Patients, methods, and results

We studied 63 patients with newly diagnosed acute myeloid leukaemia but without known heart disease who had not previously received digoxin. They were randomised to serve as controls or to receive digoxin (average 0.25 mg daily) or vitamin E (200 mg thrice daily). These drugs were given throughout the study, and patient compliance was confirmed by regular measurements of plasma concentrations. Patients were then given induction treatment for leukaemia of cytarabine 50 mg/m² by continuous intravenous infusion for five days, thioguanine 100 mg/m² by mouth twice daily for five days, and doxorubicin 30 mg/m² intravenously over five minutes on the fifth and sixth days. Induction treatment was repeated once or twice every 10 days. Maintenance treatment with doxorubicin (45 mg/m² intravenously) was given monthly for at least one year. No patient received radiotherapy to the mediastinum.

Systolic time intervals were measured before and two weeks after each doxorubicin treatment by simultaneously recording the electrocardiogram, phonocardiogram, and carotid pulse tracing with a multichannel photographic system.⁴ The ratio of the pre-ejection period to the left ventricular ejection time was used to evaluate left ventricular function, and an increase in ratio greater than 0.08 above the ratio recorded before treatment with doxorubicin indicated cardiac damage.^{4,5}

None of the patients studied showed clinical or cardiographic changes or important changes in systolic time intervals at dosages of doxorubicin below 400 mg/m². Only 41 patients entered remission, of whom 25 survived to receive a total doxorubicin dose above 400 mg/m². The table shows the maximum change in the ratio of the pre-ejection period to the left ventricular ejection time from the baseline reading in these 25 patients. Analysis of covariance, which allowed for different total dosages of doxorubicin between patients, showed a significant difference ($p < 0.05$) between the control group and the group treated with digoxin but no significant difference between the control group and the group treated with vitamin E.

Changes in ratio of pre-ejection period to left ventricular ejection time in patients receiving total dosages of doxorubicin above 400 mg/m²

Case No	Maximum change in ratio*	Total dosage of doxorubicin (mg/m ²)	No of systolic time intervals recorded at dosages above 400 mg/m ²
<i>Controls</i>			
1†	0.143	620	8
2†	0.168	585	7
3	0.117	482	6
4	0.01	480	3
5	0.132	569	2
6	0.090	559	5
7	0.132	1016	11
8	0.076	612	6
<i>Patients given digoxin</i>			
9	0.035	426	2
10	0.073	445	3
11	0.08	468	3
12	0.072	413	1
13	0.063	581	5
14	0.058	775	8
15	0.048	659	6
16	0.080	742	7
17	0.038	794	7
18	0.017	625	5
<i>Patients given vitamin E</i>			
19	0.120	642	8
20	0.137	470	3
21	0.035	485	3
22†	0.151	749	9
23	0.030	478	3
24	0.031	572	5
25	0.025	530	3

*Increase in ratio above baseline ratio measured before treatment with doxorubicin began.

†Doxorubicin withdrawn because of large increases in ratio (cases 1 and 22) or heart failure and large increase in ratio (case 2).

Comment

Systolic time intervals provide a simple yet sensitive measurement of myocardial damage⁴ and have been used previously to assess patients receiving doxorubicin.⁵ Our results show that doxorubicin may be given safely to a high total dosage if systolic time intervals are monitored regularly. Although nine patients showed evidence of heart damage (table), we were able to continue using doxorubicin in their treatment with frequent monitoring of the ratio of the pre-ejection period to the left ventricular ejection time. Three patients (one of whom had mild clinical left ventricular failure) showed progressive increases in this ratio, which returned slowly to normal when doxorubicin was stopped.

Patients treated with digoxin before doxorubicin was started did not develop significant changes in the ratio of the pre-ejection period to left ventricular ejection time, suggesting that digoxin may protect the heart against damage by doxorubicin. Digoxin may, however,

simply be masking changes caused by doxorubicin, and absolute confirmation of digoxin's protective role must await pathological studies. If digoxin was masking damage to the heart by reducing changes in the ratio, the ratio would be expected to increase when digoxin was withdrawn. Three patients completed treatment for acute myeloid leukaemia and stopped both doxorubicin and digoxin. Subsequent serial readings of systolic time intervals in all three patients did not show any appreciable increase in the ratio.

