentration at	0.25 h	1.2608	NS	0.9294	NS
	0.5 h	1.3871	NS	0.7393	NS
	0.75 h	5.4249	< 0.01	0.5226	NS
	1.0 h	6.7729	< 0.01	0.8632	NS
	1.5 h	4.1230	< 0.01	1.6141	NS
	2.0 h	2.3125	NS	1.4852	NS
	3.0 h	1.6093	NS	2.0917	NS
	4.0 h	3.6520	< 0.05	5.0670	< 0.01
	5.0 h	3.3611	< 0.05	4.4853	< 0.01
$C_{\max}$		0.8774	NS	2.6583	NS
$t_{\max}$		5.2597	< 0.01	3.8442	< 0.05
$AUC_{0-2\text{ h}}$		5.8418	< 0.01	1.5142	NS
$AUC_{0-5\text{ h}}$		1.2833	NS	4.6581	< 0.01

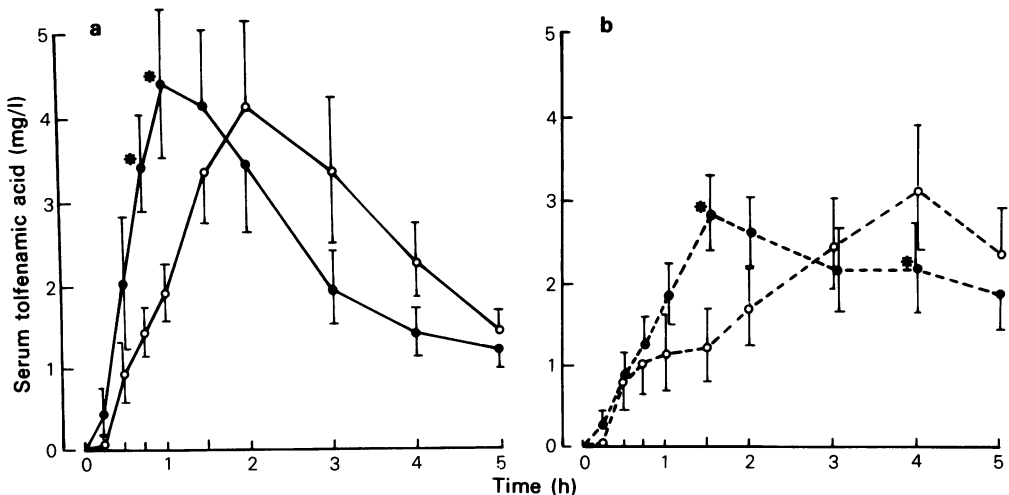


**Figure 2** Effects of migraine attack and rectally administered metoclopramide (M 20 mg) on the areas under the serum tolfenamic acid concentration-time curves ( $n = 7$ ). (a) =  $AUC_{0-2h}$ , (b) =  $AUC_{0-5h}$ . The results are shown as mean values  $\pm$  s.e. mean. P placebo.

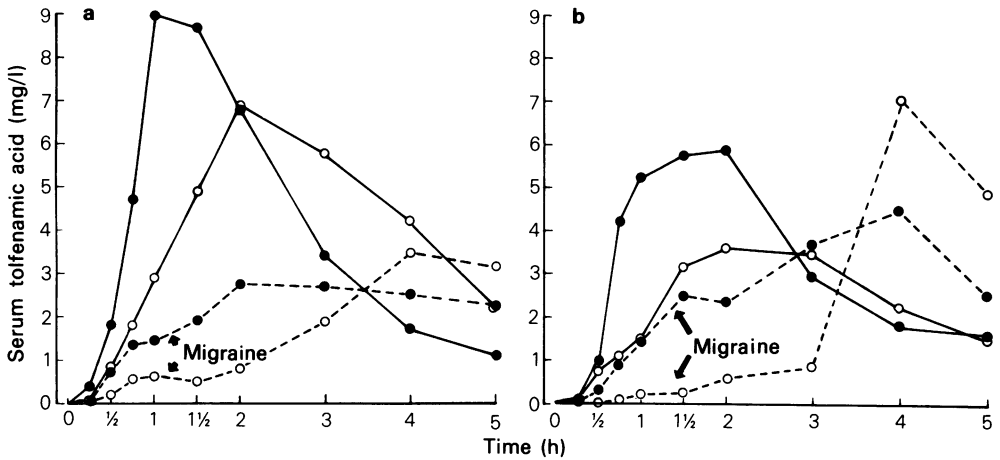
placebo and of metoclopramide suppositories and one patient only before metoclopramide. They did not vomit later.

