SHORT REPORTS

Amiodarone increases plasma digoxin concentrations

As treatment regimens become more complex the dangers of drug interaction increase. We observed that several patients receiving maintenance digoxin treatment abruptly developed clinical evidence of toxicity when amiodarone, a newly available antiarrhythmic agent, was administered in addition. We therefore studied several patients to determine the response of plasma digoxin concentrations to treatment with amiodarone.

Patients, methods, and results

Seven patients receiving maintenance digoxin treatment were given amiodarone to control refractory arrhythmias. All had paroxysmal or sustained atrial fibrillation and three had had other supraventricular arrhythmias. Maintenance doses of digoxin had been constant for at least two weeks before the study. Plasma digoxin concentrations were measured daily for seven days using a radioimmunoassay technique¹; samples were drawn eight hours after administration of digoxin.

On days 3-7 amiodarone 200 mg was administered thrice daily; plasma digoxin concentrations increased progressively by an average of 69% (mean 1.17 to 1.98 $\mu\text{g/l}$ (figure). Four patients developed symptoms compatible with digoxin toxicity.

Mean percentage change in daily plasma digoxin concentrations in seven patients treated with digoxin with amiodarone added from day 3 (o) and six controls treated with digoxin alone (x).

Two additional patients were studied in a similar manner, but maintenance amiodarone was increased from 200 to 600 mg daily rather than introduced on the third day. Plasma digoxin concentrations increased by 0.4 and 0.7 $\mu\text{g/l}$ respectively over the subsequent five-day period.

Plasma digoxin concentrations were measured daily for seven days in six patients with supraventricular arrhythmias receiving maintenance digoxin alone. No trends towards increased concentrations were found. At no time were falsely positive results of digoxin assays obtained in four patients taking amiodarone alone. Amiodarone added in vitro did not affect the results of the radioimmunoassay. Four of the patients given amiodarone and all six controls were admitted to hospital from the first day of the serial observations.

Comment

Amiodarone is a powerful antiarrhythmic agent unrelated to conventional drugs and widely used in Europe and South America. Though introduced in 1967, it has only recently been licensed for use in Britain. It is most often used alone but also serves as a useful adjunct to digoxin in the treatment of supraventricular arrhythmias inadequately controlled by cardiac glycosides.² Thus the finding that amiodarone increases plasma digoxin concentrations and perhaps precipitates some manifestations of toxicity is of considerable practical importance. Quinidine also increases plasma digoxin concentrations.³

Our observation was based on manifestations of neurotoxicity and unexpectedly high plasma digoxin concentrations in several patients newly treated with amiodarone but previously managed with stable digoxin regimens. During the subsequent study, which did not include the patients who originally showed toxicity, all patients showed progressive increases in digoxin concentrations after amiodarone was added or its dosage increased. An increase in plasma concentration because of better compliance seems an unlikely explanation for every patient, especially since none of our control group showed this tendency. Results of digoxin radioimmunoassay were always negative in patients receiving amiodarone treatment alone, and we found no evidence of interference in the assay when amiodarone was added in vitro.

Amiodarone is avidly tissue bound, and concentrations of digoxin in some tissues are more than 100 times those found in plasma.⁴ Amiodarone may displace tissue-bound glycoside or interfere with digoxin excretion, but the mechanism has not yet been investigated in detail. High plasma concentrations of digoxin without commensurate increases in myocardial concentrations would be expected to cause neurotoxicity rather than direct cardiac toxicity; but heart rhythm may be influenced by both mechanisms.⁵

We do not know whether the interaction we have noted is dangerous in terms of arrhythmogenic potential, but nausea and other manifestations of glycoside toxicity that occur may be interpreted incorrectly as a direct effect of amiodarone, leading to inappropriate modification to treatment. Our present practice is to halve maintenance digoxin doses when amiodarone is introduced.

¹ Smith TW, Butler VP Jr, Haber E. Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. *N Engl J Med* 1969;281:1212-6.

² Wheeler PJ, Puritz R, Ingram DV, Chamberlain DA. Amiodarone in the treatment of refractory supraventricular and ventricular arrhythmias. *Postgrad Med J* 1979;55:1-9.

