SHORT REPORTS

Confusion after admission to hospital in elderly patients using benzodiazepines

During 1983 and 1984 the alcohol and drug services unit at the Royal Newcastle Hospital was often asked to help in the management of elderly patients who had developed confusion while in hospital, after the withdrawal of benzodiazepine drugs. We therefore carried out a prospective study to document prior use of benzodiazepines in a group of elderly patients admitted to hospital and to record the development in hospital of signs and symptoms that might be manifestations of withdrawal reactions.

Patients, methods, and results

All patients over 65 years of age admitted to the department of medicine, Royal Newcastle Hospital, were included in this study, except for those requiring urgent resuscitation. Approval was obtained from the Royal Newcastle Hospital ethics committee, and informed consent was obtained from all subjects. Each patient was interviewed within 24 hours, a detailed drug history was taken, and a urine sample was obtained for drug analysis. On each successive day the patient's pulse, blood pressure, and temperature were recorded, and a note was made of confusion, disorientation, or seizures. Urine samples were assayed qualitatively for benzodiazepine using the enzyme multiplied immunoassay technique urine benzodiazepine assay (Syva Diagnostics, Palo Alto Ca),[1] modified by inclusion of a hydrolysis step.[2] The patient's attending doctors were not told of results of the assessments or the urine analysis.

In all, 103 patients, 49 men and 54 women, were studied. Fifty two patients had a positive result from a urine test for benzodiazepines on admission. Fifty one of these said they had taken benzodiazepines. The stated dose varied from 2·5-40 mg of diazepam or its equivalent per day with a mean of 7·75 mg. There were 24 men and 28 women in this group and their mean age was 74·4 (range 65-90) years. In 33 patients the benzodiazepines were stopped on admission. The mean age of the 51 patients who did not use the drug was 75·6 (range 65-86) years.

The table shows the clinical diagnoses made in both groups. Confusion and disorientation with or without hallucinations developed in 10 patients: two non-users and eight users. The increased incidence for users (eight out of 52 compared with two out of 51) was significant ($p=0·049$, Fisher's exact test). Seven of the eight users who developed confusion had had their benzodiazepines stopped on admission. Six were treated with diazepam and responded promptly. The diazepam was then gradually reduced over seven to 10 days. Three of these patients had developed hallucinations. The 10 patients who developed confusion did not have preceding sympathetic hyperactivity, and no episodes of derealisation or other perceptual changes occurred in this series.

*Distribution of diagnoses in users and non-users of benzodiazepines on admission to hospital**

	Users	Non-users
Ischaemic heart disease	14	5
Congestive cardiac failure	8	11
Chronic airways disease	6	9
Pleurisy or pleural effusion	3	2
Malignancy	3	3
Cerebrovascular accident	2	3
Gastrointestinal haemorrhage	2	2
Peripheral vascular disease	2	1
Others	12	15

*Diagnoses quoted are those appearing in the patients' admission notes.

Comment

In this prospective study of 103 patients aged 65 years or more half were found to be using benzodiazepine drugs, and these patients had an increased risk of developing a confusional state in hospital. The risk appeared to be particularly high in those whose drugs were stopped abruptly. In contrast to reports in younger patients, withdrawal of benzodiazepine treatment in these older people did not appear to precipitate the well described milder reactions of anxiety, insomnia, and perceptual changes.[3,4]

Although patients were not randomly assigned to continuation or cessation of benzodiazepine treatment, we think that withdrawal was the major cause of confusion as the patients who developed confusion had nothing else in common, and in six patients the reaction resolved promptly when benzodiazepine treatment was restarted. It is now widely recommended that benzodiazepines should be prescribed only for predetermined short periods, and intermittent rather than regular doses should be used to minimise the risk of dependence.[5] In addition, we would advise that benzodiazepine treatment should not be stopped abruptly in elderly patients.

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Hepatic cholestasis induced by trimethoprim

Cholestasis during treatment with a combination of trimethoprim and sulphamethoxazole has been reported previously and has usually been attributed to the sulphonamide component.[1-3] I report on a patient who developed jaundice when treated with trimethoprim-sulphamethoxazole and during subsequent re-exposure to trimethoprim.

Case report

A 49 year old woman presented in March 1985 with a three week history of jaundice and intense pruritus. Two weeks before the onset of jaundice she had been given a five day course of trimethoprim-sulphamethoxazole for a symptomatic infection of the middle ear. Towards the end of this course she had felt generally unwell and nauseated with mild non-specific upper abdominal discomfort. She had not had any injections or blood transfusions recently, and there was no history of contact with hepatitis, foreign travel, or jaundice in the family. She was not taking the oral contraceptive pill or any other drugs and had never been pregnant.

