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 anti-inflammatory 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. 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. 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 enhanced 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.


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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. 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

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

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.
Successful treatment of apparent eosinophilic leukaemia

Apparent eosinophilic leukaemia is a life-threatening manifestation of the hypereosinophilic syndrome, characterised by extreme debility, fever, bone pain, blood eosinophilia of leukemic proportions, splenomegaly, and cardiac disease. Complete recovery with sustained remission after treatment has been described briefly once before.1 We report another such case.

Case report

A 45-year-old Scottish lorry driver who had never travelled abroad was admitted to hospital with one month's general malaise, night sweats, and increasingly severe skeletal pain. He dated his illness to receipt of tetanus toxoid and intramuscular penicillin after soft-tissue injury to his left hand. He was ill, had a fever of 38°C, and ungual splatten haemorrhages. A small left supraventricular node, slight splenic enlargement, and percussable tenderness over the upper arms, thighs, thoracic spine, and ribs were evident. Jugular venous pressure was raised; a precordial pystosolic murmur was heard.

The results of investigations included: haemoglobin 10·8 g/dl; white cell count 198×10^6 (198 000/mm^3); differential count: 72% mature eosinophils, 10% eosinophil metamyelocytes, 4% eosinophil myelocytes, 3% basophils, 5% neutrophils, 2% monoocytes, 4% lymphocytes; platelets 132×10^6 (132 000/mm^3). Marrow examination showed normoblastic haematopoesis with greatly increased myeloid:erythroid ratio, reflecting a preponderance of eosinophils at all stages of development although promyelocytes and blasts were not unduly prominent, accounting for 2·7% and 1·3%, respectively of 300 consecutive myeloid cells counted. Chest X-ray picture and concentrations of serum electrolytes, proteins, urate, aspartate aminotransferase, alkaline and acid phosphatases were normal. The electrocardiogram (ECG) showed S-T depression in lateral chest leads with widespread T wave inversion. The Wassermann reaction was negative, blood cultures sterile, and no faecal ova, cysts, or parasites were found.

A diagnosis of eosinophilic leukaemia was entertained and treatment with prednisolone and busulphan begun. The haematological response to treatment and its discontinuation is depicted in the figure. At first progress was slow, with cardiovascular deterioration—jugular venous pressure increased, a diastolic murmur developed, and ECG T wave inversion deepened. Within six weeks considerable improvement was evident; by three months he had returned to work. The diastolic murmur disappeared and the ECG returned to normal, but the spleen remained palpable for over a year and the eosinophil count did not revert to normal until 28 months after the beginning of the illness—a year after discontinuing prednisolone. He has remained off treatment, symptom- and sign-free for four years, with normal haematological values for three years. At recent review peripheral blood and marrow aspirate were morphologically and cytogenetically normal with chest X-ray pictures, electrocardiograms, and echocardiograms unremarkable.

Discussion

Ever since Stillman's description of eosinophilic leukaemia in 1912 the existence of such a diagnosis has been disputed because of difficulty in distinguishing between a truly neoplastic process and the malignant consequences of tissue infiltration and damage associated with eosinophilic leukaemoid reactions.2 In the light of such controversy two aspects of our case merit attention—the patient's dating his illness to administration of tetanus toxoid and penicillin and the haematological response on and off treatment. Treatment presumably arrested and reversed the leukaemoid reaction and prevented heart failure, the usual mode of death in this syndrome. Treatment was discontinued, however, while eosinophilia persisted, but over the next year the eosinophil count fell spontaneously and remained normal three years later. Such findings would seem to favour the concept that the syndrome of apparent eosinophilic leukaemia is an unusual manifestation of hypersensitivity, which may, if promptly treated, as in this instance, be arrested and cured. We suggest that use of the dismal and emotive word leukaemia for this syndrome is misplaced and should be reserved for those rare instances of demonstrable blast-cell transformation.

Successful treatment of patient with apparent eosinophilic leukaemia with prednisolone and busulphan. Conversion: SI to traditional units—Leucocytes 1.0×10^12/l=1000/mm^3.

We thank Dr David Short for referring this patient to us and for his continuing interest.

2 Stillman, R G, Medical Record, 1912, 81, 594.

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