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THE EFFECT OF METOCLOPRAMIDE ON THE ABSORPTION OF EFFERVESCENT ASPIRIN IN MIGRAINE

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1 The absorption of effervescent aspirin was studied in two groups of patients during attacks of migraine. The first group received effervescent aspirin alone whilst the second group received intramuscular metoclopramide before effervescent aspirin.

2 After effervescent aspirin alone there was significant impairment in the rate of aspirin absorption during migraine attacks compared with the rate of aspirin absorption in normal volunteers and in the same patients when headache-free.

3 When metoclopramide was given before effervescent aspirin the rate of aspirin absorption during migraine attacks was not significantly different from that obtained in normal volunteers given effervescent aspirin alone or from that obtained in the patients themselves when given both metoclopramide and effervescent aspirin when headache-free.

4 It is concluded that the impairment of absorption of effervescent aspirin during migraine attacks is related to impaired gastro-intestinal motility with delayed gastric emptying and that this impaired motility can be overcome by parenteral metoclopramide.

Introduction

Recent investigations have demonstrated impairment of the rate of absorption of effervescent aspirin during migraine attacks (Volans, 1974b). It is thought that impaired drug absorption during migraine may be the cause of many cases of therapeutic failure (Wilkinson, 1971) and it is probable that a treatment which improved the rate of drug absorption would be of clinical relevance. During migraine attacks there is evidence of increased sympathetic nervous activity (Sacks, 1970) and of gastric stasis (Kaufman & Levine, 1936; Kreel, 1973) and it is possible that the impairment of drug absorption is caused by delayed gastric emptying. Metoclopramide is known to be capable of increasing the rate of gastric emptying and the rate of absorption of paracetamol (Nimmo, Heading, Tothill & Prescott, 1973). The present study was designed to test the hypothesis that metoclopramide is capable of increasing the rate of drug absorption during a migraine attack.

Methods

Subjects

Forty patients were studied when they attended the Princess Margaret Migraine Clinic during migraine attacks. All gave informed consent to the investigation and all were considered to fulfil the diagnostic criteria of migraine (World Federation of Neurology Research Group in Migraine and Headache, 1970). Since it was found that most patients attending the clinic had not taken food for at least 4 h (Volans, 1974b) and since food has been shown to reduce the absorption of effervescent aspirin (Volans, 1974a), patients who had eaten within that time were excluded from the study. Patients were also not included if there was any evidence of other disease, if there was any history of dyspepsia or if analgesics or anti-emetic drugs had been taken within 24 h prior to arrival at the clinic.

Twenty non-migrainous volunteer subjects were taken from the hospital medical, nursing and administrative staff. All had fasted overnight before the study and all gave negative histories for headaches and gastro-intestinal disease.

Materials

Metoclopramide was given as a single dose of metoclopramide hydrochloride (10 mg, Injection Primperan, Berk Pharmaceuticals Ltd) into the gluteus maximus. Effervescent aspirin was given as

a single dose of three tablets containing a total of 900 mg acetylsalicylic acid in an effervescent base equivalent to 1800 mg sodium bicarbonate and 1200 mg arhydrous citric acid (Tabs. Claradin, Nicholas Laboratories Ltd) dissolved in 150 ml of water.

Analysis

Plasma samples were deep frozen and were stored for up to two weeks before analysis. After thawing, plasma salicylate levels were estimated by the method of Saltzman (1948) using an Aminco-Bowman spectrofluorimeter. Preliminary studies established that neither metoclopramide nor its metabolites interfered with this estimation.

Design

Under ideal circumstances an individual-centred design would have been used where each patient was treated in two migraine attacks and each would have received treatment with effervescent aspirin alone and effervescent aspirin after metoclopramide. In practice, however, only a small percentage of patients are able to attend the clinic during more than one acute attack and the collection of data for such a comparison would probably have taken some years with wastage of much information from patients in whom only one attack had been studied.

