which sets the disease process in motion in the susceptible patient (Lehr, 1972).

In each of our three cases a hypersensitivity vasculitis seemed to develop within seven days of starting alclofenac therapy. This suggests therefore that alclofenac should be included in the list of drugs known to be capable in initiating a vasculitis. Prompt withdrawal of the drug at the first sign of reaction may reduce the risk of inducing a chronic vascular disorder.

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Absorption of Effervescent Aspirin during Migraine

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Summary

The absorption of effervescent aspirin was studied in 42 patients during acute attacks of migraine. When compared with normal controls and with themselves between attacks 19 out of the 42 patients showed impairment of absorption. Impairment of absorption seemed to correlate with the severity of the headache and the gastrointestinal symptoms at the time of treatment but not with the duration of the attack or with the type of migraine. This study probably underestimated the prevalence of impairment of absorption in migraine attacks, and it is concluded that the treatment of acute migraine symptoms by oral drugs should use those formulations which are rapidly absorbed under normal conditions.

Introduction

Gastrointestinal symptoms have been recognized as a major characteristic of migraine since the second century A.D. (Crichtley, 1967) and they remain one of the current clinical criteria for diagnosis of migraine (World Federation of Neurology, 1970). It has also been suggested that the gastrointestinal disturbances in migraine could impair the absorption of drugs given orally as treatment during the acute attack (Nimmo,

1973), and to overcome this many of the drugs used in migraine may be administered other than as oral preparations (Wilkinson, 1971). Clinical trials on the administration of ergotamine tartrate (Graham et al., 1960; Sutherland and Eadie, 1961) provide evidence that the efficacy of treatment is related to the route of administration. The relatively poor efficacy of the oral route could be due to impaired absorption of the drug by the gastrointestinal tract. There are at present no methods capable of measuring ergotamine tartrate blood levels from therapeutic doses, however, and none of the studies have been directly concerned with assessment of gastrointestinal symptoms and their relationship to absorption of the drug. This paper reports the gastrointestinal symptoms and the absorption of effervescent aspirin in a group of patients treated during acute migraine attacks.

Patients and Methods

Forty-two patients suffering from acute headaches were studied at the Princess Margaret Migraine Clinic. All gave informed consent to the investigation. The diagnoses were made according to the criteria of the World Federation of Neurology (1970) and were confirmed by at least one other member of the clinic medical staff. Patients were not included in the study if there was any evidence of other illness, any history of dyspepsia, or if analgesic drugs had been taken within 24 hours before arrival at the clinic. Twenty control subjects were taken from the hospital medical, nursing, and administrative staffs. None had a history of headaches or gastrointestinal disease. The controls were not deliberately matched with the patients but the groups were of similar age, weight, and sex distribution (table I).

Aspirin was given as a single dose of three tablets containing a total of 900 mg acetylsalicylic acid in an effervescent base equivalent to 1,800 mg sodium bicarbonate and 1,200 mg anhydrous citric acid (Claradin) dissolved in 150 ml of water.

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TABLE I—Comparison between Groups of Age, Sex, and Weight

	No. of Subjects	Sex		Mean Age ($\pm$ S.D.) (Years)	Mean Weight ($\pm$ S.D.) (kg)
		M.	F.		
Controls ..	20	11	9	29.3 $\pm$ 8.1	66.9 $\pm$ 10.3
Migraine group 1 ..	22	11	11	36.1 $\pm$ 12.7	67.5 $\pm$ 13.1
Migraine group 2 ..	20	6	14	37.4 $\pm$ 11.4	65.7 $\pm$ 8.7
Total migraine group ..	42	17	25	36.8 $\pm$ 12.1	66.6 $\pm$ 10.9

Blood was collected into heparinized tubes via an indwelling venous catheter or by simple venepuncture. Plasma samples were deep frozen and stored for up to two weeks before analysis. After thawing plasma salicylic acid levels were estimated by the method of Saltzman (1948) with an Aminco-Bowman spectrofluorimeter. A control blood sample was collected by venepuncture in all cases before administration of the aspirin.

Control Subjects.—Preliminary studies in eight control subjects were used to establish the absorption profile for the aspirin preparation and to determine the effects of food and exercise upon this absorption (Volans, 1974). The peak salicylate levels were achieved within 60 minutes, and non-fasting subjects showed reduced absorption which was attenuated with time until after 60 minutes when the plasma levels were similar (see fig.). Moderate activity resulted in no significant changes in absorption compared with that at rest and there was no interaction between the effects of resting and non-resting and fasting and non-fasting on absorption. From these observations the control studies were extended to 20 subjects. Blood samples were collected at 30 and 60 minutes after ingestion of aspirin in the fasting state and after a standard breakfast. The subjects continued with their normal activities in the laboratory, clinic, or office.