Her urine was dark and positive for bile, and her stools were pale. On examination there were no signs of chronic liver disease, but she was deeply jaundiced. The liver was palpable (span 14 cm) and tender. She had an excoriated rash, especially over the lower legs. Investigations showed a total bilirubin concentration of 243 μmol/l (14·2 mg/100 ml) (normal <17 μmol/l; <1·0 mg/100 ml), alkaline phosphatase 362 U/l (normal <90 U/l), and aspartate transaminase 87 U/l (normal <40 U/l); haemoglobin concentration was 119 g/l with a white cell count of $7·0 \times 10^9$/l (no eosinophilia) and occasional target cells; erythrocyte sedimentation rate was 50 mm in the first hour. Hepatic ultrasonography did not show any duct distension; the gall bladder appeared to be thick walled, but appearances were otherwise normal. Liver biopsy did not show any disturbance of hepatic architecture, but there was considerable centrilobular cholestasis with no inflammation. Portal tracts were normal.

As it was considered that this might be a cholestatic phase of viral hepatitis she was given oral prednisolone (starting at 40 mg a day) for six weeks. Subsequent investigations did not show any markers of infection with hepatitis B; hepatitis A IgM was not detected, and screening for autoantibodies yielded negative results. Her pruritus resolved within five days and the jaundice in two weeks, and results of all liver function tests were normal eight weeks after presentation.

She remained well until February 1986, when she was given trimethoprim for a urinary tract infection. She felt unwell within hours after taking the first tablet but finished the five day course of treatment. Pruritus developed on the last day, her urine became dark, and she became jaundiced. There were no other symptoms. Again the liver was slightly tender and abdominal ultrasonography did not show any abnormality. Liver function tests again showed a cholestatic picture: total bilirubin concentration was 58 μmol/l (3·4 mg/100 ml), alkaline phosphatase 399 U/l, and aspartate transaminase 42 U/l. Serum albumin concentration was normal throughout. As she had appreciable symptoms four weeks later she was given a month's course of rapidly reducing prednisolone with immediate resolution of her symptoms and the biochemical abnormalities.

Comment

Reports to the Committee on Safety of Medicines show that skin reactions are the commonest adverse reaction to trimethoprim; the committee has had a few reports of cholestatic jaundice due to trimethoprim and to trimethoprim-sulphamethoxazole. Manufacturers of trimethoprim (Duphar) have received four reports of hepatic reactions: hepatitis (two), jaundice (one), and cholestatic jaundice (one). In previous reports similar hepatic reactions to combination antibiotics have been attributed to the sulphonamide component. I suspect that some of these reactions were due to trimethoprim. The mechanism for such cholestasis is obscure as trimethoprim interferes primarily with the metabolism of folic acid. As the reaction occurred late in life in this patient and was clearly related to exposure to the drug it is unlikely to have been any other form of benign cholestasis.

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Possible interaction between heparin and a sulphonylurea a cause of prolonged hypoglycaemia?

Glipizide, a second generation sulphonylurea, has pharmacokinetic properties that lessen the risk of hypoglycaemia. Nevertheless, we describe a patient who suffered recurring hypoglycaemia that lasted for four days after a single 5 mg dose of glipizide.

Case report

A 64 year old diabetic man with peripheral vascular disease was found to be hypoglycaemic (blood glucose 1·9 mmol/l (34·2 mg/100 ml)) immediately before an operation for debridement of a foot ulcer. He had been taking glipizide 5 mg daily since diabetes was diagnosed six months before, with fair control (HbA_1 10·2% (normal 6-9%)) and without hypoglycaemia. He had had his usual dose and food intake the previous day and had been fasting for 10½ hours. He received 25 g glucose intravenously and then a 5% dextrose intravenous infusion during the brief operation. Four hours later hypoglycaemia recurred, and over the ensuing 68 hours five symptomatic episodes occurred (blood glucose 1·4-1·8 mmol/l (25·2-32·4 mg/100 ml)) despite continuous infusions of 5% or 10% dextrose 500 ml every four hours and satisfactory eating. The last episode occurred 99 hours after the last dose of glipizide. Five days later glipizide was represcribed, as he was then hyperglycaemic (glucose 13 mmol/l (234·3 mg/100 ml)), but after only one dose of 5 mg he had four hypoglycaemic attacks (glucose 1·0-1·8 mmol/l (18·0-32·4 mg/100 ml)) over the next 36 hours, convulsing during one, again despite eating and continuous intravenous infusion of dextrose. Subsequent hyperglycaemia during four months of follow up was controlled by metformin without trouble.