It was therefore decided to use an inter-group comparison of the two treatments in migraine patients. The first twenty patients entered into the study received treatment with effervescent aspirin alone (Group A) whilst the second twenty patients received treatment with metoclopramide before effervescent aspirin (Group B). For further comparison twenty non-migrainous subjects received effervescent aspirin alone (Group C) and where possible each migraine patient was retested when headache-free but under conditions which were otherwise identical to those during the acute attack (Control groups A and B).

No attempt was made to match the groups for age, sex or weight but these parameters were recorded for each subject. Similarly the migraine groups were not matched for duration or severity of the migraine attack but these factors were recorded as described in the previous study (Volans, 1974b).

Procedure

A control blood sample was collected by venepuncture into heparinized tubes in all subjects before the administration of any drug. From the normal volunteers (Group C) and the first group of migraine patients (Group A) further blood samples were collected at 30 and 60 min after the ingestion of aspirin.

The second group of migraine patients (Group B) received intramuscular metoclopramide immediately after the collection of the first control blood sample. Ten minutes later a further blood sample was collected and immediately after this the patient took the oral effervescent aspirin. Samples were then collected at 30 and 60 min after the ingestion of aspirin.

During the study all patients lay on a couch in a darkened room. Movement was not restricted and visits to the toilet were permitted but the subject was not allowed to rest in the left lateral position as that position has been shown to reduce the rate of drug absorption (Truitt & Morgan, 1964; Martin, 1971). The normal volunteers were allowed to continue with moderate activity during the study as this has been shown not to influence the absorption of effervescent aspirin (Volans, 1974a).

Results

Table 1 compares the age, sex and weight distributions of the three groups. It is noted that

Table 1 Intergroup comparisons of age, sex and weight

Group	*Number of subjects*	*Sex*	*Mean age (years)*	*Mean weight (kg)*
C	20	11 M 9 F	29.3 (±8.1)	66.9 (±10.3)
A	20	7 M 13 F	38.9 (±11.1)	68.2 (±13.9)
B	20	5 M 15 F	29.7 (±12.0)	58.4 (±9.3)

s.d. indicated in brackets.

Group A patients tended to be slightly older than the other two groups and that Group B contained more females and tended towards lower weights than the other two groups.

Table 2 compares the diagnoses and symptoms in the two migraine groups. Group A contained a larger number of patients with common migraine whilst in Group B there were equal numbers with common and classical migraine. However, when the severity of the headache, nausea and vomiting before treatment is compared by the Kolmogorov-Smirnov Two Sample Test there is no significant difference between the two groups.

Further evidence for the comparability of the results is shown in Fig. 1 which demonstrates the plasma salicylate levels at 30 and 60 min in one patient who, by chance, presented in both groups. In this patient the duration and the severity of the symptoms were almost identical in the two attacks. During the attack treated with effervescent aspirin alone the absorption was markedly reduced whilst the levels obtained in the attack treated with metoclopramide before the effervescent aspirin were similar to those obtained on the two control days.

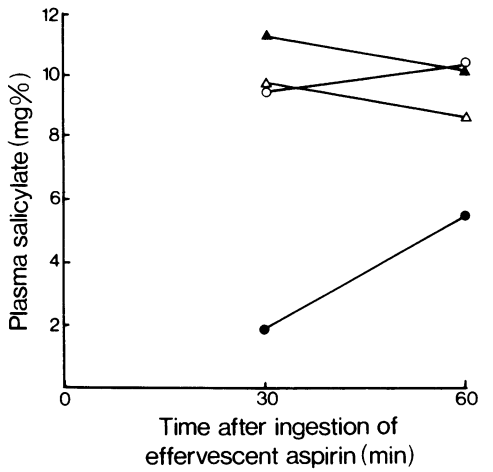

Figure 1 Comparison of plasma salicylate levels in one subject (L.B., female, 49 years) after effervescent aspirin in two similar migraine attacks and on two headache-free days: (●) migraine attack, (○) headache-free, after effervescent aspirin (900 mg) alone. (▲) migraine attack, (△) headache-free, after metoclopramide (10 mg, i.m.) and effervescent aspirin (900 mg).

