Maintenance Digoxin in Elderly Patients

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British Medical Journal, 1970, 2, 705–706

Summary: Digitalis glycosides remain the cornerstone of treatment in cardiac failure. The increasing frequency of toxic effects is a cause for concern. Review of 80 elderly patients receiving digoxin on a maintenance basis, some of whom had toxic effects, shows that in almost three-quarters of the group digoxin was stopped without detriment. Elderly patients on maintenance treatment should be reviewed, and in the absence of a known primary cardiac lesion an attempt should be made to withdraw digoxin.

Introduction

In the past 10 years reports of toxic effects of digitalis glycosides have appeared with increasing frequency. In one recent report almost 20% of patients receiving the drug showed adverse effects (Hurwitz and Wade, 1969). Elderly patients as a group appear to be more liable to toxic effects (Von Capeller *et al.*, 1959; Soffer, 1961; Caird, 1963; *British Medical Journal*, 1964; Dall, 1965).

A group of patients on maintenance digoxin had treatment stopped in order to see whether it was necessary. There were 80 patients, 18 men aged 58 to 99 (mean 74·3) years and 62 women aged 63 to 94 (mean 78·9) years. Fifty-three were symptomless (group A) when digoxin was withdrawn and in 27 treatment was stopped because of toxic effects (group B). Patients were observed over a period of three months and withdrawal of digoxin was regarded as successful if the signs of cardiac decompensation did not recur during this period.

Group A

Information obtained from hospital case records and general practitioners' notes showed the reason for starting treatment in these cases. These reasons were examined in greater detail in the light of subsequent investigations in order to see whether the decision to use digoxin on a maintenance basis was justified (Table I).

TABLE I.—*Reasons for Starting Treatment in 53 Patients*

Tachycardia	23	
Cardiac failure	12	(4)*
Oedema	8	(1)*
Hypertension	6	
Bronchitis	4	

*Numbers in parentheses represent number restarted on digoxin.

In the 23 cases of tachycardia iron-deficiency anaemia was the principal factor in eight, thyrotoxicosis in four, chronic renal failure in four, chronic arthritis in four, gastrointestinal bleeding in two, and myeloma in one. Despite the treatment of these underlying causes, treatment with digoxin, once established, had been continued on a maintenance basis until reviewed. Digoxin was successfully withdrawn in all these cases. Of the 12 cases of "cardiac failure" seven had a history of coronary disease (in four the evidence of cardiac failure recurred on stopping digoxin and treatment was restarted), three had respiratory infection, one had pernicious anaemia (untreated), and one had atherosclerotic heart disease. Of eight cases of "oedema" one had known coronary disease and was subsequently restarted on digoxin, two had gross varicose veins, two had hypoproteinaemia, and three (chairbound patients) had immobility due to rheumatoid arthritis or arteriosclerotic Parkinsonism. The six patients with hypertension had not shown unequivocal signs of failure at any time. Only one had a raised diastolic pressure (>100 untreated) and he had no recollection of oedema or undue breathlessness, two had Paget's disease, and in the other three the diastolic pressure was <100 (untreated). In the group of chronic bronchitics exertional dyspnoea in keeping with impaired respiratory function was present, without evidence of right heart failure.

In a group of 53 patients taking maintenance digoxin treatment was successfully withdrawn in 48 cases.

Group B. Toxic Effects

In this group of 27 patients, 20 were taking thiazide diuretics and only 14 had been given potassium supplements. These were being taken erratically or not at all. Twenty-five patients had E.C.G.s and 23 showed digitalis effect. Some patients exhibited more than one toxic feature (Table II). Seventeen had some form of toxic arrhythmia: ventricular tachycardia in two, supraventricular tachycardia in one, paroxysmal atrial tachycardia with block in two, coupled extrasystoles in four, and frequent extrasystoles in eight. One patient died when ventricular tachycardia, controlled initially by propranolol, recurred several hours later. Arrhythmia was the commonest single toxic effect. Nausea and vomiting occurred in eight cases, mental confusion in seven. Refractory cardiac failure responding only after the withdrawal of digoxin was seen in five cases and was associated with potassium depletion. Gynaecomastia was found in two cases and xanthopsia in one case. Sixteen patients were subsequently restarted on digoxin in a lower dosage and 11 were not restarted.

TABLE II.—*Toxic Effects*

Arrhythmias	17
Nausea and vomiting	8
Mental confusion	7
Refractory cardiac failure	5
Gynaecomastia	2
Xanthopsia	1

Discussion

In group A no patient was in cardiac failure when seen, and treatment was successfully withdrawn in 48 cases. In this group the average dose of digoxin was less than 0·25 mg. daily. Ten patients—eight with previous coronary incidents, one with atherosclerotic heart disease, and one with a diastolic hypertension of more than 110 mm.Hg—had primary cardiac disease and five (50%) of them were restarted on digoxin. The other 43 had symptoms attributed to cardiac disease. In this group any evidence of cardiac failure present initially was secondary to anaemia, thyrotoxicosis, or respiratory disease which was treated, but treatment with digoxin was continued. All of these 43 patients had digoxin stopped without the appearance of signs of cardiac failure. In group A 48 were taking digoxin, at risk of toxic effects, without any therapeutic requirement of the drug.

In group B 11 patients who showed toxic effects had treatment stopped permanently. Sixteen patients who had

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treatment restarted in this group were taking an average dose of 15 tablets (3·75 mg.) weekly when toxic effects were noted and were discharged subsequently on an average of 10 tablets (2·5 mg.) weekly. All patients were given potassium supplements to take whether diuretic treatment was envisaged or not.

