thereby permitting the fairly confident exclusion of hypertension as such as the precipitating factor. It was considered possible that phenobarbitone present in the serum might interfere with the laboratory procedure and result in artificially low oestriol values, but this was discounted after evidence showed that the behaviour of the assay was not appreciably affected by the in-vitro addition of phenobarbitone in amounts considerably above those reached during normal treatment.

Comment

Even in the normal dose range (30–120 mg/day) for men and women, phenobarbitone is known to be a powerful inducer of the hepatic microsomal detoxicating enzyme system, an effect greatly potentiated by the presence of polyunsaturated fatty acids in the diet.² In view of the relatively short half life of free oestriol in plasma (about eight minutes),³ it is tempting to speculate that even a minimally enhanced conjugation rate may exert a profound effect on concentrations of unconjugated oestriol.

Until these findings have been confirmed and their cause more fully elucidated, it would be prudent to temper concern with caution in interpreting falling unconjugated oestriol concentrations in patients receiving phenobarbitone.

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² Marshall WJ. Enzyme induction by drugs: its relevance to clinical biochemistry. *Ann Clin Biochem* 1978;**15**:55–64.

³ Klopfer A, Buchan P, Wilson G. The plasma half-life of placental hormones. *Br J Obstet Gynaecol* 1978;**85**:738–47.

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Departments of Pathology and Obstetrics and Gynaecology, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

A H BASALAMAH, MD, MRCOG, dean, College of Medicine and Allied Science

M J HARDY, BA, DPHIL, assistant professor

Severe diarrhoea due to small intestinal colonisation during cimetidine treatment

Diarrhoea is occasionally encountered during cimetidine treatment but no satisfactory pathophysiological mechanism has been proposed. The case described here suggests that severe diarrhoea and malabsorption may be due to a reversible bacterial colonisation of the small intestine.

Case report

A 77-year-old woman, admitted to hospital with chest pains, gave a history of recent severe diarrhoea and weight loss of about 5 kg. Two months previously she had been prescribed cimetidine 200 mg thrice daily and 400 mg at night for a duodenal ulcer. The ulcer symptoms had rapidly resolved, but about two weeks after starting cimetidine she had developed diarrhoea with progressive weight loss. Salazopyrine was prescribed without benefit, and cimetidine was continued. When admitted for chest pain she was passing 8–12 pale, offensive, frothy, and floating stools a day and was thought to have steatorrhoea. Cimetidine was continued during her recovery from uncomplicated myocardial infarction. The diarrhoea was then investigated. The results of the following examinations and tests were normal: sigmoidoscopy; stool culture and microscopy; jejunal biopsy; Lundh test of pancreatic function; serum iron and folate; barium enema; small bowel enema. Gastroscopy showed scarring on the lesser curve but no duodenal ulcer. Faecal fat was 4.8 g/day; urinary indican excretion was low normal on two successive days. The lactulose-hydrogen breath test was strongly positive, suggesting intestinal bacterial overgrowth. This was confirmed when jejunal aspirate grew per ml 6×10^6 enterococci, 6×10^5 *Streptococcus viridans*, 4×10^4 coliforms, 1×10^5 staphylococci, and 1×10^6 *bacteroides* spp.

After completion of investigations the cimetidine was stopped and the diarrhoea gradually improved. Two months later she had gained 4 kg in weight and her bowels were acting normally with one solid motion a day. Repeat investigations at that time showed that she was not achlorhydric (gastric pH 3.7) and jejunal aspirate produced only an insignificant growth of *Str viridans* (8×10^2 per ml) with no anaerobes. A lactulose-hydrogen

breath test produced no hydrogen. At no time during this period had she received antibiotics. She has remained well, taking no cimetidine, and had no recurrence of diarrhoea or abdominal pain.