³ Ejvinsson G. Effect of quinidine on plasma concentrations of digoxin. *Br Med J* 1978;i:279-80.

⁴ Coltart J, Howard M, Chamberlain D. Myocardial and skeletal muscle concentrations of digoxin in patients on long-term therapy. *Br Med J* 1972;iii:318-9.

⁵ Gillis RA, Pearle DL, Levitt B. Digitalis: a neuroexcitatory drug. *Circulation* 1975;52:739-42.

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Home blood glucose monitoring: a sticky artefact

Monitoring blood glucose concentrations at home is now established in diabetic management¹ and is used by many diabetic children attending the Oxford Paediatric Diabetic Clinic. Some families find it particularly useful to be able to measure their child's blood glucose concentration after treatment of a nocturnal hypoglycaemic episode and thus differentiate drowsiness due to continuing hypoglycaemia from the natural desire to go back to sleep. Great care should be used in the procedure, however, since contamination with glucose may result in a false reading.

Case report

A 14-year-old diabetic boy woke his parents after a nightmare at 2 am. His blood glucose concentration was measured using an indicator stick and capillary blood from a finger. It was <2 mmol/l (36 mg/100 ml), and with a slight struggle (because he was confused) his parents encouraged him to swallow 15 ml 100% glucose-maltose solution. Despite this he became increasingly drowsy and unrousable over the next half-hour. At 3 am his

capillary blood glucose concentration was checked again and appeared to have rebounded to >22 mmol/l (396 mg/100 ml). Doubting this, his parents repeated the test and obtained a value of 10-13 mmol/l (180-234 mg/100 ml). The child was admitted to hospital, where a venous blood glucose concentration was 2 mmol/l. It was concluded that the apparent rebound to hyperglycaemia had been due to glucose contamination of the indicator stick.

Comment

Administering glucose to a struggling child may be a sticky affair, but to investigate the problem further I measured my own blood glucose concentration from a finger prick before and after handling a cup which was sticky on the outside with glucose solution. The capillary blood glucose concentration before handling was 7 mmol/l (126 mg/100 ml) and after was 13 mmol/l (234 mg/100 ml). When a few drops of glucose solution, blackcurrant cordial, or strawberry jam were rubbed rather than washed off my hands the capillary blood glucose concentration in a finger-prick sample was measured as 22-24 mmol/l (396-793 mg/100 ml). The same was true when a paper tissue contaminated with glucose was used to blot the indicator stick.

Users of home blood glucose monitoring systems should be warned of this artefact, which may result in delayed treatment of severe hypoglycaemia at night.

¹ Tattersall RB. Home blood glucose monitoring. *Diabetologia* 1979;16:71-4.

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Primary liver cell cancer in autoimmune chronic liver disease

Primary liver cell cancer is a complication of cirrhosis and is more common in men. It is usually related to chronic hepatitis B virus infection¹ or alcoholism,² and more rarely to α_1 -antitrypsin deficiency, haemochromatosis, or primary biliary cirrhosis.³

We report the development of primary liver cell cancer in two women with autoimmune chronic liver disease, an association which has not been described.

Case 1

A 34-year-old Caucasian woman presented in 1969 with unresolved hepatitis. Physical examination showed no abnormality apart from jaundice. The serum bilirubin concentration was 75 μ mol/l (4.4 mg/100 ml) (normal range 5-17 μ mol/l (0.3-1 mg/100 ml)), alkaline phosphatase 12 King-Armstrong units (3-13), aspartate transaminase 180 IU/l (5-15), albumin 39 g/l (36-50), prothrombin index 67%, and gammaglobulin 24 g/l (5-15). The lupus erythematosus cell preparation was strongly positive, the anti-nuclear and smooth muscle antibody titres were greater than 1/40. Tests were negative for hepatitis B surface antigen (HBsAg). Copper studies excluded Wilson's disease. "Lupoid" chronic active liver disease was diagnosed and prednisolone treatment was started with good response.