The search for anthracycline drugs that do not cause cardiac damage continues, but for the moment it seems prudent to treat patients receiving anthracyclines with digoxin and to monitor their cardiac function carefully by measuring systolic time intervals or by echocardiography.

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Danger of dead space in U100 insulin syringes

"Dead" space in a syringe is defined as the volume of a solution retained in the hub and needle when the plunger of the syringe is fully depressed. It is a potential source of error when two different fluids are drawn out, measured, and mixed in the same syringe, as in the case of insulin mixtures. With the recent changeover to U100 insulin any dead space in glass insulin syringes will be more important, and this problem has been assessed in Australia and the United States, where U100 insulin is already used.^{1,2} We report a case of hypoglycaemia which was probably caused by incorrect dosage due to the dead space in the syringe. We subsequently measured the dead space in BS 1619 glass syringes and disposable plastic insulin syringes.

Case report and subsequent investigation

Case report—A 40 year old man who had had diabetes for 17 years started having attacks of hypoglycaemia in the late morning and before his evening meal after changing to the new U100 strength insulin. He had been receiving a mixture of 10 units of neutral insulin and 10 units of isophane insulin, drawing the neutral insulin up first. He noticed that when the plunger was retracted after taking in the neutral insulin 14 units were present in the syringe, and he realised that this would alter the ratio of the short acting to long acting types of insulin. After a reduction of the neutral and an increase of the isophane insulin the hypoglycaemic attacks stopped.

Investigation and results—We used the specific gravity of aniline to measure the dead space in insulin syringes. We weighed an empty syringe, drew up aniline to a graduated mark, excluding all air bubbles, and reweighed the syringe. The difference in weights divided by the specific gravity of aniline gave the volume actually drawn up, and the difference between this and the nominal graduation mark gave the volume of the dead space. This procedure was repeated for the major graduation marks of four types of syringe, and the table shows the results. The dead space in the new BS 1619 glass syringes had a volume equivalent to around 5 units of U100 insulin whether the 0.5 ml or 1 ml size was used, whereas the old BS 1619 glass syringe had dead space equivalent to 1.26 units of U20 insulin, 2.52 units of U40 insulin, and 5.04 units of U80 insulin. In contrast, 1 ml plastic disposable U100 syringes had a negligible dead space.

Volume of dead space and equivalent units of insulin in five syringes

Type of syringe	Volume of dead space (ml)	Equivalent units of insulin
Old BS 1619 2 ml glass insulin syringe (U20 insulin) + 26 gauge, 0.5 inch needle (Everett)	0.063	1.26 (U20), 2.52 (U40)
New BS 1619 1 ml glass insulin syringe (U100 insulin) + 26 gauge, 0.5 inch needle (Rand Rocket)	0.051	5.1 (U100)
New BS 1619 0.5 ml glass insulin syringe (U100 insulin) + 26 gauge, 0.5 inch needle (Rand Rocket)	0.05	5 (U100)
BD Plastipak 1 ml plastic disposable syringe (U100 insulin) with integral 27 gauge, 0.5 inch needle	0.011	1.1 (U100)

Comment

The importance of dead space may be seen from the following example. A patient prescribed a mixture of 10 units of neutral insulin and 20 units of insulin zinc suspension and using a U100 glass syringe, which has a dead space equivalent to 5 units, will draw into the syringe 15 units of neutral insulin and 20 units of insulin zinc suspension (assuming the usual protocol is followed whereby first clear and then cloudy insulin is drawn up); he will inject around 13.5 units of neutral insulin and 16.5 units of insulin zinc suspension. The inaccuracy of such a typical regimen could certainly cause a hypoglycaemic episode.

The error produced by dead space obviously varies with the total dose, the proportions, and the order of mixing the insulins. If a patient's condition is stabilised with a particular technique and syringe there should not be any problem, but when the syringe and possibly the technique are changed, as in the changeover to U100 insulin, there may be an appreciable change in control of diabetes.

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Can amiodarone induce hyperglycaemia and hypertriglyceridaemia?

Amiodarone is an iodinated derivative of benzofuran and is structurally similar to thyroxine. Its long term use has caused thyroid gland dysfunction,¹ corneal microdeposits and cutaneous pigmentation,² pneumonitis and pulmonary fibrosis,³ neuropathy,⁴ and potentiation of anticoagulation with warfarin.⁵ We report on three patients treated with amiodarone who presented with abnormalities of carbohydrate and lipid metabolism but normal thyroid function.