Comment

Cimetidine causes bacterial overgrowth in the stomachs of patients with gastric and duodenal ulcers, presumably by reducing acid secretion.¹ A raised gastric pH is associated with an increase in jejunal bacteria,² but a clinical syndrome of diarrhoea and malabsorption due to intestinal bacterial overgrowth has not been convincingly demonstrated in the absence of an anatomical lesion or severe motility disorder. Bacterial overgrowth was postulated as the cause of malnutrition in a group of elderly patients who responded to antibiotics, but intestinal bacteriology was not performed.³ Our clinical impression of steatorrhoea was not confirmed by the results of faecal fat estimation. Steatorrhoea due to bacterial overgrowth is often intermittent. Although our patient's diarrhoea continued during investigation its character varied and no longer suggested steatorrhoea when investigated. Urinary indican excretion is often normal even with established bacterial overgrowth.⁴

In view of the weight loss and severe diarrhoea there seems little doubt that our patient had "malabsorption." Malnutrition and malabsorption have many causes in association with intestinal overgrowth in addition to fat malabsorption, including impaired fluid and electrolyte absorption, intestinal breakdown and malabsorption of dietary protein, protein-losing enteropathy, and calorie consumption by the bacteria themselves.⁵ The "stagnant loop syndrome" has not been satisfactorily documented in a normal small bowel. In our patient it was presumed to be due to the cimetidine treatment. Long-term treatment with potent gastric antiseptics agents may have undesirable nutritional consequences, particularly in elderly hypochlorhydric patients, who may already have a tendency to bacterial overgrowth in the small intestine.

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Department of Medicine, St James's University Hospital, Leeds LS9 7TF

W S J RUDDELL, MD, MRCP, senior registrar

M S LOSOWSKY, MD, FRCP, professor of medicine

Hydrallazine-induced lupus erythematosus-like syndrome in a patient of the rapid acetylator phenotype

Human populations show a bimodal distribution for the rate of acetylation of certain drugs.¹ The lupus erythematosus-like syndrome associated with hydrallazine is almost exclusively confined to slow acetylators,² there being only two cases reported of this syndrome occurring in the rapid acetylator phenotype. In the first of these² very large doses were given, and in the second the idiopathic variety of lupus was subsequently considered a more likely diagnosis.³ We describe here a rapid acetylator of sulphadimidine in whom the acetylation of hydrallazine has also been studied.

Case report

A 49-year-old woman began treatment for hypertension in 1961. She was treated for epilepsy between 1969 and 1976. In August 1975 hydrallazine

150 mg daily was started. The dose was increased to 200 mg daily in September 1977. At this time her other drugs were propranolol, guanethidine, and bendrofluazide. In February 1977 she developed pains in the anterior abdomen and thorax. Over the next nine months the pain spread to her wrists, elbows, shoulders, and right knee. She suffered from malaise and lost 6.4 kg. On admission to hospital in November 1978 her abdominal muscles were tender and she had conjunctivitis of the right eye. Two days after admission while still taking hydralazine, she developed diplopia and an inferior oblique muscle palsy and ptosis on the right side were observed. Results of investigations included erythrocyte sedimentation rate 92 mm in 1 hour, haemoglobin 10.3 g/dl; white cell count $2.4 \times 10^9/l$, normal differential count; normal appearances of bone marrow aspirate; no proteinuria; normal serum urea, creatinine, and immunoglobulin concentrations. Antinuclear antibody titre was 1/640 (IgG, homogeneous) and DNA binding was 12% (normal range 0-30%). The result of the latex fixation test was negative. A complement screen was normal. C1q binding material was found in fluid aspirated from the right knee. It was found in serum on only one out of five occasions.

Hydralazine was stopped and prazosin substituted. The diplopia resolved within three days. The joint and muscle pains improved slowly but continuously, the patient being almost symptom free four months later. Her weight returned to normal over a similar period. The leucopenia recovered over two to three weeks (figure). Three months after stopping the drug the antinuclear antibody titre was 1/160 and the ESR was 46 mm in 1 hour.

Response of total white cell count (●) and neutrophil count (○) to withdrawal of hydralazine. Hatching represents treatment with hydralazine 100 mg twice daily.