A liver biopsy specimen in April 1973 showed cirrhosis with moderate piecemeal necrosis and a chronic inflammatory cell infiltrate in the portal tracts. In 1978, after a fourth relapse, treatment with prednisolone 15 mg and azathioprine 100 mg daily was necessary to maintain remission. In March 1980 she became jaundiced and developed hepatic encephalopathy. Serum bilirubin concentration and prothrombin time increased greatly, her tests remained positive for smooth-muscle antibody and antinuclear antibody (1/40) and for antibody to double-stranded DNA. Radioimmunoassay showed a serum α -fetoprotein concentration of 16 000 IU/ml and primary liver cell cancer was diagnosed. Serum tests by radioimmunoassay for HBsAg and hepatitis B surface, core, and e antibodies were negative, excluding past or persistent infection with hepatitis B virus.

The patient deteriorated rapidly and died after a massive haemorrhage from oesophageal varices. At necropsy a tumour was found in the hilum of the liver, invading the portal vein, with additional foci in both lobes.

Histological examination confirmed a trabecular primary liver cell cancer arising in an inactive cirrhotic liver.

Case 2

A 59-year-old Caucasian woman presented in 1960 with unresolved acute hepatitis. Chronic active hepatitis was diagnosed and she was treated with prednisolone. In 1965 a liver biopsy specimen taken during a pyloroplasty showed mild piecemeal necrosis, a chronic inflammatory infiltrate in the portal tracts, but no cirrhosis. In 1969 she presented at this hospital with hepatosplenomegaly; results of biochemical tests were normal. Tests were positive for smooth-muscle antibody (1/40) but negative for antinuclear antibody, mitochondrial antibody, and HBsAg. A liver biopsy specimen showed inactive cirrhosis so prednisolone was discontinued. Relapses, in 1974 and 1976, responded to treatment with prednisolone.

In August 1979 she became ill and developed ascites. A 10-cm epigastric mass was palpated contiguous with the liver, but no bruit was heard. The serum aspartate transaminase concentration was 24 IU/l; results of other biochemical tests were normal. The serum α -fetoprotein concentration was raised (15 000 IU/ml). Tests were negative for HBsAg, antiHBs, anti-HBc, and anti-HBe. Tests remained positive for smooth-muscle antibody. Liver biopsy confirmed a primary liver cell cancer with bile in the tumour cells. Hepatic arteriography showed tumour in both lobes. Adriamycin and mitomycin C were started but without clinical benefit, and the serum α -fetoprotein concentration rose to 72 000 IU/ml. Arterial embolisation of the major tumour mass with gelfoam and dura mater (Liodura (Macarthy's)) was performed. This was technically successful but the patient deteriorated further and died at home five weeks later.

Comment

Both patients developing primary liver cell cancer were women and had serum autoantibodies, suggesting that the chronic liver disease was autoimmune. Neither patient had evidence of past or present hepatitis B virus infection, had a definite history of alcoholism, had taken oral contraceptives or anabolic steroids, or had received blood transfusions. In both patients cirrhosis proved by histological examination was present for several years (case 1, 7 years; case 2, 10 years) before the development of primary liver cell cancer. Primary liver cell cancer was diagnosed from grossly raised serum α -fetoprotein concentrations and typical histological appearances.

The association of primary liver cell cancer with hepatic cirrhosis has been emphasised³ and is possibly related to malignant transformation developing in regenerating nodules. While primary liver cell cancer has been described in cirrhosis associated with hepatitis B virus,¹ alcohol abuse,² haemochromatosis, α_1 -antitrypsin deficiency, and primary biliary cirrhosis,³ it has not been described in cirrhosis related to autoimmune (lupoid) chronic liver disease. A higher incidence of non-hepatic tumours has been described in treated and untreated patients with HBsAg-negative chronic active liver disease.⁴ These patients show immunodeficiency, and it has been suggested that this is another factor predisposing to malignant change.⁵ Primary liver cell cancer must be considered as a possible cause of clinical deterioration in patients with longstanding autoimmune chronic liver disease.

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⁴ Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in Hepatitis B surface antigen negative chronic active hepatitis. *Gut* 1980;21:78-83.

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