Case reports

Case 1—A 71 year old woman who was taking digoxin and frusemide 25 mg every other day for heart failure had blood glucose, triglyceride, and cholesterol concentrations in the normal range. She was given oral amiodarone 200 mg every other day for rapid atrial fibrillation. One year later she developed hyperglycaemia, glycosuria (0.28 mol (50 g)/24 h), hypercholesterolaemia, and hypertriglyceridaemia (table). Serum concentrations of triiodothyronine, thyroxine, and thyroid stimulating hormone were in the normal range (2.2 nmol/l (142 ng/100 ml), 98 nmol/l (7.5 µg/100 ml), and 7.2 mU/l respectively). Amiodarone was stopped, but treatment with diuretics was not changed. Twenty days later she showed normal fasting and postprandial blood glucose concentrations and reduced cholesterol and triglyceride concentrations (table); she did not need further treatment with insulin.

Case 2—A 62 year old man was taking digoxin, diuretics (amiloride 5 mg, and hydrochlorothiazide 50 mg daily), and nifedipine for hypertensive

cardiomyopathy with angina pectoris. His triglyceride and cholesterol concentrations were in the normal range (table), but he had a slightly increased fasting blood glucose concentration and gave a borderline response to an oral glucose tolerance test. He was treated for ventricular arrhythmias with oral amiodarone 200 mg daily after a loading dose. Treatment with other drugs was not changed. Seven months later he had hyperglycaemia, glycosuria (0.28 mol (50 g)/24 h), hypertriglyceridaemia, and a borderline cholesterol concentration (table). Serum triiodothyronine and thyroxine concentrations were in the normal range (2.3 nmol/l (149 ng/100 ml) and 80 nmol/l (6.2 µg/100 ml) respectively). Amiodarone was stopped, and 45 days later he had normal cholesterol and triglyceride concentrations and only slight hyperglycaemia (table), for which he needed minimal further treatment.

Case 3—A 58 year old man was admitted to hospital for an anterior myocardial infarction with subsequent ventricular aneurysm complicated by three episodes of ventricular fibrillation and peripheral emboli. He was given coumarins, diuretics (spironolactone 25 mg and hydrochlorothiazide 25 mg daily), dipyridamole 75 mg, isosorbide dinitrate 50 mg, and mexiletine 50 mg all thrice daily, and oral amiodarone 1.6 g weekly after a loading dose. Before treatment he had normal cholesterol, triglyceride, and fasting blood glucose concentrations. We were unable subsequently to stop treatment with amiodarone despite a progressive moderate increase in triglyceride concentration. Cholesterol, fasting blood glucose, serum triiodothyronine (1.3 nmol/l (85 ng/100 ml)) and thyroxine (124 nmol/l (9.6 µg/100 ml)) concentrations remained normal (table) without any change in dosage of diuretics. One month after the dosage of amiodarone was reduced to 1.0 g weekly, however, the triglyceride concentration had decreased to 2.3 mmol/l (207 mg/100 ml) and cholesterol concentration to 5 mmol/l (193 mg/100 ml) without any change in fasting blood glucose concentration.

Fasting blood glucose and lipid concentrations and presence of glycosuria before, during, and after treatment with amiodarone in three patients

	Blood glucose (mmol/l)	Blood cholesterol (mmol/l)	Blood triglycerides (mmol/l)
		<i>Case 1</i>	
Before	5	4.7	1.8
During*	24	11.6	14.7
After	5.3	4.6	1.7
		<i>Case 2</i>	
Before	6	5.7	1.9
During*	12.2	6.3	7.8
After	8.8	5.7	2.2
		<i>Case 3</i>	
Before	5.2	4.1	1.6
During	5.3	6.2	3.8
After	5.2	5	2.3

*Glycosuria developed during treatment.

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Cholesterol: 1 mmol/l ≈ 38.7 mg/100 ml. Triglycerides: 1 mmol/l ≈ 88.6 mg/100 ml.

Comment

Even though one of our patients (case 2) already had slightly impaired glucose tolerance before treatment and in another (case 3) we were unable to withdraw amiodarone to show complete reversal of hypertriglyceridaemia, our findings indicate that hyperglycaemia and hypertriglyceridaemia are possible side effects of treatment with amiodarone.

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