CLINICAL TRIAL OF AMINO-METHYLBENZOL-SULPHONYL-CYCLOHEXYLUREA ('METAHEXAMIDE') IN DIABETICS AFTER FAILURE OF TOLBUTAMIDE

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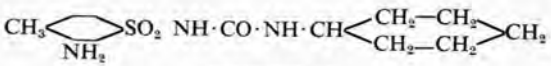
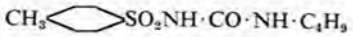
Metahexamide* is a sulphonyl urea derivative, N. 3 amino 4 methylbenzol-sulphonyl-N¹-cyclohexylureum, with a structural formula (compared with tolbutamide) as follows:



Metahexamide



Tolbutamide

Like its analogues, tolbutamide and chlorpropamide, it is capable of lowering the blood sugar in normal subjects and in some diabetics; not in diabetes of the juvenile type. Its breakdown and excretion are slower than with tolbutamide, the blood level being reduced 50% from a maximum in about 20 hours.

Toxic Effects in Man

Occasional allergic skin reactions and gastro-intestinal irritation appeared to be the only effects of metahexamide at first. Unfortunately, while we were in the process of performing a clinical trial of this substance, the makers reported that severe hepatic disturbances had occurred in some patients while taking it, and consequently they very correctly withdrew all supplies.

We report below, briefly and for record purposes, our results until the cessation of the trial.

* The metahexamide and the scientific data thereon were kindly supplied by Messrs. Hoechst Pharmaceuticals of South Africa. Noristan Laboratories (Pretoria) also supplied some tablets, which had not been used by the time the trial was discontinued.

Methods

The patients chosen for the trial had diabetes of maturity-onset type, had never had ketosis and, except one, were all over 40. The duration of their diabetes varied from 1 to 20 years, and just over half had received insulin previously. *All* cases, however, had failed to respond adequately to both diet and tolbutamide, so that this trial aimed at being rather a searching test for metahexamide.

The subjects were out-patients attending a diabetic clinic and seen for the most part weekly. Several fasting blood sugars were estimated in the weeks before metahexamide was started, while the patient was taking no drug or was on tolbutamide only. Urine samples were tested at the clinic and also by the patient at home. In some cases the 24-hour urine sugar was estimated on several occasions. Weekly weight records were kept. As discussed previously,[1] we consider it essential that a period on *no* treatment other than diet should precede the evaluation of an oral drug.

The patients were started on 50 or 100 mg. of metahexamide and this was increased gradually to a maximum of 300 mg., taken in a single daily dose.

Results

Results are classed as 'success' if the blood sugar is brought within normal range (though we realize that carbohydrate tolerance may still be grossly abnormal) and the urine tests showed 'nil' or 'trace'. A 'partial success' indicates a distinct improvement, and 'failure' no apparent effect at all.

The patients receiving the drug numbered 28, and the effects are assessed in 27; one patient had to stop therapy

because of nausea, vomiting and headaches. The make-up of the patients was as follows:

'RACE'		BODY BUILD	
White	20	Slim	10
Coloured (i.e. half-caste) ..	7	Medium ..	15
		Fat	2
	27		27

PRIOR RESPONSE TO TOLBUTAMIDE

Primary failure	13
Secondary failure, following initial success	11
Partial success	3
	27

The response to metahexamide was classed as follows:

Success	3
Partial success	6
Failure	18
	27

The 3 'successes' were aged 32, 65 and 71; none was obese; the 2 older patients had never had insulin. The response of the younger patient is shown in Fig. 1.

The response to metahexamide bore no relation to the tolbutamide response; for instance, 1 'success' and 3 'partial successes' had been primary tolbutamide failures.

No obvious trend in total white-cell count or serum-cholesterol level was evident from metahexamide therapy. The serum cholesterol in one patient, however, who responded successfully to metahexamide, dropped from 237 mg. per 100 ml. to 179 in 10 weeks (Fig. 1). These were the only levels obtained in that patient.

Comment

Body build. It is noteworthy that on analysis of our figures we found not a single over-weight patient in the White racial group who received metahexamide, although the patients in the trial were quite unselected, apart from being tolbutamide failures and able to attend regularly. This indicates our reluctance to use the sulphonyl-ureas in obese subjects, who are better treated by dietary measures. In the poorer, Coloured patients the position is different—it is usually impossible to achieve success with diets in these people.

Efficacy of metahexamide. The results of metahexamide in tolbutamide-failed cases were not impressive—nevertheless a maximum of only 300 mg. of metahexamide was used, as againste 1 - 3 g. per day of tolbutamide. Where it does work, metahexamide would appear to be more powerful, dose for dose.

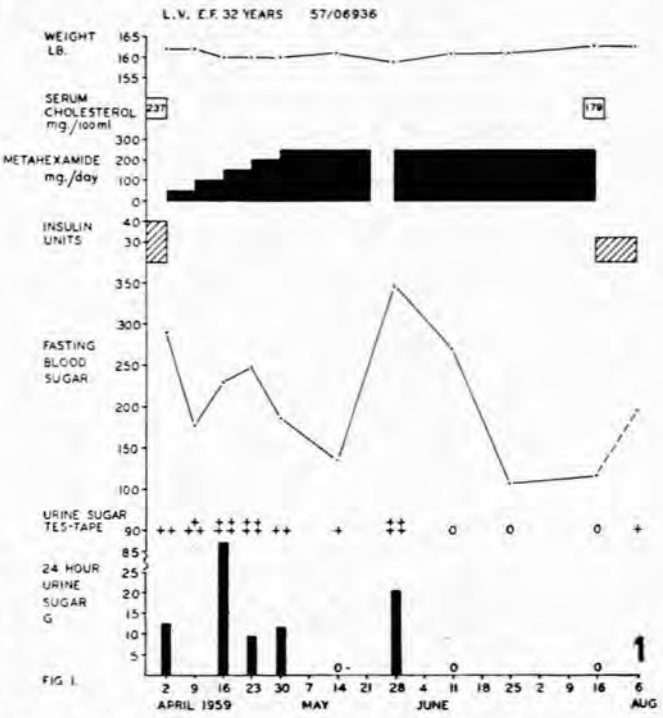


Fig. 1. This shows one of the more satisfactory responses to metahexamide. The patient was the only one in the series under 40 years of age, and had failed previously to respond adequately to tolbutamide. The high blood-sugar level with a corresponding peak in urine sugar following a period of 5 days without therapy is noteworthy.

SUMMARY

A trial of metahexamide was made in a group of diabetic patients who were believed to be suitable for oral sulphonyl-urea therapy but who had failed to respond adequately to tolbutamide. A few responded better to metahexamide but on the whole the results were disappointing. Metahexamide is no longer available.

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REFERENCE

1. Jackson, W. P. U. (1958): S. Afr. Med. J., 32, 153.