Mean plasma salicylate levels in eight subjects, fasting (O) and non-fasting (●), after ingestion of 900 mg aspirin from an effervescent formulation. (Reproduced by permission of the British Journal of Clinical Pharmacology.)

Patients.—Since the patients came into the clinic as emergencies it was not possible to control their food intake or their exercise before the study. The recorded history, therefore, included details of the duration of the attack before treatment and of the most recent food intake. Patients who had taken no food for more than four hours were considered to be fasting and the remainder were considered to be non-fasting. The severity of the headache and the gastrointestinal symptoms at the time of treatment were assessed by asking the patient

whether the symptoms were slight, moderate, or severe as compared with his or her own experience of migraine attacks. During the study the patient 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 drug absorption (Martin 1971; Truitt and Morgan, 1964). Blood samples were collected at 30 minutes in all cases and also at 60 minutes in later studies. Some of the patients were studied also when they were headache free but under the same conditions.

Results

Comparison of Groups.—Since it was desirable to keep venepunctures to a minimum in patients suffering from migraine the earlier patients were studied at 30 minutes only after an ingestion of aspirin (migraine group 1; table I). When it became clear that some patients showed impaired absorption it was considered justifiable to extend the studies to 60 minutes in subsequent patients (migraine group 2). As this was the only criterion applied in the separation into two groups and since table I shows similar age and weight distributions in the two migraine groups the results in the migraine patients were combined in the following analysis.

Results in Fasting Subjects.—Thirty-five of the 42 patients were fasting at the time of the acute headache. The mean plasma salicylate levels achieved by these patients at 30 and 60 minutes after ingestion of effervescent aspirin with the levels achieved by the normal controls and by the patients who were studied when headache free are shown in table II. After 30 minutes the plasma salicylate levels during migraine were significantly lower than those found in normal controls ($t = 4.4$, $P < 0.001$). Taking as the criterion of poor absorption the lower 2½% confidence limit of plasma salicylate levels in normal controls—that is, (4.42 mg/100 ml), 16 of the 35 patients were found to be “poor absorbers” during the migraine attack. Of these poor absorbers 14 were retested when headache-free, at which time the salicylate levels achieved were not significantly different from those found in normal controls ($t = 1.09$, $P > 0.1$). Absorption in these patients was, however, significantly impaired during the migraine attack (correlated $t = 10.00$, $P < 0.0001$). After 60 minutes the plasma salicylate levels were studied in 18 patients. Again, the plasma salicylate levels achieved during migraine were significantly lower than those found in fasting normal controls ($t = 3.02$, $P < 0.001$). Nine of the patients who were poor absorbers at 30 minutes were retested when headache-free at 60 minutes. On that occasion the plasma salicylate levels again resembled those found in the normal controls ($t = 0.92$, $P > 0.1$) though the patients had continued to show significant impairment of absorption during the migraine attack (correlated $t = 2.20$, $P < 0.05$).

Results in Non-fasting Patients.—Only seven out of the 42 migraine patients were non-fasting at the time of investigation. This small number was considered insufficient for detailed statistical analysis, but when the 30-minute plasma salicylate levels were compared with the results from non-fasting normal controls (mean plasma salicylate ($\pm$ S.E.) 5.18 $\pm$ 0.37 mg/100 ml) three patients had plasma levels below the 2½% confidence limits (mean level for the three patients 1.64 mg/100 ml). When

TABLE II—Mean Plasma Salicylate Levels ($\pm$ S.E.) in Fasting Subjects after Ingestion of 900 mg Effervescent Aspirin

	Migraine Patients during Attack	Controls	Patient Controls
After 30 Minutes			
No. of Subjects	35	20	14
Plasma salicylate (mg/100 ml)	4.97 $\pm$ 0.52	7.88 $\pm$ 0.40	7.11 $\pm$ 0.59
After 60 Minutes			
No. of Subjects	18	20	9
Plasma salicylate (mg/100 ml)	6.63 $\pm$ 0.30	8.15 $\pm$ 0.29	7.59 $\pm$ 0.53

TABLE III—Relationship of Sex, Diagnosis, and Migraine Symptoms to Quality of Absorption after 30 Minutes

