CLINICAL NOTES

Trial of Chlorpropamide in Subclinical Diabetes

By

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Summary. A trial is described of the use of small doses of Chlorpropamide for subclinical diabetes, defined as chemical diabetes with a normal fasting blood sugar and without diabetic symptoms. Subjects with subclinical diabetes were investigated for symptomless glycosuria or because of one or more of a number of clinical characteristics known often to be associated with diabetes. Glucose tolerance was measured initially and at intervals by the intravenous technique, the results being expressed numerically as Increment Indices. Precautions were taken to exclude the non-specific influences of loss of excess weight, of bed rest and of pregnancy when assessing the long-term effect of small doses of Chlorpropamide. The Chlorpropamide treatment was temporarily discontinued some three weeks before performing the sequential intravenous glucose tolerance test. Results on 107 subjects showed improvement in glucose tolerance in 78, no change in 2 and deterioration in 27. The most favourable results were obtained in the 30 women under 35 years of age who achieved a normal Increment Index after an average of $12\frac{1}{2}$ months treatment of Chlorpropamide. A larger scale, double-blind trial is being performed under the auspices of the Medical & Scientific Section of the British Diabetic Association using a placebo-treated control group.

Résumé. L'auteur rapporte un essai d'utilisation de petites doses de Chlorpropamide dans les cas de diabète subclinique; le diabète subclinique est défini comme un diabète chimique avec glycémie normale à jeun et absence de symptômes diabétiques. Des sujets avec diabète subclinique ont été examinés pour glycosurie sans autres symptômes associés ou bien pour d'autres caractéristiques cliniques que l'on sait être souvent associées au diabète. La tolérance au glucose a été déterminée initialement et ensuite à intervalles précis à l'aide de la technique intraveineuse; les résultats ont été exprimés numériquement en Index d'Incrément. Pour établir l'effet à long terme de petites doses de Chlorpropamide des précautions ont été prises en vue d'exclure les influences non-spécifiques d'une perte excessive de poids, du repos au lit, et de la grossesse. Le traitement au Chlorpropamide a été temporairement interrompu, environ trois semaines

avant d'exécuter les tests intraveineux de tolérance au glucose successifs. Les résultats obtenus sur 107 sujets ont montré une amélioration de la tolérance au glucose chez 78 sujets, pas de modifications chez 2, une détérioration chez 27. Les résultats les plus favorables ont été obtenus chez 30 femmes âgées de moins de 35 ans qui ont atteint un Index d'Incrément normal après une période de 10 mois et demi de traitement en moyenne par le Chlorpropamide. Actuellement un «double blind trial» est effectué sur une plus grande échelle sous les auspices de la Section Médicale et Scientifique de la «British Diabetic Association» en utilisant un groupe de malades témoins traités par placebo.

Zusammenfassung. Es wird der Versuch beschrieben, kleine Dosen Chlorpropamid zur Behandlung des latenten Diabetes zu verwenden. Der latente Diabetes wurde als chemischer Diabetes mit normalem Nüchternblutzucker und fehlenden diabetischen Symptomen definiert. Die Personen mit latentem Diabetes wurden wegen symptomloser Glykosurie oder wegen eines oder mehrerer klinischer, häufig mit Diabetes verbundener Zeichen untersucht. Die Glukosetoleranz wurde am Beginn und in bestimmten Intervallen mit der intravenösen Technik bestimmt. Die Ergebnisse wurden in Zahlen als Index des Anstiegs ausgedrückt. Bei der Beurteilung des Langzeit-Effektes kleiner Dosen Chlorpropamid wurden Vorkehrungen getroffen, um den unspezifischen Einfluß der Entfettung, der Bettruhe und der Schwangerschaft auszuschließen. Etwa drei Wochen vor dem nachfolgenden intravenösen Glukosetoleranztest wurde die Chlorpropamidtherapie zeitweise unterbrochen. Die Ergebnisse von 107 Personen zeigten eine Verbesserung der Glukosetoleranz in 78, keine Änderung in 2 und eine Verschlechterung in 27 Fällen. Die günstigsten Ergebnisse zeigten sich bei 30 Frauen unter 35 Jahren, die nach einer durchschnittlichen Chlorpropamidbehandlung von $10\frac{1}{2}$ Monaten einen normalen Index des Anstiegs erreichen. Zur Zeit wird in Zusammenarbeit mit der medizinischen-wissenschaftlichen Sektion der British Diabetic Association ein umfangreicherer Doppelblindversuch durchgeführt, wobei auch eine nur mit Placebo behandelte Gruppe untersucht wird.

