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$_{0-2}$) 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$_{0-5.5}$ 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$_{0-5.5}$ 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-aminobenzoamide 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 neurotransmission. 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., 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® 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 (VAS0–100). 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.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>AUC$_{0-2}$ (mg l$^{-1}$h)</th>
<th>Placebo pretreatment</th>
<th>Metoclopramide pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC$_{0-2h}$ (mg l$^{-1}$)</td>
<td>t$_{max}$ (h)</td>
<td>C$_{max}$ (mg l$^{-1}$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without migraine</td>
<td>Without migraine</td>
<td>Without migraine</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
<td>68</td>
<td>0.62</td>
<td>5.07</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>51</td>
<td>5.16</td>
<td>6.01</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>70</td>
<td>3.00</td>
<td>2.47</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>54</td>
<td>2.80</td>
<td>3.61</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>53</td>
<td>0.36</td>
<td>3.51</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>58</td>
<td>1.21</td>
<td>1.95</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>65</td>
<td>0.85</td>
<td>5.89</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean</th>
<th>s.e. mean</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>60</td>
<td>2.00</td>
<td>0.66</td>
<td>2.86</td>
<td>1.69</td>
</tr>
</tbody>
</table>

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

Statistical analysis

For each of the cross-over studies, differences between the mean weight of the group were examined by a two-way analysis of variance (ANOVA) applied to complete block design. The ordinary t-test was used to test for any significant differences between the groups. Possible correlation between the patients was estimated using the Spearman correlation test. Means ± s.e. mean are given.

Pharmacokinetic analyses

The absorption of tolfenamic acid was characterized by the time to peak concentration (t$_{max}$), the area under the serum concentration-time curve between zero and 5 hr (AUC$_{0-5}$), which were calculated by the trapezoidal rule. The same parameters were determined for metoclopramide.

Drug analyses

Tolfenamic acid was measured by high pressure liquid chromatography (HPLC). Serum samples were taken at baseline and at 0.5 hr after the oral administration of metoclopamide, 0.5 mg, was used as internal standard. The mobile phase was acetonitrile-0.2 M orthophosphoric acid (pH 4.0) at 0.1 ml min$^{-1}$ and 4% methanol. The column was a reverse-phase (Waters, Milford, Mass.) microbore (10 mm, 4.0 angstroms). The detector was a variable-wavelength detector (Waters, Milford, Mass., a 1030 B model). A solvent delivery pump system (Water Associates, Milford, Mass.) and a 1030 B model (Waters, Milford, Mass.) were used. The wavelength was 290 nm. The 0.5 mg dose was taken as 100%.

Migraine, metoclopramide and tolfenamic acid absorption
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 AUC0–2 h, \((T = 1, P < 0.05)\) and an increase in the \(t_{\text{max}}\) \((T = 1.5, P < 0.05)\) were observed during migraine. On the other hand, the bioavailability of tolfenamic acid, measured as the AUC0–5 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 \((\text{AUC}_0–5\ h)\) of tolfenamic acid was not significantly different in the four phases of the study (Figure 2b, Table 2).

![Figure 1](image) Effect of migraine attack on the absorption of a single 300 mg oral dose of tolfenamic acid \((n = 7)\) without migraine \(\text{O}---\text{O},\) during migraine \(\text{O}---\text{O}.\) The serum concentrations are expressed as mean values ± 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, \(C_{\text{max}}\) \((67 ± 6 \mu g/l without migraine and 39 ± 6 \mu g/l in migraine)\) and the AUC0–5.5 h \((278 ± 27 \mu g \cdot l^{-1} \cdot h) without migraine and 159 \mu g \cdot l^{-1} \cdot h in migraine; T = 0, P < 0.05;\) Figure 5).

Clinical data

The duration of migraine attacks before the beginning of the kinetic study was 3.4 ± 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Between phases ((d.f. 3, 18))</th>
<th>Between patients ((d.f. 6, 18))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum concentration</td>
<td>(0.25\ h) 1.2608 NS</td>
<td>(0.25\ h) 0.9294 NS</td>
</tr>
<tr>
<td></td>
<td>(0.5\ h) 1.3871 NS</td>
<td>(0.5\ h) 0.7393 NS</td>
</tr>
<tr>
<td></td>
<td>(0.75\ h) 5.4249 &lt; 0.01</td>
<td>(0.75\ h) 0.5226 NS</td>
</tr>
<tr>
<td></td>
<td>(1.0\ h) 6.7729 &lt; 0.01</td>
<td>(1.0\ h) 0.8632 NS</td>
</tr>
<tr>
<td></td>
<td>(1.5\ h) 4.1230 &lt; 0.01</td>
<td>(1.5\ h) 1.6141 NS</td>
</tr>
<tr>
<td></td>
<td>(2.0\ h) 2.3125 NS</td>
<td>(2.0\ h) 1.4852 NS</td>
</tr>
<tr>
<td></td>
<td>(3.0\ h) 1.6093 NS</td>
<td>(3.0\ h) 2.0917 NS</td>
</tr>
<tr>
<td></td>
<td>(4.0\ h) 3.6520 &lt; 0.05</td>
<td>(4.0\ h) 5.0670 &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>(5.0\ h) 3.3611 &lt; 0.05</td>
<td>(5.0\ h) 4.4853 &lt; 0.01</td>
</tr>
<tr>
<td>(C_{\text{max}})</td>
<td>0.8774 NS</td>
<td>0.8774 NS</td>
</tr>
<tr>
<td>(t_{\text{max}})</td>
<td>5.2597 &lt; 0.01</td>
<td>5.2597 &lt; 0.01</td>
</tr>
<tr>
<td>(\text{AUC}_{0–2\ h})</td>
<td>5.8418 &lt; 0.01</td>
<td>5.8418 &lt; 0.01</td>
</tr>
<tr>
<td>(\text{AUC}_{0–5\ h})</td>
<td>1.2833 NS</td>
<td>1.2833 NS</td>
</tr>
</tbody>
</table>
Migraine, metoclopramide and tolfenamic acid absorption

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 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) = AUC0–2h, (b) = AUC0–5h. The results are shown as mean values ± s.e. mean. P placebo.

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 ± s.e. mean are given. *P < 0.05.
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).

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,
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 tofenamic acid even from the stomach.

In the present study measurable serum concentrations of tofenamic 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 tofenamic 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 tofenamic 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 tofenamic 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 $t_{\text{max}}$ and the bioavailability of tofenamic acid measured as the $\text{AUC}_{0-5 \text h}$. The $\text{AUC}_{0-5 \text h}$ varied from 2- to 4-fold between the patients.

The bioavailability of tofenamic 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 tofenamic 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 (Pentikainen 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-

![Migraine, metoclopramide and tofenamic acid absorption](image)

Figure 6  Mean gastrointestinal symptom and pain intensity scores during migraine attacks up to 5 h after tofenamic 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.
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 β-adrenergic-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.

References


(Received July 4, 1983, accepted September 8, 1983)