	Sex		Diagnosis		Severity of Headache			Severity of Nausea				Vomiting		
	Male	Female	Common Migraine	Classical Migraine	Intense	Moderate	Slight	Intense	Moderate	Slight	None	<4 hr before Test	During Test	After Test
No. of poor absorbers ..	8	11	10	9	9	10	0	4	6	4	5	5	0	3
No. of good absorbers ..	9	14	12	11	4	11	8	2	1	10	10	2	1	0
Total ..	17	25	22	20	13	21	8	6	7	14	15	7	1	3
Grand Total ..	42		42		42			42				11		

these patients were retested under controlled conditions, which included the taking of identical meals, they all achieved 30-minute plasma salicylate levels well within the normal range (mean for the three patients 8.30 mg/100 ml).

Factors Affecting Absorption during Migraine Attacks.—From these results it can be seen that 19 out of 42 patients studied during migraine attacks showed absorption of effervescent aspirin which was below the 2½% confidence limit for normal subjects. This impairment of absorption was not shown, however, when the same subjects were retested under controlled headache-free conditions. To investigate the relationship of the clinical features to this impairment of absorption a number of other indices were assessed during the attack (table III). The poor absorbers were distributed almost equally between the two sexes and between cases of classical and common migraine. Poor absorption was found more frequently with increasing severity of headache (Kolmogorov-Smirnov two sample test $D_{\max} = 0.348$; $P < 0.05$ for one-tailed test). The association of increasing severity of nausea with poor absorption was also found to be significant (Kolmogorov-Smirnov two sample test $D_{\max} = 0.396$; $P < 0.03$ for one-tailed test). No patients with "slight headache" showed poor absorption while absorption was impaired in five out of 15 patients who denied feelings of nausea. Only 11 out of 42 patients vomited during the attacks which were studied and only one patient vomited during the absorption test. This subject must have retained most of the aspirin since normal salicylate levels were achieved. Of the remaining 10 subjects all vomited within four hours before the test and one hour after its completion. Eight of these were poor absorbers. All the cases in which absorption was impaired occurred during the first 15 hours of the attack, but there was no obvious correlation between the duration of the attack and the plasma salicylate level after 30 minutes (table IV).

TABLE IV—Relationship between Duration of Symptoms at Time of Treatment and Quality of Absorption after 30 Minutes. Results are Numbers of Patients

Duration of Attack	Poor Absorbers	Good Absorbers	Total
0-3 hr	8	11	19
-6 hr	7	5	12
-24 hr	4	3	7
>24 hr	0	4	4
Total ..	19	23	42

Response to Treatment with Effervescent Aspirin.—The response to treatment in these patients was not a direct concern of the present study. Nevertheless, preliminary examination of the clinical records showed that two-thirds of the patients improved without additional treatment. The patients who showed impaired absorption were more likely to have received further treatment than those who showed normal absorption. Furthermore, though the time taken to respond to treatment was probably influenced by many factors it does seem that the poor absorbers were slower to recover. It is hoped that full analysis of these and other records will provide information on the response to treatment, which will be discussed as a separate communication.

Discussion

Though gastrointestinal symptoms are recognized as an important feature of a migraine attack it is relatively unusual to find precise information about the incidence of such symptoms since most studies have been, not surprisingly, more concerned with the headache and its associated neurological symptoms. Lance and Anthony (1966), however, reported a series of 500 migraine patients referred to an outpatient clinic in which greater attention was paid to the gastrointestinal disturbance. They found that 16% experienced nausea, vomiting, and diarrhoea; 59% reported nausea and vomiting, and 18% noticed nausea only.

The patients included in the present study were attending as emergencies rather than for routine consultations and it was thought likely that the attacks studied would not represent the most severe attacks experienced by the same patients since at such times many feel unable to travel from their home or their work to the clinic. Evidence for this is seen in table V where it is shown that this group of patients has a similar overall incidence of gastrointestinal symptoms to that described by Lance and Anthony, but the incidence of symptoms at the time of the study was reduced by almost one-third. In spite of the tendency to under-represent the incidence of gastrointestinal symptoms in this study it was found that about 45% of the patients showed impairment of the rate of absorption of a drug which is normally rapidly absorbed. Since it was also shown that the same patients showed normal absorption when free from migraine symptoms it may be deduced that the impairment of absorption was a feature of the migraine attack.

