ACETOHEXAMIDE ('DIMELOR') IN DIABETES

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The sulphonylurea drugs, tolbutamide and chlorpropamide, have been used extensively in our Diabetes Clinic in the management of adult patients with the stable type of disease who are non-ketotic. They have also occasionally been used in the rarer, younger subjects with asymptomatic diabetes discovered accidentally.

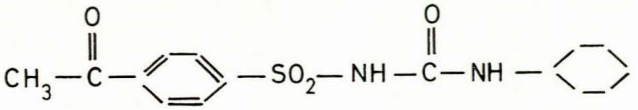
Sulphonylureas act by releasing endogenous insulin from the beta cells of the pancreas, providing the pancreas is not severely damaged.

Tolbutamide ('rastinon', 'artosin') can be considered almost completely safe. Severe hypoglycaemia is not a danger. The maximum dose should never exceed 3 G (6 tablets) per day. One disadvantage is that it has to be given in divided doses.

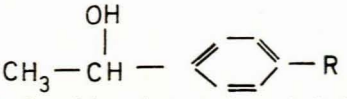
Chlorpropamide ('diabinese')—a much more powerful hypoglycaemic agent than tolbutamide—produces better results in more severe diabetics (excluding ketosis, of course). Further, it is long-acting and can be taken in 1 daily dose. It is, however, known to produce occasional important toxic effects, especially skin rashes and intrahepatic obstructive jaundice with damage to the liver cells. Owing to the fact that it is not detoxicated in the body and is slowly excreted there is a greater danger of severe hypoglycaemia. Daily dose should, in any event, never exceed 500 mg. (2 tablets) and preferably be reduced to 250 mg. where possible.

The ideal sulphonylurea might therefore be one that falls between these 2 in potency, has no toxic effects and can be taken in 1 daily dose.

Recently short-term experiments have been carried out to study the efficiency of a new oral sulphonylurea, acetohexamide [N-(p-acetylbenzenesulphonyl) - N - cyclohexylurea], which was synthesized in the Lilly Research Laboratories. Its chemical structure differs from that of the earlier sulphonylureas in the substitution of an acetyl group in the para position on the phenyl ring and a cyclohexyl group on the urea radicle:



Acetohexamide



Reduced form (principal metabolite)

Both acetohexamide and its metabolic product (formed by the reduction of the p-acetyl group) have the same hypoglycaemic activity in man and animals as do tolbutamide and chlorpropamide,[1] differing only in duration of action and potency. (Actually, in the rat, acetohexamide is about 4 times as active as tolbutamide and twice as active as chlorpropamide.[2]) The fact that its metabolic product is also physiologically active probably accounts for its prolonged action (24 - 48 hours). A single daily dose is therefore sufficient. In practice, acetohexamide probably falls between the other 2 sulphonylureas in potency. In price, dose for dose, the 3 sulphonylureas are comparable.

CLINICAL STUDIES—METHODS

The purpose of this report is to present preliminary data which have accumulated over a period of 6 months on 50 patients treated with acetohexamide in the Diabetes Clinic at Groote Schuur Hospital (Table I). Duration of treatment with acetohexamide has ranged from 2 - 6 months. All patients were of maturity-onset type and appeared to be suitable for trial of therapy with a sulphonylurea (except case 3, mentioned below).

Subjects

Patients were seen initially at weekly or bi-weekly intervals and thereafter monthly. There were 13 Whites and 37 non-Whites. Females outnumbered the males by 39 to 11, and the ages ranged from 36 to 82 years with an average of 55. Twenty patients (40%) were of recent onset, a further 16 (32%) had been diabetic for under 7 years, and the remaining 14 (28%) had been diabetic for over 7 years. Average duration of the diabetes was 5½ years.

The weights ranged from 96 to 289 lb. Twenty patients weighed under 150 lb., 26 weighed between 150 and 200 lb. and 4 were 200 lb. and over. As 78% of the patients were females, it follows that many of them were definitely overweight. Eleven patients were known to have retinopathy, 2 had myocardial ischaemia, 2 peripheral vascular disease, and 1 parkinsonism.

