ment of thyroid-hormone synthesis by iodine-125 therapy may produce an increased thyrotophin stimulus on mitotically competent cells—a situation which favours tumour development in the thyroid. In animals Gross et al. found that iodine-125 induced more thyroid tumours than equivalent microcurie doses of iodine-131. We are, however, unaware of any reports of thyroid malignancy following iodine-125 therapy in man.

In the perithyroidal region, the relative effects of iodine-125 and iodine-131 are very different from those found in the thyroid. "The radiation doses incurred by iodine-125 and iodine-131 are very different from those of 125I therapy than they are with 131I therapy. Thus . . . post cricoid cancer might arise". Greig

It is impossible to state categorically whether or not the laryngeal tumour in our patient was caused by her radiiodine therapy. There are, however, certain disturbing features. The time between administration of the iodine-125 and presentation of the tumour (8 years) is within the range reported for the appearance of thyroid and extrathyroidal tumours after external irradiation of the neck. There was evidence of radiation damage around the tumour and the tumour itself showed striking nuclear pleomorphism, possibly related to radiation. Moreover, the tumour is of a type which only rarely arises spontaneously in the larynx.

The evidence suggests a possible link between iodine-125 and the development of malignancy in this patient. The case emphasises the need for careful long-term follow-up of patients treated with iodine-125 and reminds us that, because of radiobiological differences, the apparent safety of iodine-131 therapy for thyrotoxicosis may not apply to iodine-125.

REFERENCES

Preliminary Communications

ASPIRIN PROPHYLAXIS IN MIGRAINE

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Summary A prospective double-blind trial of aspirin prophylaxis demonstrated a reduction of more than 50% in headache frequency in 9 of 12 migraine patients. Response to aspirin did not correlate with age, duration of headache history, family history, or platelet ultrastructure. There is some evidence that response to aspirin is associated with raised platelet aggregation. This pilot study indicates that aspirin is effective in migraine prophylaxis.

INTRODUCTION

The head pain which is the most prominent feature of migraine results from vasodilatation of the cephalic circulation—primarily branches of the external carotid artery. The mechanism of vasodilatation in migraine was originally attributed to a fall in plasma-serotonin, an agent which directly affects smooth-muscle tone. Recent evidence suggests that vascular smooth-muscle tone may be diminished by a number of other factors and that these factors may also participate in the abnormal vasodilatation of migraine.

Any agent that directly or indirectly affects smooth muscle of the cephalic circulation may be an effective agent in migraine. This report describes our experience with aspirin in migraine prophylaxis. Aspirin is a potent inhibitor of prostaglandin synthesis and platelet aggregation. Since increased platelet aggregation and subsequent diminution in platelet-serotonin are features of many migraine attacks, an agent which reduces platelet aggregation might be expected to produce clinical improvement of migraine.

PATIENTS AND METHODS

Patients

12 adult migraine patients with paroxysmal, throbbing, unilateral or bilateral head pain took part in the study. Headaches were associated with various combinations of photophobia, nausea, vomiting, visual symptoms, focal neurological symptoms, and a family history of migraine. All patients had more than one migraine headache per month. No patient with ophthalmoplegic, hemiplegic, or basilar-artery migraine was included.

Before the study, all patients had hematological assessment, including hematocrit, hemoglobin, white-blood-cell counts (total and differential), and platelet-count. All patients were examined by one of the authors. Informed, witnessed consent was obtained from all participants. Abortive therapy for migraine, but no other prophylaxis, was permitted. None of the female patients was receiving hormonal therapy (e.g., oral contraceptives) during the study. Cigarettes and alcohol were permitted but not encouraged.

Study Design

A double-blind crossover study of twice-daily aspirin (U.S.P., 650 mg) and placebo was carried out. Each agent was studied for 3 consecutive months in each patient. Patients were seen at monthly intervals by one of the authors. A monthly calendar and a month's supply of capsules were pro-
vided at each visit. Patients kept a record of their headaches, indicating on the calendar the day of attack, qualitative assessment of the headache, and abortive therapy used. Calendars were collected at each visit. Blood measurements were made at each visit. The data were collected by individuals not directly involved in the study, and all data were reviewed after completion of the study.