The purpose of this short communication is to report the progress of a trial of small doses of Chlorpropamide for subclinical diabetes, a preliminary account having already appeared in *Diabetes* 1962¹. At that time results were available in only 11 subjects, but the number has now risen to 107, allowing firmer conclusions to be drawn. The thesis on which the trial is based is that the sulphonylurea drugs may have a curative action at certain early stages of human dia-

betes, just as they have been shown to have in certain types of experimental diabetes in animals^{2,3}. In keeping with this possibility is the fact that long term therapy with the sulphonylureas more often produces actual improvement in carbohydrate tolerance in symptomatic diabetes when its duration has been short rather than long⁴. Histological evidence in humans published by MacLEAN and OGILVIE⁵ has shown that hypoplasia of the pancreatic beta cells

progresses with time, so that it is to be anticipated that a drug with betacytotropic action would have more scope in the early stages of diabetes. FAJANS and CONN⁶ have already reported improvement in the oral glucose tolerance of young mild diabetics given long-term treatment with tolbutamide.

Conduct of the trial

In the present trial subjects were selected who had chemical evidence for diabetes but no associated symptoms. Since they were by definition asymptomatic (i.e. subclinical) special efforts had to be made to find them. Some were referred to the Diabetic Clinic for investigation of symptomless glycosuria and others were tested because of suspicious clinical features such as:

- Strong family history of diabetes
- Mother of baby over 4.5 kg (10 lb.) at birth
- Mother of 10 or more children
- 2 or more "unexplained" stillbirths
- Islet hyperplasia of the pancreas of stillborn (not due to Rh incompatibility)
- Excessive weight gain in pregnancy
- Precocious onset of arterial disease, especially in women

Such individuals were tested for chemical diabetes using the intravenous glucose tolerance test described by DUNCAN⁷ and expressing results numerically as Increment Indices. Statistical comparison between sequential tests was thus simplified compared with the use of oral glucose tolerance testing. The Increment Index rather than the total index or K index was used since it has been shown to be relatively independent of the amount of glucose injected⁷ and to be derived from a line giving a better fit to a logarithmic function than is attained when absolute rather than increment blood sugars above the fasting level are used⁸.

In the use of sequential glucose tolerance tests as a measure of changes induced by drugs precautions have to be taken to exclude other factors which would affect the tests. Thus subjects have not been included in the trial if their weight exceeded the standard described by KEMSLEY⁹ by more than 10%, although they were not excluded from the trial if, as sometimes happened, the weight increased significantly during it. If subjects were more than 10% above their KEMSLEY standard weight when first tested, the test was repeated after adequate weight loss and the subjects were included in the trial only if the Increment Indices were still abnormal. Subjects were always tested when fully ambulant in view of the known effect of bed rest to impair glucose tolerance. If the subclinical diabetes was first detected during pregnancy or within 48 hr. of delivery the intravenous glucose tolerance test was invariably repeated when the effect of the pregnancy had passed and the subject included in the trial only if the Increment Index was still abnormal.