Dosage

All new patients were given a loading dose of 3 tablets (1,500 mg.) administered as the first dose, followed by 2 tablets (1,000 mg.) on the second day and 1 tablet (500 mg.) daily thereafter. Those poorly controlled on other therapy—with 1 or 2 exceptions—were also given a loading dose for a start. Those patients who were well-controlled on other therapy but transferred to acetohexamide as part of the trial, were given the regular maintenance dose of 1 tablet daily. Those who failed on this dose had their therapy increased to 1½ (5 patients) and 2 tablets (4 patients). Thirty-eight of the 50 (76%) were on 1 tablet daily.

Evaluation of Control

Results were based on clinical and biochemical findings. Response was considered 'successful' when the patient became asymptomatic, glycosuria throughout the day was either absent or much reduced, and the blood-sugar level was either normal (below 120 mg. per 100 ml., fasting) or much reduced from previous levels and in any event below 200 mg. In a few instances sufficient blood-sugar levels were not available, and in these complete aglycosuria was demanded.

Response was considered a 'partial success' when only some of the above conditions obtained—e.g. disappearance of symptoms, considerable reduction of glycosuria, and some reduction in blood-sugar levels; others failed.

RESULTS

The response to treatment with acetohexamide is summarized in Table I.

Thirty-five of the 50 patients (70%) treated with acetohexamide achieved success, 7 (14%) partial success and 8 (16%) failed, with 2 secondary drug failures. Six out of the 11 males (54·5%) achieved success; 2 partial success and 3 failed. Of the 39 females, 29 (74%) had success, 5 partial success and 5 failed. In the younger age group (under 40) 2 of 4 were successful, 1 had partial success and 1 failed. In the 40 - 60 year group, which comprised 60% of the total, 24 (75%) had success, 5 partial success and 4 failed. In the older age group—60 - 85 years—9 out of the 13 patients (70%) were successful, 1 partially successful and 3 failed.

Diabetics in whom the condition was of recent onset scored 15 successes out of a possible 20 (75%), 3 partial successes and 2 failures. In others who had been diabetic for under 7 years, 8 out of 16 (50%) were successful, 3 out of 16 were partially successful and 5 out of 16 failed. In the 7 years and over group, 12 out of 14 (85·7%) were successful, 1 partially successful and 1 failed.

Four patients were successfully maintained on half a tablet daily. On 1 tablet daily, 25 out of 36 (70%) were successful, 5 were partially successful and 6 failed. Four were successful and 1 partially successful on 1½ tablets daily; 2 succeeded, 1 partially succeeded and 1 failed on 2 tablets per day.

Three patients whose blood-sugar levels were between 360 and 385 mg. per 100 ml. initially, did very well on acetohexamide. Two other patients who failed on diet alone initially, were then adequately controlled on acetohexamide, later taken off the tablets and then became well-controlled on diet alone.

TABLE II. RESPONSE TO ACETOHEXAMIDE OF PATIENTS ON VARIOUS PREVIOUS THERAPIES

Previous therapy	*Total*	*Success*	*Partial success*	*Failure*
Diet alone	25	20	3	2
Insulin	1	1	—	—
Chlorpropamide ..	4	3	—	1
Tolbutamide ..	15	10	2	3
Diguanide ..	3	1	1	1
Chlorpropamide +diguanide	2	—	1	1
	50	35	7	8

Comparison with Previous Therapy (Table II)

All new patients were first instructed to take a strict diet only. When there had been no response after 1 week or longer, acetohexamide was started. Of the 25 new patients, 20 (80%) were successful, 3 had partial success and 2 failed. Of the 20 successful cases, 2 subsequently became secondary failures (1 almost certainly through lack of dietary control).

