DRUG INTERACTIONS AND LONG-TERM ANTIDIABETIC THERAPY

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1 A study has been carried out on a representative sample (709 patients) of the Aberdeen Diabetic Clinic. The aims were to measure the occurrence and attempt to assess the clinical significance of drug interactions involving antidiabetic agents.

2 In the month before interview, 63% of the patients were taking between one and nine additional prescribed medicines. Fifty-one per cent of the patients had been exposed to one to five drugs with a potential to interact with their anti-diabetic therapy. Only 22% of the patients had taken no drugs other than their anti-diabetic medication.

3 The degree of control of diabetes, based on arbitrary criteria on data from seven consecutive out-patient visits, was significantly worse for sulphonylurea-treated patients exposed to drugs with the potential to interact compared to patients not taking such drugs. In particular, control was adversely affected in older patients taking concurrent barbiturate or diuretic therapy. No such influence of interacting drugs on control was evident in patients on insulin or biguanide therapy.

4 A system designed to prevent the unintentional initiation of drug interactions in patients on hypoglycaemic agents is described.

Introduction

The clinical importance of drug interactions involving anticoagulant, antihypertensive and anti-depressant drugs is well known (Dollery, George and Orme, 1975; Stockley, 1974). Numerous theoretical interactions between antidiabetic agents and other drugs have been reported (Martin, 1971; Garb, 1971), but the importance of these interactions in clinical practice has not been assessed. This study measures the occurrence and attempts to assess the clinical importance of drug interactions in patients on long-term antidiabetic therapy.

Methods

The Aberdeen Diabetic Clinic serves a fairly static population of almost half a million people. Patients who had review appointments to attend randomly selected clinics were invited by letter to bring all medicines, either prescribed or self-medication, taken in the 4 week period prior to the

visit. The proportion of patients on treatment with insulin, sulphonylureas or biguanides corresponded closely with two independent work studies carried out in the clinic around the time of the survey (Lockhart, 1973). At the time of the interview immediately before the routine clinic visit all drugs were identified. In addition the frequency and results of home tests for glycosuria and the reported incidence of hypoglycaemic attacks since the previous appointment were noted. The blood sugar and urinalysis results for the interview visit and for the six consecutive previous visits were also recorded, along with alterations in therapy in this period.

An assessment of the control of the diabetic state of each patient was made by devising arbitrary criteria based on the results of the above tests (Table 1). The findings were coded and the analysis handled largely by computer. The quality of control was compared in patients taking or not taking drugs with the potential to interact. This was examined for the whole population and then

Table 1 Arbitrary criteria for control of diabetic state based on information from current and six previous consecutive visits

Category of control	Number of unsatisfactory tests*			
	Blood sugar	Urine analysis Clinic	Home (all tests)	Hypoglycaemic episodes since last appointment
Excellent	0	0	0	Not >1
Good	Not >2	Not >2	< $\frac{1}{2}$	Not >2
Fair	Not >4	Not >4	< $\frac{2}{3}$	Not >3
Poor	>4	>4	> $\frac{2}{3}$	>3

*Unsatisfactory blood sugar level (capillary—Hoffman technique) >200 mg % (11.1 mmol/l) or <60 mg % (3.3 mmol/l);

Unsatisfactory urinalysis—2% glycosuria (Clinitest) or ketonuria (ferric chloride).

within the groups of patients taking insulin, or sulphonylureas, or biguanides.

Results

Seven hundred and nine interviews of patients (390 female) on long-term anti-diabetic therapy were available for analysis. Insulin was the treatment in 328 patients (46%), sulphonylureas in 244 patients and biguanides in 207 patients. Seventy-three patients were taking sulphonylurea and biguanide therapy and one patient was on insulin and biguanide.

In the 4 weeks before interview, only 22% of the patients had taken no drugs other than their antidiabetic therapy. A range of one to nine additional prescribed medicines had been taken by 456 patients (63%) and one to four self-medication preparations by 244 patients (34%). Half the patients (51%) were taking from one to five additional drugs with the potential to interact (Table 2). Salicylates (23%), diuretics (11%) and barbiturates (9%) were the principal drugs.