The sequential intravenous glucose tolerance tests were performed about three weeks after the Chlorpropamide had been temporarily discontinued, because the tests were being done not to measure the hypoglycaemic action of the drug but its possible action of

inducing hyperplasia of the pancreatic beta cells. Initially the dose of Chlorpropamide used was 100 mg daily with breakfast, but with the accumulation of experience it became apparent that older subjects, particularly with Increment Indices below 2.00 would tolerate a larger dose. More recently therefore subjects over 50 years of age with initial Increment Indices of 2.00 or under have received 250 mg. of Chlorpropamide daily in a single dose.

In the interpretation of the results of the intravenous glucose tolerance tests the combined data of DUNCAN and of AMATUZIO and his colleagues¹⁰ have been used for the definition of practical standards. These were as follows:—

- Normal — greater than 2.97 — Increment Index
- Diabetic — less than 2.46 — Increment Index
- Intermediate — 2.46 to 2.97 — Increment Index

It is recognised that such standards should probably be made to vary with age, but no adequate information is available on this point. In all the subclinical diabetics included in this trial the fasting blood sugar was less than 115 mg./100 ml in capillary blood by the glucose oxidase method.

Results

The overall results are summarized in Table 1.

No.	Mean Initial Increment Index (I.I.)	Mean Final I.I.	Mean of number of months on treatment with Chlorpropamide
107	2.14	2.84	14

Thus as a whole the Increment Index improved from a figure in the definitely diabetic range to one in the intermediate range approaching the normal figure. Of the 107 subjects in the trial 42 (just over 39%) achieved normal Increment Indices, the best result 50%) being obtained in the 30 women under 35 years of age at the start of the trial. It appeared in the course of the trial that the response was significantly better in the younger compared with the older women but analysis of the results up to July 1965 does not confirm that this difference is of statistical significance. Nevertheless the situation contrasts with the general experience that in symptomatic diabetes those over 35 years of age respond significantly better to sulphonylureas than do younger diabetics.

No.	Mean Age and Range	Mean Initial I.I.	Mean Final I.I.	Change	Mean of number of months on treatment
30	27 (8–34) years	2.15	3.03	+0.88	12.5

No.	Mean Age and Range	Mean Initial I.I.	Mean Final I.I.	Change	Mean of number of months on treatment
33	52 (35–72) years	1.98	2.75	+0.77	15

Table 3 gives the results in the 44 men similarly divided according to age on joining the trial.

Table 3

<i>Males under 35 years of age</i>					
No.	Mean Age and Range	Mean Initial I.I.	Mean Final I.I.	Change	Mean of number of months on treatment
9	26 (29–32) years	2.51	2.92	+0.41	11
<i>Males over 35 years of age</i>					
35	57 (38–87) years	2.19	2.76	+0.57	15

Thus the men appear to have responded rather less favourably than the women but the difference is not statistically significant.

When the increment index has improved from the diabetic well into the normal range in certain subjects the opportunity has been taken to discontinue the chlorpropamide for a number of months to see how long the improvement is maintained. Of 11 subjects in this category 8 have maintained a normal increment index after 6–14 months without chlorpropamide and 3 have relapsed after 8, 10 and 13 months respectively. Two of the three have again achieved a normal increment index on restarting therapy, although one is in a double blind trial and it is not known at present whether he is having chlorpropamide or a placebo. The third has shown no significant change in increment index after resumption of treatment with chlorpropamide for a year.

The value of the observations here reported is limited by the absence of a control group followed up in the same way but given no Chlorpropamide treatment. Since November, 1963 the Medical and Scientific Section of the British Diabetic Association has been running such a trial organized on a double-blind basis so that randomised groups of subclinical diabetics are treated either by Chlorpropamide 100 mg daily or a placebo which appears identical. A harmless marker substance has been added to both sorts of tablets so that a check can be made that they are actually being

taken. If sequential tests show evidence of significant deterioration in glucose tolerance, this is first confirmed and then the individual is removed from the trial to be given standard treatment. Evidence of such deterioration has been obtained before the development of any diabetic symptoms. Too few results are available yet to be statistically significant.

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