COMBINED ORAL THERAPY IN DIABETES

SULPHONYLUREA* PLUS DIGUANIDE*

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The sulphonylurea drugs, tolbutamide and chlorpropamide, are extensively used in the management of maturity-onset diabetic patients. However, a number of people fail to respond to these drugs for no apparent reason,[1] a further number respond only partially, while some who respond well at first lose their sensitivity to the drug later and become 'secondary failures'.

The diguanides were introduced largely in an attempt to cope with these various failures. Phenformin was certainly capable of reducing the blood sugar in many of them, but the gastro-intestinal side-effects were considered sufficiently severe to render this drug a very doubtful asset.[2] Metformin may have been somewhat less unpleasant in this regard, but was rather weaker in action.[3] (Phenformin is now available for trial in slowly disintegrating capsules and is being re-evaluated in this form; a report on this may appear later, but the present trial concerns phenformin in 25 mg. tablet form).

The sulphonylureas almost certainly act by stimulating the patient's pancreatic islets to produce or to expel more insulin, while the diguanides in some way render the peripheral action of insulin more efficient. It was therefore reasonable to try a combination of these in the hope that this might be effective where each individual drug had failed, or that the dosage requirement of each might be reduced.

Previous Reports

Successful use of such combinations has been reported by Beaser in 1958,[4] Unger *et al.* in 1960[5] and Bloom and Richards in 1961.[6] Bloom and Richards report on 47 patients who failed to respond to tolbutamide (1 gram twice a day) or chlorpropamide (500 mg. daily), but were well controlled when phenformin was added as 1 tablet, 25 mg., 3 times a day, or as slow-acting capsules. They remark that this control by the mixture might have meant *either* that the additive effect of each drug was necessary, *or* that phenformin alone was the active member, in which case the tolbutamide or chlorpropamide was redundant. An inpatient trial including 36 diabetics who had failed to respond to chlorpropamide was therefore undertaken. In 9 of these, phenformin alone produced successful control of the diabetes. In 14 who had failed to respond to either drug separately, control was obtained when the tablets at the same dosage were given together. In 13 patients tablets proved unsuccessful and insulin was then used.

PRESENT SERIES

The following is an analysis of those patients treated by the oral combination at Groote Schuur Hospital, almost all in the Diabetes Clinic, whose records were readily available and in whom there had been sufficient time to indicate the likely outcome of the therapy by 1 May 1962. This is not the result of a planned investigation, and it includes only the short-term responses of patients treated by different physicians in different dosage schedules. Few patients have yet received a combination for more than one year.

The 51 patients were all classed as having the 'mild', not ketosis-prone type of diabetes, and all were over 30 years of age except one obese child aged 14 with mild asymptomatic diabetes accidentally discovered, and a slightly overweight girl of 29. Of this series 11 were males and 40 females, and 25 were White and 26 Coloured. Three weighed more than 200 lb., and a number of others were overweight and had failed to reduce properly despite continued exhortation, but most were within 15% of their correct weight.

Patients were seen at the Clinic at varying intervals. At these visits their urine was tested and blood-sugar estimations, mostly in the fasting state, were performed. Almost all the subjects tested their own urine at home, using Benedict's reagent, 'clinitest', or 'testape'. Response was also judged by alleviation of symptoms and gain in weight in those who were believed to have lost excessively through glycosuria.

The response was considered 'successful' when the patient became asymptomatic, glycosuria throughout the day was absent or much reduced, and the fasting blood-sugar level was either normal (below 120 mg. per 100 ml.) or much reduced from previous levels and in any event below 180 mg. The response was considered 'doubtful' or 'partial' when there was probably some, but insufficient, improvement; others 'failed'.

Drugs and Doses

All patients had failed to respond to tolbutamide or chlorpropamide or both in adequate dosage** when given alone; 14 had also failed to respond to phenformin or metformin.

The sulphonylurea used in the combination was tolbutamide in 5 instances (1 - 3 grams daily). In the rest, chlorpropamide was used (1, 1½ or 2 tablets daily, i.e. 250 - 500 mg.).

Metformin ('glucophage') was used in 26 cases, doses usually being 2 - 6 tablets (1 - 3 grams) daily in divided doses, but in 2 instances as little as half a tablet daily (250 mg.) was given. Phenformin ('insoral') was given to the rest of the patients as half a tablet twice daily up to 3 tablets (75 mg.) in divided doses. The diguanide drugs were taken with or directly after food.

Although a reduction in glycosuria may be expected to occur within a few days if the combination is going to be successful, the trial in each patient was allowed to continue for at least 2 weeks. (Metformin may actually be slower in its effect than phenformin.)

* The sulphonylureas concerned are tolbutamide (Rastinon, Hoechst; Artosin, Boehringer) and chlorpropamide (Diabinese, Pfizer). The diguanides are phenformin (D.B.I., Insoral, U.S. Vitamin Corporation, supplied in South Africa by Messrs Warners) and metformin (glucophage, Rona Laboratories, supplied in South Africa by Protea Pan Africa Ltd.).

** 'Adequate dosage' means 2 tablets of chlorpropamide daily or at least one tablet of tolbutamide t.d.s.

TABLE I. RESULTS OF TREATMENT

Outcome of treatment	*Combination treatment, all cases*	*Cases previously failed on both sulphonylurea and diguanide used separately*	*Only one tablet of diguanide daily used in combination*	*Duration of diabetes over 10 years*
Successful	24	5	5	5
'Partial or doubtful'	5	1	2	1
Failed — Stopped for side-effects	3		2	
Failed — No control of sugar	19	8	2	6
Failed — Total	22		4	
Total	51	14	11	12

RESULTS

It is impossible to express the results in a fully logical and definitive manner because of the considerable differences in types of patient, method of previous handling, doses of each drug used and duration of observations. What follows is really an approximate summary of the position to date.