**Clinical Studies**

Platelet aggregation was measured and platelet ultrastructure assessed in 7 of the patients for attempted correlation with clinical response to aspirin.

The ultrastructural appearance of platelets was examined during each treatment period. A platelet pellet was prepared from E.D.T.A.-anticoagulated blood with a standard technique. All samples were examined by a consultant who had no knowledge of the treatment. All photographs were studied after completion of the project, and the appearances of platelets during treatment and placebo periods was compared.

Platelet aggregation was determined by the optical-density method using a single-channel aggregometer. We used 0-1% adrenaline at a concentration of 1-0 µg/ml and adenosine diphosphate 2-0 µg/mg as aggregating agents. All determinations were done in duplicate. The slope of a line drawn from the start of the aggregation reaction to a point half way to the maximal rise for adrenaline was taken as the rate of aggregation.

**Statistical Methods**

The only statistical method thought to be reliable for the small number of patients was the paired t-test. All calculations were done at the Statistical Research Laboratory of the University of Michigan Computing Center with preconstructed programs.

**RESULTS**

The results are summarised in the accompanying table. The age-range was 18 to 53 years. 6 patients (50%) had a family history of migraine. 3 patients (25%) had classical migraine and 9 (75%) had common migraine. The cohort included 5 women and 7 men. The duration of migraine symptoms ranged from 3 to 40 years.

A positive clinical response to aspirin prophylaxis was defined as a greater than 50% reduction in headache frequency over 3 months. 9 patients (75%) demonstrated such a response. With the paired t-test, the significance level is \( t = 5.78 \) for 11 degrees of freedom, \( p < 0.0001 \). Individual headaches during aspirin therapy were subjectively judged to be less intense in 4 of the responders. No significance can be attached to this, however, since all patients were permitted to use abortive therapy once a migraine attack had started. Amounts of medication required to abort migraine during placebo and aspirin periods were similar. 7 patients started on placebo and 5 on aspirin: no order effect was seen.

The 3 patients with classical migraine and 6 of the 9 patients with common migraine responded to aspirin. The 3 non-responders were therefore patients with common migraine. None of the patients with classical migraine had partial symptoms (e.g., visual disturbances) during aspirin treatment. All 5 women responded to aspirin, whereas only 4 of the 7 men responded.

Side-effects were slight and were restricted to symptoms of mild gastritis in 3 patients, unaccompanied by melena, haematemesis, or a change in hematocrit. In 2 of the 3 patients symptoms subsided with antacid administration. 1 patient withdrew from the study after 4 months because of gastritis symptoms. This patient had no headaches during the month on aspirin, compared with 4 to 6 per month during the 3-month placebo period. He was included in the analysis as an aspirin responder because of the dramatic change in headache frequency.

Platelets from 7 migraine patients (patients 1–7, see table) were examined by electron microscopy. No sample was obtained during a headache. Samples were obtained from all 7 patients during both the placebo and aspirin treatment periods. All platelets examined were normal, containing dense granules that were normal in configuration, density, and distribution. Many platelets contained small clumps of glycogen. No differences were detected in sex, age, or duration of symptoms.

The same 7 patients also had platelet-aggregation determinations before the study. 5 of these 7 patients were aspirin responders, and 3 of these 5 had hyperaggregable platelets (see table). 1 of the 2 non-responders also had hyperaggregable platelets.

**DISCUSSION**

This study demonstrates the usefulness of aspirin in the prophylaxis of migraine. The 75% reduction in headache frequency compares favourably with responses to other prophylactic agents. Since a placebo response has been demonstrated in 20–40% of patients, we decided, after discussion with statisticians and a review of the literature, that a significant result should exceed a response-rate of 50%. The cohort size and

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<th>Patient no.</th>
<th>Age</th>
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*Hyperaggregable (control=27-3 mm/min).*
duration of study are comparable to those in other reported studies.