Plasma salicylate levels after 30 min

When the distribution of plasma salicylate levels in each group after 30 min were compared (Fig. 2, Table 3), the findings were as follows:

Treatment with effervescent aspirin alone

The plasma salicylate levels achieved during migraine attacks (Group A) were significantly lower than those achieved in normal volunteers (Group C) ($t = 4.06$, $P < 0.0005$, 1 tailed). In the patients who were retested under headache-free conditions (Control group A) the levels were not significantly different from those in normal volunteers ($t = 1.12$, $P > 0.02$). A within subjects comparison confirmed that absorption was signi-

Table 2 Comparison of diagnosis and severity of symptoms between the two groups of migraine patients

	Group A	*Group B*	D_{max}	P
Diagnosis				
Common migraine	15	10		
Classical migraine	5	10		
Severity of headache				
Intense	8	4		
Moderate	9	12	1.6	>0.30
Slight	3	4		
Severity of nausea				
Intense	4	2		
Moderate	5	8	0.1	>0.90
Slight	6	3		
Nil	5	7		
Vomiting				
>4 h before test	0	4		
<4 h before test	5	7	2.1	>0.30
During test	0	0		
After test	1	0		

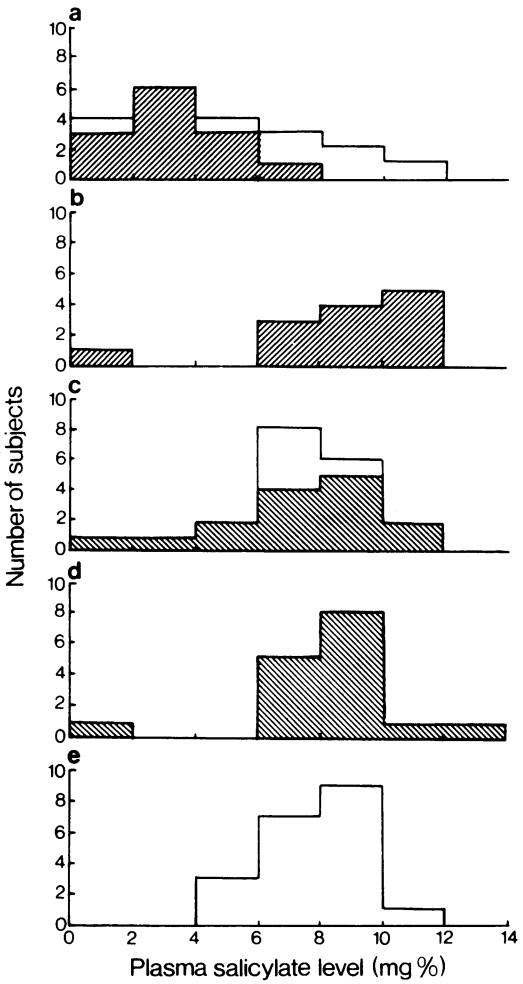

Figure 2 Comparison of the distribution of plasma salicylate levels 30 min after ingestion of effervescent aspirin (900 mg) in three groups: (a) Group A, migraine patients, aspirin alone (n = 20); (b) Group A control (n = 13); (c) Group B, migraine patients, metoclopramide before aspirin (n = 20); (d) Group B control (n = 16); (e) Group C, non-migrainous volunteers, aspirin alone (n = 20). Shaded area indicates those patients for whom both acute and control results were obtained.

ficantly reduced during the migraine attack (correl $t = 3.05, P < 0.005$, 1 tailed).

Treatment with effervescent aspirin after intramuscular metoclopramide

The plasma salicylate levels achieved during migraine attacks (Group B) were greater than those achieved after treatment with effervescent aspirin alone ($t = 3.13$, $P < 0.005$, 1 tailed) but were not significantly different from the levels in normal volunteers treated with effervescent aspirin alone ($t = 0.53$, $P > 0.6$), or from the levels obtained in the same patients when headache-free (Control group B) (correl $t = 1.60, P > 0.2$).

Plasma salicylate levels after 60 min

As with the results at 30 min the distribution of the plasma salicylate levels after 60 min have been compared (Table 4).