Using the arbitrary criteria (Table 1) the control of the diabetic state was compared in the groups of patients taking or not taking additional interacting drugs. This latter group (345 patients)

Table 2 Number of patients on drugs which interact with anti-diabetic agents

Drug	Number of patients	Drug	Number of patients
Salicylates (a, e, f)	162 (23%)	Oral contraceptives (b)	10
Diuretics (b)	81	Adrenergic neurone blockers (a)	6
Barbiturates (7d)	67	Ergotamine (7a)	4
Sympathomimetic (b)	38	Phenylbutazone (e, 7c, f)	4
Phenothiazine (b)	34	Oestrogens (b)	3
Clofibrate (e, 7f)	28	Phenytoin (b, 7d)	3
Glucocorticoids (b)	25	Monoamine oxidase inhibitors (a)	2
Thyroxine (b)	25	Oral anticoagulant (c, f)	2
Tricyclics (7b)	23	β -adrenoceptor blocking drug (a)	3
Sulphonamides (e, 7c)	13	Anti-tuberculous (b)	1
		Others†	0

† Others include ethacrynic acid (e), chloramphenicol (d), anabolic steroids (a), cyclophosphamide (a) and ganglion blockers (a).

a effect on glucose metabolism to potentiate hypoglycaemia

b effect on glucose metabolism to antagonise hypoglycaemia

c drug metabolising microsomal enzyme inhibition, to potentiate hypoglycaemia

d drug metabolising microsomal enzyme induction, to antagonise hypoglycaemia

e displacement from plasma drug protein-binding sites, to potentiate hypoglycaemia

f delayed excretion.

Table 3 Arbitrary criteria of control and percentage of patients in each category who had taken, or not taken drugs with the potential to interact with the antidiabetic drugs (709 patients).

Category of control	All patients (709)	Concurrent interacting drugs	
		Taken (364 patients)	Not taken (345 patients)
	%	%	%
Excellent	37.6	37.6	37.7
Good	23.7	24.4	22.9
Fair	21.7	20.9	22.6
Poor	16.9	17.0	16.8

Table 4 Arbitrary criteria of control and number and percentage of patients taking and not taking drugs with the potential to interact with antidiabetic drugs

	Insulin		Biguanide		Sulphonylurea	
	Yes	No	Yes	No	Yes	No
Concurrent interacting drugs						
Number of patients	160	169	120	87	120	124
Category of control						
Excellent (%)	8.1	3.0	59.2	63.2	49.2*	69.3*
Good (%)	16.3	26.6	30.8	20.7	38.3	21
Fair (%)	40.0	36.7	10	16.1	12.5	9.7
Poor (%)	35.6	33.7				

* χ^2 9.73, $P < 0.01$

was well matched by numbers, age and sex with the group taking medicines with the potential to interact. The results are shown in Table 3. No significant overall differences in control were evident.

The analysis was also applied to the groups after subdivision into insulin, sulphonylurea and biguanide treatment (Table 4). No overall difference was detected in the patients on insulin or biguanide therapy taking or not taking additional drugs with the potential to interact. Worse control was found in the group of patients on sulphonylurea therapy taking interacting drugs ($P < 0.01$). This difference was most marked in the group of patients over 60 years of age, who also had the highest intake of potentially interacting drugs (57%; <35 years-37%).

The control of the diabetic state was also examined in each of the antidiabetic drug groups for the principal interacting drugs shown in Table 2. In the sulphonylurea-treated group of patients taking either barbiturates or diuretics a lower number had 'excellent' control ($P < 0.05$) (Table

5). With regard to barbiturates, in the poorer control categories, there was an excess of patients taking tolazamide, or other sulphonylureas which undergo hepatic metabolism, compared to chlorpropamide which is excreted unchanged by the kidney. Half the patients on diuretics were taking frusemide and one-third thiazides. No significant differences were seen for the other drugs in the sulphonylurea group or for any of the drugs in the insulin or biguanide groups.

Four hundred and thirty-seven patients (62% of the whole population) took alcohol at least occasionally. A comparison with the abstainers showed no differences in control for patients on insulin or biguanides. In patients on sulphonylureas the abstainers had worse control ($P < 0.01$). Another finding was that sixty-four patients admitted to symptoms of malaise and flushing when taking alcohol, a possible disulfiram-like effect. Most were on chlorpropamide (thirty-seven patients) but seventeen of these patients were on insulin and four on tolazamide.

Table 5 Degree of control by specific drugs: percentage of patients with 'excellent' control

Drug	Insulin	Biguanide	Sulphonylurea
Salicylate	6.5	89	70
Diuretics		78	46*
Barbiturates	5.3	88	47†
Patients not on interacting drugs	3.0	63	69

* $\chi^2 = 6.11$, $P < 0.05$; † $\chi^2 = 4.69$, $P < 0.05$

Discussion

Half the patients on long-term antidiabetic therapy had taken drugs with the potential to interact in the 4 weeks before interview. The control of the diabetic state, as judged by arbitrary criteria, was adversely affected in sulphonylurea-treated patients taking drugs with the potential to interact, particularly barbiturates or diuretics. In the group of patients on insulin or biguanide therapy the concurrent administration of an interacting drug did not cause an overall significant deterioration in the control of the diabetic state.