TABLE V—Incidence of Gastrointestinal Symptoms in Migraine Attacks where Absorption was Studied compared with Incidence of Same Symptoms over all Attacks experienced by 42 Patients. Results are Percentages of Patients

Symptom	This Attack	All Attacks
Nausea, Vomiting, and Diarrhoea ..	12%	21%
Nausea and Vomiting	14%	48%
Nausea Alone	38%	26%
Total gastrointestinal symptoms	64%	95%

Many of the symptoms of a migraine attack could be related to increased activity of the sympathetic nervous system (Sachs, 1970). Under such circumstances gastrointestinal motility would be reduced, and evidence for this has been found in radiological studies on patients suffering from acute migraine where delayed gastric emptying was shown, associated with either gastric dilatation (Kaufman and Levine, 1936) or prolonged gastric contraction (Kreel, 1973). Repeat studies when the patients were free from headache showed normally functioning stomachs.

Reduction of the rate of gastric emptying reduces the rate of paracetamol absorption (Nimmo *et al.*, 1973), and though aspirin is absorbed from the stomach this route of absorption is relatively inefficient, most of the drug being absorbed from the small intestine (Martin, 1964). It is, therefore, most likely that delayed gastric emptying is the cause

of the decreased absorption of aspirin which has been shown during the migraine attack. It is hoped to provide further evidence for this mechanism by absorption studies which are in progress to determine whether metoclopramide can overcome the decreased aspirin absorption during migraine attacks.

The finding of impaired gastrointestinal absorption of drugs during migraine attacks has a definite clinical significance. Most of the drugs used in acute migraine are less readily absorbed in normal individuals than effervescent aspirin and absorption of such drugs may be reduced to an even greater degree. Many migraine patients report that aspirin and paracetamol do not relieve their headaches. Since different formulations of aspirin (Martin, 1971) and paracetamol (Hedges and Kaye, 1973; Hedges *et al.*, 1974) have very different rates of absorption the failure of response in migraine may often be related to the use of formulations which are slowly absorbed even in normal circumstances. To take account of impairment of drug absorption it is recommended that in the treatment of migraine preparations should be used which are rapidly absorbed or which bypass the gastrointestinal tract. In addition, the gastrointestinal symptoms should be noted and, if necessary, treated with antiemetics.

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Host Resistance in Relation to Survival in Breast Cancer

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Summary

The degree of lymphocytic infiltration in and around breast tumours together with sinus histiocytosis and follicular hyperplasia in regional lymph nodes has been studied in 310 cases of breast cancer treated with standard radical mastectomy. The presence of these features was regarded as evidence of host resistance against the tumour and made possible the division of patients into three classes—no or poor reaction, good reaction, and strong reaction. The grading was shown to have a close correlation with prognosis. The relationship between host defensive factor grading and malignancy, nodal metastases, and survival was also examined. The results support the hypothesis that prognosis in breast cancer is closely related to a histological picture of cell-mediated immunity against the tumour.

Introduction

Among the factors thought to influence survival in cases of breast cancer treated surgically lymphocytic infiltration in and around the tumour and follicular hyperplasia and sinus histiocytosis in regional lymph nodes have received particular attention. These features have been regarded as evidence of an immunological response to the tumour but whether they correlate with a good prognosis is still open to controversy.

After the report of Foote and Stewart (1946) on lymphocytic infiltration of the stroma of medullary carcinoma the study was extended to regional lymph nodes (Black *et al.*, 1953; Anastasiades and Pryce, 1966; Cutler *et al.*, 1969; Wernicke, 1972), and a lymphocytic infiltration was found in all histological types of breast cancer (Hamlin, 1968), particularly medullary carcinoma (Bloom *et al.*, 1970).

Hamlin (1968) reviewed 272 cases of breast cancer and found a close correlation between prognosis and the intensity of lymphocytic infiltration around the tumour. In a study of 1,411 cases of breast cancer followed for 20 years Bloom *et al.* (1970) showed that the highly malignant medullary carcinoma carries a remarkably good prognosis when there is increased lymphocytic infiltration around the tumour. Recently increased benign lymphoid tissue in the lymph nodes of the apex of the axilla has been described as a favourable prognostic sign (Berg *et al.*, 1973). Other workers, however, have found that sinus histiocytosis (Kister *et al.*, 1969), follicular hyperplasia (Moore *et al.*, 1960), and lymphocytic infiltration (Morrison *et al.*, 1973) do not correlate with prognosis in breast cancer.

We have already made a preliminary report (Di Paola *et al.*, 1973) of our findings in a limited number of cases of a relation-

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