There were only insignificant differences (Wilcoxon test) between placebo and metoclopramide pretreatments as regards the VAS of

nausea/vomiting and pain at the beginning (range 40–100) or later during migraine (Figures 6a and 6b). However, when the VAS was transformed by stretching the initial maximum for each patient to 100 and the thus obtained proportional scores were tested statistically, the

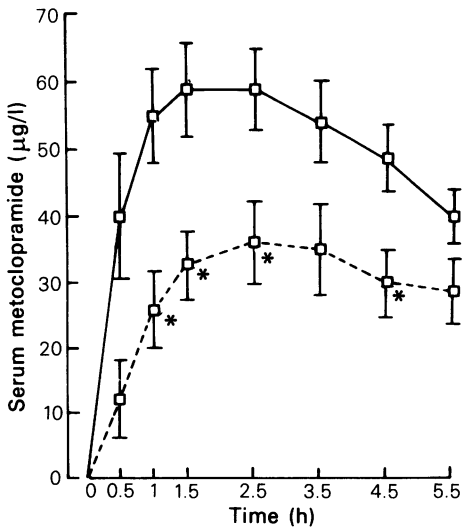


**Figure 3** Serum tolfenamic acid concentrations following a single 300 mg oral dose ( $n = 7$ ). (a) the results when the patients had not their migraine attacks and tolfenamic acid was preceded 30 min earlier by a 20 mg rectal dose of metoclopramide (●) or placebo (○). (b) the results of the same treatments during migraine attacks. Mean values  $\pm$  s.e. mean are given. \* $P < 0.05$ .



**Figure 4** Serum tolfenamic acid concentrations following a 300 mg dose administered to two representative patients in four phases of the study, when metoclopramide (●) or placebo (○) pretreatment was given.

intensity of pain 1 h after tolfenamic acid ingestion was significantly less after metoclopramide than after placebo pretreatment ( $P < 0.05$ , Wilcoxon test). The duration of the migraine attack and the severity of migraine symptoms at the beginning of the absorption studies did not correlate significantly with the absorption parameters. During the study, however, there was a good inverse correlation between increasing serum concentrations of tolfenamic acid and the intensity of pain ( $P < 0.01$ ;  $r_s = 0.654$ , Spearman test).



**Figure 5** Serum metoclopramide concentrations following a 20 mg rectal dose ( $n = 7$ ) without migraine □—□, during migraine □---□. Mean values  $\pm$  s.e. mean are given. \* $P < 0.05$ .

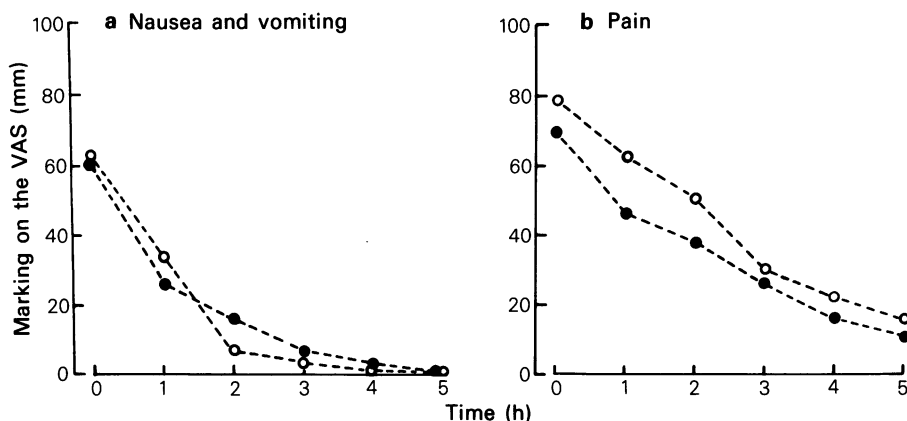
In three patients the attack ended within 5 h on both treatments. One patient (no 3) needed additional medication after 5 h. After metoclopramide two patients complained about tiredness when headache-free and three patients during migraine, and after placebo none and two patients, respectively.

### Discussion

In this study migraine attacks were found to delay the absorption of oral tolfenamic acid, as evidenced by low drug concentrations, prolonged time to peak concentration and low absorption in 2 h. Pretreatment with rectal metoclopramide prevented, however, any significant migraine-induced changes in the absorption. Metoclopramide accelerated the absorption of tolfenamic acid both during migraine attacks and migraine-free periods.

The crossover design in drug absorption studies reduces the between-patient variability, even though not all migraine attacks in a certain patient are exactly of the same quality. However, a study containing many phases is quite demanding for both patients and staff, and therefore most drug absorption studies in migraine have been done on a between-patient comparison basis. For the same reason the present study was done over a period of more than 3 years and the number of patients was limited.

In this study blood samples were taken up to 5.5 h post drug administration for determination of some pharmacokinetic parameters of drug absorption. However, the half-lives of absorption and elimination were not estimated,



**Figure 6** Mean gastrointestinal symptom and pain intensity scores during migraine attacks up to 5 h after tolfenamic acid administration (300 mg) when metoclopramide (20 mg, ●) or placebo (○) pretreatment was given ( $n = 7$ ). Wilcoxon matched pairs signed ranks test of the raw scores revealed no significant differences between the treatments.

because there were too few data points for exact calculations.