Table I shows that we may consider 24 of the total of the 51 patients to be well controlled by the combination of drugs. Several others may yet show improvement with longer follow-up and an increase in dosage of one or other drug. In 3 of the 'failed' cases the drugs were stopped by the patients themselves, because of 'side-effects'. Two of these were on the very lowest dose of diguanide being used. In 19 instances there was outright failure to improve control in the dosage so far used.

Fourteen patients had not previously been controlled after adequate trial of both sulphonylurea drugs and diguanides, used separately. Five of these became well-controlled on the combination. Example:

Case 1

A thin White nursing sister, aged 54, complained of typical diabetic symptoms of several months' duration, including loss of weight (to 102 lb.) and polyuria. Tolbutamide and chlorpropamide both failed, as did phenformin in doses up to 100 mg. daily. After a few days on a combination of 500 mg. of chlorpropamide with 100 mg. of phenformin her glycosuria and her symptoms disappeared, her fasting blood-sugar readings dropped from 220 mg. to under 140, and an alteration in ocular refraction occurred so rapidly that she felt as if a film had appeared over her eyes.

In five out of eleven patients the addition of a single tablet of a diguanide daily (given as ½ tablet b.d.) to a sulphonylurea was sufficient to produce good control.

Five out of 12 patients with diabetes of more than 10 years' duration were well controlled on the combination.

Two of the 5 patients in whom tolbutamide was the sulphonylurea used in the combination were well-controlled.

A few patients who had been poorly controlled by insulin were much better on the oral combination. Example:

Case 2

A 29-year-old physically and mentally handicapped girl with diabetes of 2 years' duration was rather unstable on 80 units of lente insulin, to her mother's discomfiture. She had never been in ketosis and was a little overweight. It was gratifying when she became perfectly controlled on a single tablet of chlorpropamide daily and half a tablet of metformin taken 3 times a day.

One patient had an episode of severe ketosis and was later satisfactorily controlled on an oral combination, while in the wards:

Case 3

A Coloured male, aged 40, with a 4-year history of diabetes was admitted to hospital with pneumonia and diabetic ketosis. Later he was readmitted with diabetic diarrhoea, loss of weight, weakness, thirst and polyuria, despite taking 80 units of insulin daily. A fasting blood-sugar reading was 264 mg. His control became excellent on 1 tablet of metformin 3 times daily plus 2 of chlorpropamide daily. A fasting blood-sugar level was 95 mg.

One patient with carcinoma of the pancreas was satisfactorily controlled:

Case 4

A Coloured male, aged 41, with proved carcinoma of the pancreas developed diabetes without ketosis, which failed to respond to tolbutamide or chlorpropamide. The addition of 1 tablet of phenformin twice daily abolished the glycosuria and reduced the fasting blood-sugar level from 220 to 140 mg. per 100 ml.

DISCUSSION

It appears to us in the Diabetes Clinic that the combination of a diguanide with a sulphonylurea is frequently valuable, either when tolbutamide and chlorpropamide alone have failed, or in order to allow a reduction in the dose of chlorpropamide. The success achieved in some cases with very small additions of diguanide strongly supports the idea that the effect of these 2 drugs may be more than merely additive. It is true that in some of our 'successes' the diguanide *alone* might be equally as effective as the combination; this can be tested only by omitting the sulphonylurea component in each case. Our present general policy, however, is to add a diguanide to chlorpropamide when the latter alone has failed, starting with the former in dosage sufficiently low as to be unlikely to produce side-effects. In fact, in the present series the trial of the combination was stopped in only 3 cases, with the complaints of headache and anorexia in one, vomiting in one, and an itching rash in the third. It may be doubted whether the drugs themselves actually caused the 'side-effects' in any of these cases.

To end with a note of caution in interpretation of 'response' to oral drugs:

Case 5

A 43-year-old male presented with severe symptoms of classical type and some ketosis (nitroprusside test on urine was strongly positive). Chlorpropamide (500 mg. daily) made no impression and the patient continued to lose weight. The combination of chlorpropamide with phenformin (25 mg. 3 times daily) produced rapid and complete control. A little later the phenformin was withdrawn and control remained excellent with only 375 mg. of chlorpropamide daily.

SUMMARY

The use of a combination of the 2 types of oral drug for diabetes (sulphonylurea and diguanide) is considered. Where sulphonylurea alone had failed, the addition of phenformin or metformin was successful in controlling the diabetic state in 24 patients out of 51. Side-effects were infrequent, since this combination allowed doses to be used that were smaller than would normally be effective alone.

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REFERENCES

1. Herman, J. B. and Jackson, W. P. U. (1960): S.Afr. Med. J., **34,** 31.
2. Schneider, T., Lopis, S. and Politzer, W. M. (1960): *Ibid.*, **34,** 301.
3. Herman, J. B. and Jackson, W. P. U. (1961): *Ibid.*, **35,** 286.
4. Beaser, S. B. (1958): New Engl. J. Med., **259,** 1207.
5. Unger, R. H., Madison, L. L. and Carter, N. W. (1960): J. Amer. Med. Assoc., **174,** 2132.
6. Bloom, A. and Richards, J. G. (1961): Brit. Med. J., **1,** 1796.