One patient who had never really been sugar-free on insulin, was completely successfully controlled on acetohexamide in spite of an intercurrent infection. Of the 4 who had been on chlorpropamide, 3 were successful and 1 failed. Among the 15 previously on tolbutamide there were 10 successes, 2 partial successes and 3 failures. Of 3 previously on diguanide, there was 1 success, 1 partial success and 1 failure. Two had been on a combination of chlorpropamide plus a diguanide—1 was a partial success on acetohexamide and 1 failed.

TABLE I. RESPONSE TO ACETOHEXAMIDE

	Total patients	*Sex*		*Age in years*			*Onset of diabetes*		
		Male	*Female*	*<40*	*40-60*	*>60*	*Recent*	*<7 years*	*>7 years*
Success	35	6	29	2	24	9	15	8	12
Partial success ..	7	2	5	1	5	1	3	3	1
Failure	8	3	5	1	4	3	2	5	1
Secondary failure	(2)		(2)						
	50	11	39	4	33	13	20	16	14

A comparison of the response to acetohexamide compared with that to previous therapies is made in Table III. Of the 15 subjects previously on tolbutamide, 9 had better results, 4 were the same and 2 were possibly worse on acetohexamide. (Of these 2, 1 was not given a fair trial of acetohexamide and the other had had no therapy for 3 years.)

TABLE III. RESPONSE TO ACETOHEXAMIDE COMPARED TO PREVIOUS THERAPIES

		Acetohexamide was		
Previous therapy	*Total*	*Better*	*Same*	*Worse*
Tolbutamide ..	15	9	4	2 doubtful (see text)
Chlorpropamide ..	4	—	4	1*
Diguanide ..	3	—	2	1
Insulin	1	1		
Chlorpropamide + diguanide	2	—	—	2
	25	10	10	5+1*

*One patient previously on diet alone, failed on acetohexamide, 1 tablet daily; good response to chlorpropamide, 2 tablets daily.

All 4 cases on chlorpropamide had the same result on acetohexamide, except that 1 patient who had failed on 1 tablet of acetohexamide subsequently succeeded with 2 tablets of chlorpropamide.

Of the 3 subjects on diguanide, 2 had the same results and 1 did worse on acetohexamide.

One patient previously on insulin did better on acetohexamide. Two on a combination of chlorpropamide plus a diguanide did worse on acetohexamide.

Toxic Effects

With the exception of 1 patient who complained of occasional nausea and an urticarial rash of 1 day's duration before her visit to the clinic, there were no toxic effects. (This patient suffered from chronic diarrhoea of unknown aetiology.)

Three patients complained of mild hypoglycaemic symptoms (confirmed by blood-sugar readings in 2 cases) and their dose was reduced to half a tablet daily.

DISCUSSION

Our results appear to be very similar to those reported by other workers.[3] The initial success rate of 70% is good, but it must be remembered that only a few of these patients had failed on other therapy, and only 1 had previously been taking insulin. On the other hand, in our trial of chlorpropamide the great majority of patients had previously failed on tolbutamide[4] (20 out of 43 of these were fully successful on chlorpropamide); in our trial of phenformin ('insoral TD') most patients had failed on both sulphonylureas.[5]

Acetohexamide certainly appears to be more potent than tolbutamide and possibly equal to or slightly less potent than chlorpropamide, but we do not have sufficient data for proper comparison between these 2.

It was unexpected that the best results with acetohexamide were obtained in those patients who had been diabetic the longest (85·7% success). As we have remarked before, neither long duration of diabetes, initial blood-sugar levels of over 300 mg. per 100 ml., nor previous high insulin dosage preclude success being achieved with sulphonylureas.

As in the case of tolbutamide and chlorpropamide, acetohexamide appears to combine satisfactorily with a diguanide in some patients who have not been well-controlled on either drug alone.