In our study, all patients with classical migraine and all female patients responded to aspirin. Although this same trend has been noted in a clinical trial of propranolol as migraine prophylaxis, the cohort size in our study is too small to allow firm conclusions. In an evaluation of the effects of aspirin on deep-vein thrombosis and cerebral vascular disease, clinical response was significant only for men. Since all our female patients were premenopausal, age and sex selectivity may be in part related to hormonal factors.

The absence of correlation of ultrastructural morphology with migraine type and clinical response agrees with the studies of Grammeltvedt et al. In their study, the total platelet dense-body number was similar during and between migraine attacks. Although it is generally agreed that platelet serotonin is contained within the dense bodies, the ultrastructural appearance probably reflects calcium content rather than serotonin. Thus, normal platelet appearance does not exclude an abnormality of function. We are unaware of ultrastructural correlates of increased platelet release of serotonin during migraine to account for the drop in plasma-serotonin. Furthermore, there is little evidence of platelet sequestration during migraine to account for the decline in plasma-serotonin. Aspirin may therefore mimic the "impaired release" platelet syndrome without ultrastructural accompaniment and remain consistent with our inability to demonstrate any abnormality.

There is evidence that in migraine normal platelets aggregate abnormally. Platelets from migraine patients are hyperaggregable in vitro. They may be more aggregable before and during an attack as well as in headache-free periods. Blood taken from a migraine patient during an attack will cause platelet aggregation in blood drawn during a headache-free period. With the increase in platelet aggregation platelet serotonin is released in a way similar to its release after tissue injury. No correlation was found, however, between aggregation and the severity of the attack, associated neurological signs, or headache subtype. No previous study has correlated medication effect and platelet aggregation in migraine. This pilot study demonstrates trends that now should be evaluated in more definitive tests. Specifically, the likelihood that migraine patients with hyperaggregable platelets are more likely to respond to aspirin prophylaxis, as suggested by this study, is now being examined (J. R. Saper and J. S. Penner, unpublished).

Aspirin inhibits platelet aggregation and secretion of platelet factors (such as serotonin) by preventing synthesis of prostaglandin thromboxane A₂. There is no evidence that human platelets become refractory to the inhibitory effects of aspirin after long-term administration. If there is some inherent abnormality of platelet function in migraine, aspirin and similar preparations should be effective. Indomethacin is unsuccessful in migraine. Although similar to aspirin in being a non-steroidal anti-inflammatory drug, its effect on platelet aggregation is brief. The observed effect of aspirin on headache frequency is unlikely to be due to the drug's analgesic effect alone, since indomethacin and paracetamol (acetaminophen), similar to aspirin in analgesic potency, are ineffective in migraine prophylaxis.

Propranolol and methysergide are ineffective analgesics but are effective in migraine prophylaxis. A specific prostaglandin inhibitor, flufenamic acid, will abort a migraine attack but is ineffective in prophylaxis. Aspirin should not be used prophylactically in patients with peptic ulcer, aspirin sensitivity, or platelet disorders. Mild dyspepsia can be managed with antacid therapy, but persistent gastrointestinal complaints and/or the appearance of blood at the orifices are indications for discontinuation of the drug.

We thank Ms Mary Rasmussen and Dr Theodore Beals of the VA Hospital, Ann Arbor, Michigan, for hematomatological and electron-microscopic studies. We also thank Lee Vahlsing, M.s., for help with the statistics, and Ms Suzanne Lank for secretarial assistance.

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REFERENCES


DOES ETHANOL INTOXICATION PROMOTE BRAIN INFARCTION IN YOUNG ADULTS?

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Summary 76 consecutive patients aged under 40 with ischemic brain infarction verified by carotid angiography and/or serial brain scanning were studied. In at least 15 cases (20%) the onset of symptoms was preceded within 24 hours by a bout of alcohol drinking. Ethanol-related cases comprised 40%, 25%, and 13% of the patients in the age-groups 16–19, 20–29, and 30–39 years, respectively. Ethanol intoxication preceding the stroke was 2–3 times as common in