Treatment with effervescent aspirin alone

Again, the plasma salicylate levels during migraine attacks (Group A) were lower than those found in normal volunteers (Group C) ($t = 2.45$, $P < 0.01$, 1 tailed) and also lower than those found in the same patients when headache-free (Control group A) (correl $t = 2.20$, $P < 0.05$, 1 tailed). However there was no significant difference between the levels obtained in the headache-free patients and those found in normal volunteers ($t = 0.92$, $P > 0.10$).

Treatment with effervescent aspirin after intramuscular metoclopramide

As would be expected from the 30 min results, the patients who were treated with metochlopramide

Table 3 Plasma salicylate levels in fasting subjects 30 min after ingestion of effervescent aspirin (900 mg)

Group	*Number of subjects*	*Mean plasma salicylate level (mg% ± s.e. mean)*
C	20	7.88 ± 0.40
A	20	4.77 ± 0.43
Control A	13	7.04 ± 0.64
B	20	7.50 ± 0.58
Control B	16	8.27 ± 0.71

Table 4 Plasma salicylate levels in fasting subjects 60 min after ingestion of effervescent aspirin (900 mg)

Group	*Number of subjects*	*Mean plasma salicylate level (mg% ± s.e. mean)*
C	20	8.15 ± 0.29
A	18	6.62 ± 0.55
Control A	9	7.59 ± 0.92
B	19	8.54 ± 0.43
Control B	15	8.36 ± 0.54

(Group B) achieved plasma salicylate levels during the attack at 60 min which were not significantly different from those in normal subjects (Group C) after effervescent aspirin alone ($t = 0.76$, $P > 0.30$) or from themselves when headache free (Control group B) (correl $t = 0.76$, $P > 0.40$). However, the salicylate levels after metoclopramide during migraine attacks were higher than those after effervescent aspirin alone during attacks ($t = 2.75$, $P < 0.01$, 1 tailed).

When metoclopramide was given to migraine patients who were headache-free the plasma salicylate levels achieved at both times were not significantly different from those achieved by headache-free migraine patients given effervescent aspirin alone ($P > 0.2$ in all cases).

Discussion

For a given drug formulation the rate of absorption from the gastro-intestinal tract in fasting individuals could be modified by alterations in mucosal blood flow, digestive secretions and alimentary motility (Smythe, 1964). The impairment of drug absorption during a migraine attack could be related to changes in all these factors but there is at present no technique suitable for measurement of mucosal blood flow in man (Bynum & Jacobson, 1971) and no techniques have been described for the measurement of digestive secretions during drug absorption studies. However, radiological observations during migraine have demonstrated reduced gastric motility (Kaufman & Levine, 1936; Kreel, 1973) and metoclopramide is known to promote gastro-intestinal motility and gastric emptying in man (Bhaduri & Bradley, 1969; Connell & George, 1969; Howarth, Cockel & Hawkins, 1967; Johnson, 1973; Howard & Sharp, 1973; Nimmo *et al.*, 1973). In addition it is known that metoclopramide has no effect on gastric acid secretion (Connell & George, 1969) and no central haemodynamic effects (Thorburn & Sowton, 1973) although its effects on mucosal blood flow have not been reported. The use of metoclopramide, therefore, offers a clinically acceptable pharmacological approach to the study of gastro-intestinal activity and of drug absorption in migraine.

Since the present investigation employed an inter-group study it is important to establish that the two groups of patients are comparable before drawing any conclusions. In fact the two groups differ slightly in age, sex and weight distributions. Little is known about changes in drug absorption with age in adults but no clinically significant alterations have been observed in geriatric patients (Hall, 1973) and it, therefore, seems unlikely that the small age differences observed here would have any effect. Blood salicylate levels demonstrate an inverse correlation with body weight in males (Cummings & Martin, 1964) and the author's observations in female subjects suggest a similar effect although the overall mg/kg levels were lower (Volans, 1974a). These findings would suggest that the plasma salicylate levels in group B were likely to be higher than those in Group A but in practice, whilst the results differed between the groups in the acute attack, there was no significant difference between the control observations in the two groups. In contrast to the differences in age, sex and weight, it is important that the two groups were experiencing symptoms of a similar severity at the time of study as it has been shown that impairment of absorption during migraine correlates with the severity of the symptoms although not with their duration (Volans, 1974b).