The original diagnosis of diabetes had been confirmed by a glucose tolerance test, the fasting and two hour capillary blood glucose concentrations being 10 mmol/l (180·2 mg/100 ml) and 14 mmol/l (252·3 mg/100 ml) respectively. During one of his hypoglycaemic episodes (glucose 1·4 mmol/l (25·2 mg/100 ml)) plasma insulin and cortisol concentrations were measured. The insulin concentration was causally increased at 429·1 pmol/l (59·8 mU/l), and cortisol concentration was 0·61 μmol/l (22·1 μg/100 ml). A repeat measurement of cortisol during another episode was 0·82 μmol/l (29·7 μg/100 ml). Concentrations of thyroxine and thyroid stimulating hormone, plasma urea, and creatinine were normal, as were the results of standard liver function tests.

Comment

Glipizide has a short half life (mean four hours) and is metabolised by the liver; its metabolites, which are excreted by the kidneys, are inactive.[1] It is therefore judged less likely to cause hypoglycaemia in patients with renal impairment and safer to use in the elderly. Prolonged hypoglycaemia of up to 36 hours, however, has been reported in the presence of impaired liver function, treatment with aspirin, or gastroenteritis.[2] In our patient there was no recognised precipitating factor. The results of standard tests of liver and kidney function were normal. His food intake in addition to substantial intravenous glucose was adequate. There was also an adequate cortisol response to hypoglycaemia, which was confirmed to be due to hyperinsulinaemia. That this was secondary to glipizide seems evident.

It was difficult to understand why he should suddenly have become sensitive to glipizide after six months of uncomplicated treatment. He had not received any counteracting diabetogenic drug before admission. The only other drugs given to him in hospital were diamorphine and subcutaneous heparin calcium, neither of which have been reported as interacting with sulphonylureas. Sulphonylureas, however, are highly bound to protein,[3] and even small doses of heparin decrease indirectly the binding of drugs by increasing free fatty acid concentrations, an effect more pronounced in patients with diabetes.[4] Moreover, glipizide may be more susceptible to drug displacement interactions because of its low volume of distribution.[5] The heparin, 5000 units every 12 hours, was begun 36 hours before his last (preoperative) glipizide dose and continued during three weeks of postoperative immobility. Despite glipizide's short half life and the expected compensatory rapid elimination of an increased concentration of unbound drug a sufficiently large amount of free glipizide displaced by heparin could possibly have caused the protracted hyperinsulinaemia and hypoglycaemia. Heparin could possibly also have inhibited the metabolism or excretion of glipizide. Oral anticoagulants may potentiate sulphonylureas,[1 3] but we are unaware of any reports implicating heparin.

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Carotid artery stenosis exposed by an adverse effect of captopril

Captopril is being administered to an increasing number of patients with arterial hypertension. Cerebral complications are rarely reported. We use the short term captopril test to evaluate patients with hypertension. During this test we observed reversible cerebral symptoms in two patients.

Case reports

Arterial blood pressure and heart rate in the supine position are measured before and every 15 minutes for 90 minutes after the administration of captopril 6·25 mg orally. Plasma renin activity is measured before and 90 minutes after the administration of captopril.

Case 1—The patient was a 67 year old woman who had had hypertension for over 35 years. Sympathectomy in 1954 had not had any appreciable effect. The blood pressure was 220/130 mm Hg, decreasing spontaneously to 160/110 mm Hg. She was treated with prazosin 10 mg, atenolol 25 mg, and a combination of hydrochlorothiazide 50 mg and amiloride 5 mg, all twice daily. Plasma renin activity was 95 mU/l (normal 6-60 mU/l), and serum creatinine concentration 128 μmol/l (1·45 mg/100 ml). Renography and computed tomography of the kidneys showed complete lack of renal function on the left side and a contracted kidney. Seventy five minutes after the administration of captopril she became absent, complaining of paraesthesia of both hands and spots before the eyes. The blood pressure had dropped to 100/85 mm Hg, and the heart rate was 100 beats/min and stable. She regained consciousness within a couple of minutes without any sequelae. Digital subtraction angiography showed stenosis of the internal carotid artery, external carotid artery, and vertebral artery on the right side. This had not been apparent on auscultation of the vessels.

Case 2—This 67 year old man had had ischaemic heart disease since the age of 58. Hypertension had been diagnosed six months previously, and three years previously an aortic prosthesis had been inserted because of intermittent claudication. Blood pressure was 190/120 mm Hg, and he was treated with clonidine 75 μg twice daily, methyldopa 125 mg thrice daily, and bendrofluazide 5 mg twice daily. Serum creatinine and plasma electrolyte concentrations and clearance of edetic acid labelled with chromium-51 were normal. Catheterisation of the renal veins showed a plasma renin activity of 1000-2000 mU/l on the right