The mean duration of migraine before the start of kinetic studies was 3.4 h. If the drugs had been given at the very beginning of the attack, differences in drug absorption might have been smaller, but if they had been given too late vomiting could have complicated interpretation of the results.

Tolfenamic acid is an acidic drug which is non-ionized but poorly soluble at the gastric pH. Its solubility in water increases steeply as the pH rises above 6.5. When the gastric secretion is low, e.g. during sympathetic stimulation, or when the acidic contents of the stomach have been removed by vomiting, the intragastric milieu might thus theoretically allow absorption of tolfenamic acid even from the stomach.

In the present study measurable serum concentrations of tolfenamic acid were found during migraine-free periods at 0.25 h post intake in all patients on metoclopramide and four on placebo pretreatment, but during migraine attacks without metoclopramide pretreatment only in one patient. These results give further support to the theory that gastric emptying is the principal factor limiting the rate of absorption of tolfenamic acid.

Thirty minutes seems to be a long enough time for the effect of metoclopramide to appear, although in this study its influence on the absorption of tolfenamic acid might have been more pronounced, had the timespan between the doses been longer.

Metoclopramide enhances the rate of absorption of many drugs, but, in general, the total bioavailability of orally given drugs is not

changed by it. It has enhanced the bioavailability of L-dopa (Mearrick *et al.*, 1974) but decreased that of certain digoxin tablets with a slow dissolution rate, when used concomitantly (Manninen *et al.*, 1973).

In accordance with earlier observations, metoclopramide in the present study caused greater changes in the absorption of oral tolfenamic acid during migraine attacks than during migraine-free periods, apparently because its influence on the gastric emptying rate is stronger when the gastric function is disturbed than when it is normal.

There were significant interindividual differences in the  $t_{max}$  and the bioavailability of tolfenamic acid measured as the  $AUC_{0-5 h}$ . The  $AUC_{0-5 h}$  varied from 2- to 4-fold between the patients.

The bioavailability of tolfenamic acid was not changed significantly either by metoclopramide treatment or by migraine attack. The profile of the absorption curve, e.g. for patients no. 5 and 7 supports the view that tolfenamic acid is rapidly absorbed once it has reached the small intestine, where its solubility is good and the capacity of the absorbing surface great. The absorption of the drug after oral administration to migraine patients in a migraine-free period in this study did not seem to differ from the results obtained with healthy female volunteers (Pentikäinen *et al.*, 1981).

The visual analogue scale is accurate, as reliable as and more sensitive than the four-point scale in registering the intensity of chronic pain (Joyce *et al.*, 1975). It has been increasingly used for estimation of the intensity of various acute pains. The method is more suitable for within-

subject comparisons than for those between subjects (Maxwell, 1978).

Non-parametric observations of this kind, especially in a small patient group, are best checked statistically by ordinal tests, as the Wilcoxon matched pairs signed ranks test here. A transformation of the original scores by stretching out the maximum rating for each patient to 100 and by calculating the respective proportional scores, improves the sensitivity of the VAS (Maxwell, 1978).

The response to treatment was not a primary concern in the present study. Tolfenamic acid was given open and without control drug. Nevertheless, its effect on migraine earns a positive comment, when compared to the previous history of migraine in these patients, with 12 h mean duration of the attacks.

Using between-patient comparisons and larger numbers of patients Volans (1974) has shown that impairment of absorption of effervescent aspirin during migraine correlates with the severity of the symptoms although not with their duration. In the present study with tolfenamic acid such correlations were not found, however. This may be caused by the limited number of the patients and differences in study design.

It is established that migraine attacks are accompanied by delayed gastric emptying, but the mechanism is not fully known. Pain in itself retards the emptying of the stomach (Nimmo, 1976; Malagelada, 1982). Studies with  $\beta$ -adreno-

ceptor-blockers have shown that a slight inhibition of gastric emptying is physiologically maintained by adrenergic innervation (Rees *et al.*, 1980). A migraine attack often begins in connection with emotional stress (Mathew *et al.*, 1980). Before the onset of the attack (Hsu *et al.*, 1978) and during it (Anthony, 1981) elevated concentrations of noradrenaline have been measured in plasma, and increased output of catecholamine metabolites has been observed during a migraine episode (Curran *et al.*, 1965; Lance *et al.*, 1967). If the central chemoreceptor trigger zone or the vomiting centre are stimulated by different means, the gastric motility decreases. The roles of catecholamines, acetylcholine, endogenous opiates and PGs as biochemical factors in gastrointestinal functions are still under study. The findings in the present study indirectly support the hypothesis that dopamine receptors are involved in the control of gastric motor function during migraine.

The absorption of tolfenamic acid capsules demonstrates the change in absorption caused by migraine and the need of early intake of the drug. Metoclopramide accelerates the absorption of tolfenamic acid and may be clinically useful in certain patients in the treatment of migraine. The observed interindividual differences in absorption are of clinical importance when the efficacy of drug treatment of migraine attacks is evaluated, and therefore the optimal dosage should be determined individually.

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