In the patients treated with effervescent aspirin alone there is seen to be impairment of the rate of absorption during migraine attacks. Retention of aspirin within the stomach should not completely inhibit its absorption since this drug has physico-chemical properties which would predict absorption from that part of the gut. However, aspirin absorption from the stomach is known to be a relatively inefficient process (Riegelman, 1973) and most of the drug is usually absorbed from the small intestine (Martin, 1964).

When the plasma salicylate levels in the two groups were compared, metoclopramide was seen to improve the absorption of effervescent aspirin during migraine relative to the absorption in patients treated with effervescent aspirin alone. This improvement was such that the levels achieved were not significantly different from those achieved in normal volunteers after effervescent aspirin alone. However, when given outside of a migraine attack metoclopramide did not increase the levels of plasma salicylate beyond those found after effervescent aspirin alone in normal individuals or in other migraine subjects who were headache free. This is consistent with the findings of Kendall (1973) that metoclopramide is capable of improving the absorption of xylose in subjects whose gastro-intestinal motility is reduced but that it does not alter or even reduces absorption when motility is normal before administration of metoclopramide. Likewise, the findings do not conflict with those of Nimmo and his colleagues (1973) since their subjects were selected because they were known to be consistently slow absorbers of paracetamol.

The mechanism of action of metoclopramide upon gastro-intestinal motility is not fully understood, partly because the underlying mech-

anisms of peristalsis are not fully explained. However, there is evidence in animals, *in vivo*, of effects upon local cholinergic mechanisms in the gut wall (Jacoby & Brodie, 1971) and *in vitro* studies suggest that the drug may interfere with tryptaminergic mechanisms which are involved in the maintenance and control of peristalsis (Birtley & Baines, 1973). These mechanisms alone are capable of explaining the improvement of drug absorption after metoclopramide in migraine whilst the concurrent reduction in nausea is probably due to a combination of the effect upon gastro-intestinal motility together with a central depressant action upon the chemoreceptor trigger centre (Takaori, Nakai, Matsuoka, Sasa, Fukuda & Shimamoto, 1968).

The finding of lower plasma salicylate levels during a migraine attack could be explained by the occurrence of an increased volume of distribution of the drug and it is known that fluid retention is associated with migraine in a small percentage of patients (Sacks, 1970). However, metoclopramide has no known diuretic action and it is unlikely that this drug would otherwise be capable of reversing a change in the volume of distribution of aspirin. Furthermore, although we are unable to carry out estimations of total body water in the clinic, we have been able to weigh accurately patients during attacks and when headache-free and no significant difference has been detected.

Further investigations into the absorption of drugs in migraine are being made to determine if the effect of parenteral metoclopramide occurs when the drug is taken by mouth or as a suppository. In addition it is hoped to study the effects of phenothiazine and anti-histamine anti-emetics, especially since McGarry (1973) reported that phenothiazines given during labour suppressed the symptoms of nausea and vomiting without promoting gastric emptying. There have been several reports of the successful use of metoclopramide in migraine both as a symptomatic measure (Grivaux & Lamotte-Barrillon, 1964; Wilkinson, Neylan & Rowsell, 1973; Robinson, 1973) and for prophylaxis (Bertrand, 1966; Cachin, May & Pergola, 1966). The present report was not directly concerned with the response to treatment but it may be noted that a favourable response was recorded in most patients. The observations on the use of metoclopramide made during this study will form part of a separate communication.

The clinical importance of this study may be found in its implications for treatment. Impairment of drug absorption may be a cause of therapeutic failure in migraine and this must be taken into account in the choice of preparations used. For any oral drug the most rapidly absorbable preparation should be used and if this is not fully effective metoclopramide may be used to promote absorption and to suppress gastro-intestinal symptoms.

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