In all, 59 elderly patients have been taken off digoxin. It would appear from the cases in group A that where treatment is instituted in the light of known cardiac disease, coronary artery disease, or hypertension it may have to be continued on a maintenance basis, even if the patient is symptomless, but that where treatment is started without a known primary cardiac lesion an opportunity should be taken to withdraw treatment after the heart is compensated before committing the patient to a maintenance regimen.

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Preliminary Communications

Increased Release of Gut Glucagon in Reactive Hypoglycaemia

British Medical Journal, 1970, **2**, 706–707

Summary: A patient with reactive hypoglycaemia showed hypersecretion of insulin in response to enteral beta-cell stimulation. Increased levels of gut glucagon-like immunoreactivity in serum were demonstrated by use of specific antisera. Other measurable hormones influencing carbohydrate metabolism were within normal limits. It is suggested that gut glucagon-like immunoreactivity may be of pathogenetic significance in reactive hypoglycaemia.

INTRODUCTION

Essential reactive hypoglycaemia forms about 70% of spontaneous hypoglycaemia (Conn and Seltzer, 1955). As hyperinsulinaemia alone cannot be responsible for reactive hypoglycaemia (Sussman *et al.*, 1966; Holdsworth *et al.*, 1969), the pathogenesis has remained obscure. Unger (1968) suggested that postprandial hypoglycaemia might be a consequence of pancreas glucagon deficiency. To investigate this possibility in a patient with severe reactive hypoglycaemia, serum levels of pancreas and gut glucagon-like immunoreactivity were measured with specific antisera (Heding, 1969).

One picogram equivalent of glucagon per ml. is defined as the amount of gut or pancreas glucagon-like immunoreactivity per ml. which can displace the same quantity of ^{125}I-glucagon from the antibodies as 1 picogram of crystalline pancreas glucagon per ml. It should be stressed that the dilution curve for gut glucagon-like immunoreactivity is linear in the assay.

CASE REPORT

A 55-year-old woman complained of weakness, dizziness, sweating, and anxiety three to five hours after larger meals. The symptoms had occurred four to six times a month for seven years. They were relieved by food or barley sugar. She had never become unconscious. On 23 October, 1968, she was admitted to hospital with a blood sugar of 22 mg./100 ml. and hypoglycaemic signs which were aborted by intravenous glucose. She was a thin middle-aged woman, height 5ft. 3in. (160 cm.) and weighing 42 kg. Retinopathy, palpable thyroid, enlarged liver, or surgical scars were not present. Neurological examination showed only a slightly increased patellar reflex.

Laboratory Data and Investigations. — Haemoglobin 12·7 g./100 ml., erythrocyte sedimentation rate 8 mm. per hour, white blood count 6,700/cu. mm. with a normal differential and normal red cell morphology. Urine analysis was normal. Serum creatinine, amylase, sodium, potassium, chloride, bicarbonate, calcium, and phosphate were normal. The basal metabolic rate was 113%, protein-bound iodine 4·5 μg./100 ml., and T3 test 2·8%—all within normal limits. The adrenocortical function was normal, as shown by repeated determinations of plasma hydrocortisone level, 24-hour urinary ketosteroid, and 17-ketogenic steroid excretion. *X*-ray examination of sella turcica was normal. Hypophysial function was found to be normal after the following tests: 24-hour urinary hypophysial gonadotropin excretion, metyrapone test, and serum growth hormone (Yde, 1968) levels after insulin stimulation. Serum alkaline phosphatase, aspartate aminotransferase, serum protein, and bromsulphthalein retention were all normal. Gastrointestinal function was tested, with the following results: gastric peak output of acid was 19·4 mEq/hr. after stimulation with 10 μg. of gastrin-tetrapeptide per kg. body weight; barium meal with nutritional contrast medium showed normal emptying of stomach and intestines and no evidence of ulceration; and urinary D-xylose excretion after administration of 25 g. of xylose was normal.

CARBOHYDRATE TOLERANCE TESTS

The immunoreactive insulin and glucagon-like immunoreactivity were studied (see Table). The patient was maintained on a diet containing 250 g. of carbohydrate daily, and at least three days elapsed between tests, which were all made in the morning, after the patient had fasted for 12 hours. Blood was drawn from the antecubital vein without stasis. For the glucagon assay the blood was heparinized and 1 ml. of aprotinin (Trasylol) (5,000 kallikrein inactivating units per ml.) was added per 10 ml. of blood. The blood was then shaken, immediately centrifuged, and deep-frozen at −30° C. Blood glucose was measured by a glucose oxidase method (Christensen, 1967). Plasma insulin levels were determined by the immunoassay of Ørskov (1967) and pancreas and gut glucagon-like immunoreactivity by the method of Heding (1969), using two different anti-glucagon sera—one specific for pancreatic glucagon, the other reacting with both pancreatic and gut glucagon-like immunoreactivity.

Carbohydrate Tolerance Tests

Test	Agent	Route of Administration	Dose
Prolonged glucose (6 hours)	Glucose	Oral	100 g.
Tolbutamide ..	Sodium tolbutamide	Intravenous	1 g.
Glucagon ..	Insulin-free glucagon	Intramuscular	1 mg.
Leucine	L-Leucine	Oral	250 mg./kg.
Gastrin	Gastrin-tetrapeptide	Subcutaneous	10 μg./kg.
Prolonged fasting (72 hours)			

The plasma insulin and blood glucose levels after enteral glucose-loading and parenteral stimulation with pancreatic glucagon, tolbutamide, and tetragastrin are shown in Fig. 1. Enteral stimulation produced a significantly higher insulin response than did the varied parenteral stimulation.