As we have previously stressed, the diabetic's diet is still important when a sulphonylurea is being taken. On several occasions we observed temporary deterioration of metabolic control to be readily traceable to dietary indiscretions; 1 'secondary failure' was certainly a 'dietary failure' rather than a 'drug failure'. We did also have 1 apparently true secondary acetohexamide failure, and it is to be expected that more will occur with time.

The toxicity of acetohexamide seems to be slight, but we have insufficient experience as yet to be over-sanguine about this.

Individual Cases

Summaries of a few case reports will be more informative about individual responses.

Case 1. Response despite initial high blood sugar. This Bantu male, aged 42, complained of loss of weight, polyuria, polydipsia and weakness for 2 weeks. No family history of diabetes. Weight 185 lb., glycosuria 4+; blood-sugar level 385 mg. per 100 ml. No response to diet for 1 week. On acetohexamide, 1 tablet daily, the blood sugar came down to 99 mg. He has lost 10 lb. in weight and says he feels better every visit.

Case 2. Response despite high initial blood sugar. Importance of diet. A Moslem female, aged 58 years, complained of pruritus vulvae, polyuria and polydipsia. No family history of diabetes. Weight 135 lb., no evidence of vascular disease, glycosuria 4+, and a postprandial blood-sugar level of 360 mg. per 100 ml. There was no response to diet after 1 week and the patient was given a loading dose of acetohexamide. For 4 months she remained asymptomatic, urine sugar-free, and a half-hour postprandial blood-sugar estimation was 125 mg. per 100 ml. She lost 2 lb. in weight. Subsequently glycosuria returned together with a fasting blood-sugar level of 196 mg.—she admitted to drinking condensed milk and not dieting correctly. The dose of acetohexamide was increased to 1½ tablets; on this, together with more correct dieting, she became well-controlled again.

Case 3. Response in long-duration diabetes with early onset and poor insulin control. A 38-year-old Coloured female, diabetic for 14 years, had been on insulin in increasing doses up to 68 units of lente daily; she never felt well on the insulin, and her urine was never sugar-free. Between January 1962 and January 1964 she was seen only once at Groote Schuur Hospital and that was with a septic foot. When she presented herself at the clinic she complained of loss of weight, polyuria and pain in the chest. Glycosuria was present and her blood-sugar level was 252 mg. per 100 ml. She begged not to be put back on insulin since it always made her feel ill and dizzy. She was given a loading dose of acetohexamide and a diguanide. Next seen 1 week later she had gained 4 lb. in weight, but felt shaky. No glycosuria; 5-hour postprandial blood-sugar level 76 mg. per 100 ml. The diguanide was stopped and she continued with 1 tablet of acetohexamide daily. Seen 1 week later she had gained a further pound in weight; now 104 lb.; no glycosuria; 2-hour postprandial blood-sugar level 68 mg. per 100 ml. The dose of acetohexamide was reduced to half a tablet daily, since when she has been satisfactorily maintained for 2 months up to the time of writing.

Case 4. Response after difficulties with other sulphonylureas. A non-obese White female, aged 64 years, first seen 4 years ago. Subsequently defaulted for 3 years and reappeared with typical symptoms of diabetes. She had glycosuria 3+; chlorpropamide plus a diguanide were prescribed. After a few weeks she developed a polymorphic light-eruption (patch test positive for chlorpropamide). While in the wards she was fairly well-controlled on a combination of phenformin plus tolbutamide. One month later, when seen again at the clinic, her blood-sugar level was 293 mg. per 100 ml.; glycosuria 2+. Acetohexamide was substituted for the other drugs. After 1 month control was only fair and the acetohexamide was increased to

2 tablets daily. For 2 months since this she has remained aglycosuric.

CONCLUSION

From our preliminary observations and from the literature we believe that acetohexamide compares favourably in usefulness with the other 2 sulphonylureas, tolbutamide and chlorpropamide, at low dose level. It appears to be virtually free of serious toxic effects. Nevertheless, dietary control still remains the necessary basic factor in the management of diabetics.

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*Further references may be obtained from this paper.