Metabolic studies—The patient was found to be a rapid acetylator on two occasions using sulphadimidine. A major product of acetylation of hydralazine is 3-hydroxymethyl triazolophthalazine. Both this and hydralazine were measured by gas chromatography⁴ in 0-24 h urine collections. The ratio of 3-hydroxymethyl triazolophthalazine to hydralazine is 1.1-2.5 for slow acetylators taking 200 mg hydralazine daily and 9.6-24.5 for rapid acetylators.⁵ For this patient the ratio was 3.8. Other urinary metabolites were measured and the amounts were characteristic of the slow acetylator phenotype. Details of these results and procedures will be published elsewhere.

Comment

Although this patient is a rapid acetylator of sulphadimidine her urinary metabolites when taking hydralazine were more characteristic of a slow acetylator. The metabolism of hydralazine is complex and, unlike that of sulphadimidine, includes several routes other than acetylation. One of these alternative pathways may be concerned in the development of toxicity. The activity of this pathway would probably be independent of acetylation, but slow acetylation would permit more of the drug to pass down the toxic pathway. If the toxic pathway were highly active, however, less drug would be available for acetylation and the lupus syndrome would develop despite the patient's constitution as a rapid acetylator.

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Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12 0HS

S J HARLAND, MB, MRCP, research fellow (present address: Institute of Cancer Research, Sutton, Surrey)

V FACCHINI, PHD, senior research officer

J A TIMBRELL, PHD, lecturer

Disturbed behaviour induced by high-dose antipsychotic drugs

Recently there has been a tendency to increase the doses of depot antipsychotic drugs in attempts to achieve better control of the more severe illnesses; two depot preparations have been introduced in concentrated form to facilitate this. We report on three patients with resistant schizophrenia who showed apparently paradoxical responses to high doses of these drugs.

Case reports

Case 1—A 27-year-old married woman with an eight-year history of schizophrenia relapsed after being well for three years taking fluphenazine decanoate 75 mg intramuscularly weekly when the dose was reduced. Her illnesses had always been characterised by disturbed behaviour, prominent delusions, and hallucinations. On admission the patient was severely disturbed; some control was achieved with oral chlorpromazine but, as there remained a serious management problem, intramuscular flupenthixol decanoate was substituted. The dose was titrated against symptoms and after three months 600 mg intramuscularly weekly was found to be effective and the patient was discharged without symptoms. After 10 doses she began to be excitable, restless, and overtalkative. The flupenthixol decanoate was reduced to 400 mg weekly with subsequent improvement. The patient has now been on this regimen for 2½ years and remains well. Procyclidine 10 mg three times a day has been needed throughout.

Case 2—A 20-year-old man with a four-year history of schizophrenia, most of this time spent in hospital, showed exacerbated symptoms. He had been receiving intramuscular fluphenazine decanoate 75 mg intramuscularly monthly and, after relapse, this was increased to 75 mg every three weeks; after three doses, however, he became excitable, overtalkative, and aggressive. These symptoms improved when his medication was replaced temporarily by oral chlorpromazine. He required no anti-Parkinsonian medication.

Case 3—A 27-year-old man had been admitted many times with episodes of schizophrenia characterised by florid delusions. When last discharged his illness was controlled on intramuscular flupenthixol decanoate 80 mg weekly. The patient failed to take his medication and on readmission he was again very deluded. He did not settle with oral chlorpromazine and a regimen of progressively increasing depot flupenthixol was begun. After a few weeks the intramuscular dose had reached 200 mg weekly. Two days after this injection he exhibited violent behaviour and attempted to stab a nurse with a knife. He remained excitable and aggressive but slowly settled with oral haloperidol. He needed no anti-Parkinsonian medication.

Comment

In all three cases the apparent relapse occurring with high drug dose was atypical for the patient, being characterised by excitement, restlessness, and aggression. Another brief article reported similar relapses, related to high doses of pimozide.¹

All antipsychotic drugs block postsynaptic dopamine receptors centrally. In schizophrenia there is a postulated functional hyperactivity of brain dopaminergic systems, which is supported by the finding that indirectly acting dopamine agonists, such as methylphenidate and amphetamine, may precipitate disturbed behaviour in patients with schizophrenia.² An explanation for the paradoxical responses reported may be that antipsychotic drugs have agonist