Discussion

Our findings of increased sensitivity to the tyramine-dose/pressor response test among migraine sufferers parallels closely our findings in depressed patients.¹⁵ An association between migraine and depression has been postulated by several investigators.^{16, 17} Both migraine^{1, 3, 4, 7} and depression^{18, 19} are reported to be associated with altered monoamine metabolism. Both conditions are clinically prevalent among women and have some association with the menstrual cycle. There is as yet, however, no conclusive evidence of a direct association between these two conditions. Increased tyramine sensitivity among migraine sufferers may be due to one or more factors—namely, an increase in adrenergic-receptor sensitivity; a decrease in monoamine oxidase activity; increased uptake of tyramine into noradrenaline-containing neurones; increased intraneuronal stores of noradrenaline and increased release of noradrenaline, or both. Direct evidence to confirm the validity of these factors is absent or conflicting. The observation of decreased platelet monoamine oxidase activity among migraine sufferers, however, appears to be consistent with our findings.

The apparent induction of migraine by intravenous tyramine does not agree with the results reported after oral tyramine.⁶ Although we did not give the patients a placebo injection, no suggestion was made that the injection would induce headaches or migraine. Moreover, the appreciable reduction in the incidence of post-tyramine migraine on indoramin (given under double-blind conditions alternately with placebo) suggests that pharmacological rather than psychological precipitants were responsible for the post-injection migraine.

Our results show that either excessive release of noradrenaline or sensitivity to it may be a factor in some patients with migraine. We must emphasise that migraine may well be heterogeneous

and there may be a subgroup of migraine sufferers who are sensitive to tyramine. The reduced incidence of post-tyramine migraine among patients on indoramin suggests that it may be an effective prophylactic agent. The intravenous tyramine test may be a valuable method of selecting patients who will respond to an alpha-adrenergic blocking agent such as indoramin.

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SIDE EFFECTS OF DRUGS

Peripheral neuropathy: a side effect of sulphones

To date there have been references to very few cases of peripheral neuropathy as a side effect of sulphone treatment. Most cases have been motor in type,^{1, 2} but cases of sensory neuropathy^{3, 4} have also been described. During the past year two patients with peripheral neuropathy have been seen in our clinic, which seems to indicate that neuropathy as a side effect of sulphone treatment is not so rare as was once thought. The first patient⁴ developed symptoms of the distal extremity. The second patient is described here.

Case report

A 46-year-old man had dermatitis herpetiformis for 28 years. Since 1954 he was treated with sulfapyridine, but for unknown reasons he was placed on a regimen of sulfoxone sodium 0.66-0.99 g/day, when needed. On average he received this medication two or three days a week. During the past year he has had the impression that his thumbs were sleeping during shorter or longer periods of time, irrespective of what he was doing or of other external circumstances. Sometimes the sensation became stronger and spread out over the hands to the ulnar side, but he did not notice any weakness in the affected hand. Neurological examination showed nothing abnormal except for hypoalgesia in both thumbs. Electromyography showed nothing abnormal. The neuropathy disappeared when the drug was discontinued.

Comment

It seems likely that the higher the sulphone dose, the shorter the latency period before the symptoms occur.¹⁻⁴ When the dose of sulphones is reduced,^{2, 4} the symptoms of peripheral polyneuropathy

abate gradually, indicating that neurotoxicity is dose-related. Once a patient has had symptoms of peripheral polyneuropathy⁴ he develops symptoms more rapidly when sulphones are readministered after a period of suspension.

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Interaction between azapropazone and warfarin

A Caucasian woman aged 59 underwent mitral valvotomy in 1967 for mitral stenosis. Three years later she had a cerebral embolus and was anticoagulated with warfarin. The dose was adjusted to keep the prothrombin ratio at 2.5. In February 1976 she complained of ulcer-type dyspepsia, and barium-meal examination showed a gastric ulcer, which was treated with Caved-(S) and antacids. The prothrombin ratio was then 2.8. She continued to take digoxin, frusemide, spironolactone, and allopurinol and no other medication until June, when her general practitioner prescribed azapropazone (Rheumox) in the recommended dosage of 300 mg by mouth four times a day

for back pain. Four days later (total dose 3900 mg) she was admitted to hospital as an emergency case after a haematemesis. On admission the prothrombin ratio was found to be 15.7 (prothrombin time 220 s, control 14 s). She was given four units of blood and parenteral vitamin K, and the warfarin and azapropazone were stopped. Within six hours the prothrombin time had fallen to 35 s (control 13 s). Gastroscopy showed a benign ulcer on the lesser curvature, which was presumed to be the site of the bleeding. Anticoagulants were therefore not reintroduced.