The patients interviewed were representative of the Aberdeen Diabetic Clinic (approximately 3,000 patients) and the proportion of patients on the different anti-diabetic agents coincided with a previous work study (Lockhart, 1973). The finding that half the patients were taking drugs with the theoretical potential to interact suggests that doctors have not been deterred from prescribing such drugs (as may have occurred with monoamine oxidase inhibitors) because of reports in the literature, or fears, or clinical experience of severe hypoglycaemia or hyperglycaemia. Alternative explanations for the high occurrence of potential interactions may include the low awareness and therefore recognition by doctors of drug interactions (Petrie, Howie & Durno, 1974), coupled with poor communications about drug therapy (Beveridge & Petrie, 1972), and confusion caused by contradictory statements in the literature. However, these factors are common to other drugs involved in clinically important interactions such as anticoagulants and adrenergic neurone blocking agents. In a study using similar methods in this area on the latter groups of drugs potential interactions were detected in only one-third of the patients interviewed (Starr & Petrie, 1971). This suggests that in clinical practice doctors appear to attach less importance to antidiabetic interactions.

The criteria which were devised to assess the control of the diabetic state may be criticised as unsatisfactory or too strict, or too lax. Alternative criteria might have employed only the results of

'spot' clinic blood tests and excluded the type of routine information used in everyday diabetic clinic practice such as the results of home urine tests and reports of hypoglycaemic reactions. A reliance only on clinic tests has disadvantages because a tightening of control may occur around the time of the routine visit to the diabetic clinic. In addition, the detection of poor control between visits and of adverse effects of drug interaction is reduced if information obtained from the patient, particularly in patients on insulin, is excluded. Of course the inclusion of information about home tests supplied by the patient has the obvious disadvantage that it may be unreliable, although in a well-run diabetic clinic the patient has nothing to gain by fabricating results which determine his life-long therapy.

Theoretically, interacting drugs might fail to affect diabetic control in an individual patient if the effect of one drug were counteracted by concurrent administration of another drug with an opposite effect. Such a cancelling-out action could also apply in negating any overall effect in a group analysis. However, analysis by individual interacting drugs within each group did not suggest that this was a major factor in the present study. Indeed, other factors may be more important than the influence of an interacting drug. For example, a dietary indiscretion or a variation in food intake, or a change in exercise patterns, or a deliberate variation in insulin dosage because of the use of sliding scales, or impaired renal function may more than compensate for the effect on the antidiabetic agent or on glucose metabolism of the concurrent administration of another drug. Furthermore, biguanides do not have any significant direct hypoglycaemic action. Nevertheless, despite these factors the analysis of the patients in the sulphonylurea group shows that control was adversely affected, particularly in older patients who are most at risk of polypharmacy.

In this survey only two drug groups have been shown to cause an overall significant interference with the control of the diabetic state. In the case of barbiturates the interaction is probably attri-

Table 6 Example of information about principal interactions available for attachment to clinic and general practice case records

<i>Drug group</i>	<i>Interaction with</i>	<i>Hypoglycaemic effect</i>
Insulins, oral hypoglycaemics	Drugs influencing glucose metabolism, e.g. salicylates, β -adrenoceptor blocking drugs, adrenergic neurone blockers, monoamine oxidase inhibitors	Potentiated
	Diuretics, glucocorticoids, oestrogens, sympathomimetics, barbiturates.	Antagonised
Sulphonylureas	Drug metabolising microsomal enzyme inhibitor agents: e.g. coumarin anticoagulants, monoamine oxidase inhibitors.	Potentiated
	Displacement from plasma protein drug binding sites, e.g. clofibrate, phenylbutazone, sulphonamides	Potentiated

butable to hepatic drug-metabolising enzyme induction, and this is supported by the higher proportion of patients in the poorer control categories taking those sulphonylureas which undergo hepatic metabolism compared to chlorpropamide which is excreted virtually unchanged. The effect of diuretics on glucose metabolism is well known. The failure to demonstrate interference with control by some other drugs involved in significant interactions, for example beta blockers or phenylbutazone, may be due to the small number of diabetic patients exposed to them in practice.

Of course it is well known that important interactions may occur in individual diabetic patients (Table 6) and, during the course of the survey, two patients were admitted to our ward with severe hypoglycaemia due to the interaction of phenylbutazone with chlorpropamide. Nevertheless our findings show that in a representative group of diabetic patients the overall problem of drug interaction is not as clinically important as it is in patients on oral anticoagulants, adrenergic neurone blockers or antidepressant agents.

We suggest that a solution to the problem is to prepare labels with information about the probable effects of specific additional drug therapy to stick on to the hospital and general practice case records of diabetic patients (Table 6). This approach may be more effective than the use of drug discs (Whiting, Goldberg & Waldie, 1973), or complex commercial systems. An awareness of the occurrence of the interaction should reduce unintentional drug-induced illness and alert the doctor so that appropriate modification of therapy can be made.

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