Comment

Azapropazone, a relatively new non-steroidal antirheumatic drug, closely resembles phenylbutazone chemically yet is claimed to cause fewer gastrointestinal side effects and not to constitute a hazard to patients receiving anticoagulants. The interaction between phenylbutazone and warfarin causing enhanced anticoagulation is now well recognised.¹ Initially this effect was thought to be due to displacement of warfarin from binding sites on plasma albumin, thus increasing the availability of free warfarin. Phenylbutazone is now known to affect the clearance of the R and S isomers of warfarin.² Since S warfarin is five times more potent an anticoagulant than R warfarin,

inhibition of the metabolism of S warfarin provides another explanation for the augmented anticoagulation that occurs after phenylbutazone. These considerations may apply to azapropazone because of its chemical resemblance to phenylbutazone. Until more is known about the effect of azapropazone on the prothrombin time in patients receiving anticoagulants, and about the metabolism of the isomers of warfarin, a different analgesic anti-inflammatory agent should be used in patients taking anticoagulants.

I thank Dr J D Maxwell for advice and encouragement in preparing this paper, and Dr J F Dow for permission to refer to his patient's notes.

¹ Aggeler, P M, *et al*, *New England Journal of Medicine*, 1967, **276**, 496.

² Lewis, R J, *et al*, *Journal of Clinical Investigation*, 1974, **53**, 1607.

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SHORT REPORTS

Lactulose in baby milks causing diarrhoea simulating lactose intolerance

Acquired lactose intolerance is a well-recognised complication of gastroenteritis and is suspected when diarrhoea persists or relapses on reintroduction of milk feeds. The detection by Clinitest of reducing substances in stools and control of diarrhoea by substitution of a low lactose milk provide clinical confirmation of diagnosis.

Recent experience at Alder Hey Children's Hospital has shown that patients who apparently have lactose intolerance may be reacting to lactulose, which is present in some prepacked liquid milks marketed in the UK. This report summarises our recent experience.

Patients, methods and results

Children under 2 years of age with the diagnosis of gastroenteritis have for some time been recruited into a clinical trial to compare the effect of

different feeding regimens on the course of the disease. All patients are initially given 0.18% saline in 4.3% glucose orally for 12 to 24 hours and are then, by random allocation, either given full-strength milk feeds or a graduated regimen of feeding in which there is a build up to full-strength feeds over 72 hours. All loose stools are tested for reducing substances with Clinitest, and stools with 0.5% or more of reducing substances are subjected to sugar chromatography.

This report deals with only one aspect of our results which we feel should be brought to the attention of colleagues. To date we have seen several children in whom diarrhoea has persisted or relapsed when full-strength Baby Milk Plus or Premium milk (Cow and Gate) has been introduced, whose stools gave positive Clinitest results (0.5% or more); whose diarrhoea improved on substitution of low lactose feeds; but in whom stool chromatography has not shown lactose, galactose, or glucose in appreciable amounts. Their stools have, however, shown an unusual "sugar" with a mobility on chromatography intermediate between those of lactose and galactose and which we have identified as lactulose.

Chromatography on Baby Milk Plus and Premium milk has shown that lactulose is normally present in both these products, but reconstituted powdered milk has not shown any lactulose. The figure shows the results of chromatography on the following: Baby Milk Plus; Premium; SMA; SMA with added lactulose (1:10); and SMA with added lactulose (1:100). Pure glucose, galactose, and lactose have been included for comparison. It will be seen that both Baby Milk Plus and Premium contain lactulose, which is not present in SMA*, and that the addition of lactulose to SMA produces chromatographic appearances similar to those obtained with Baby Milk Plus and Premium milks.

Comment

Lactulose is derived from lactose during the processing of milk products. It is a disaccharide which when taken by mouth is unaffected by intestinal disaccharidases and undergoes fermentation in the colon to acetic and lactic acids. Lactulose is almost completely unabsorbed from the gastrointestinal tract, and has proved useful in treating chronic constipation and hepatic encephalopathy.^{1,2}

Although the concentration of lactulose in Baby Milk Plus and Premium milk is low (crudely estimated to be about 0.25 g per 100 ml), the total amount of lactulose contained in a day's feed approaches that which has laxative effects—namely, 0.25% lactulose in 800 ml of feed given over 24 hours

$$= \frac{0.25}{100} \times 800 = 2 \text{ g lactulose}$$

Hence after gastroenteritis the child's tolerance of lactulose is apparently diminished and diarrhoea may persist because of its laxative effects. As lactulose gives a positive result with Clinitest, diarrhoea from this cause simulates lactose intolerance. Stool chromatography will clarify diagnosis but is not essential as the substitution

*This refers to SMA powdered milk. Gold cap SMA, which is a liquid prepacked milk, does contain lactulose.

Sugar chromatography on baby milks showing the presence of lactulose in two of the commonly used prepacked liquid milk formulas.