SOUTH AFRICAN MEDICAL JOURNAL

SUID-AFRIKAANSE MEDIESE TYDSKRIF

Cape Town, 31 July 1971 Volume 45 No. 30 Deel 45 Kaapstad, 31 Julie 1971

EDITORIAL *VAN DIE REDAKSIE*

Storm in a Teacup?

The United States Food and Drug Administration seems to stumble from one premature announcement to another in the field of diabetes mellitus. First they caused the drug firms to include in the notices with each package of any sulphonylurea that these drugs were contraindicated during pregnancy, and even in women of childbearing age, which we know in this country to be nonsense. Only a year or so ago they caused cyclamate sweeteners to be banned on totally inadequate evidence, and now they urge that tolbutamide **and other** oral antidiabetic agents are to be used by doctors only as a last resort in maturity-onset diabetics. This recommendation, endorsed by the Council of the American Diabetes Association, has apparently caused alarm and despondency among the estimated 1 million Americans who were taking tolbutamide and has thrown practising physicians into a tizzy, making them scared to use oral agents in case a court action is brought against them should their patient develop myocardial infarct while on the drug.

The study that caused all the fuss was conducted at 12 University medical centres.[1] Patients were mild, non-insulin dependent, recently diagnosed, maturity-onset type diabetics and were divided randomly into 4 treatment groups, each containing approximately 200 subjects, as follows: diet plus placebo, diet plus tolbutamide (1·5 g daily), diet plus fixed dose of insulin (10 - 16 units according to body surface area) and diet plus insulin according to need. Patients were maintained on these schedules and followed up for 5 - 8½ years. A fifth, phenformin-treated group, was added later but does not enter into the crucial analysis.

Analysis after 8½ years revealed 26 deaths from cardiovascular causes in the tolbutamide group, 10 in the placebo and 13 and 12 in the 2 insulin groups. The Chi-square test of significance for the tolbutamide-placebo comparison yielded a P value of 0·005. There is considerable doubt, however, whether such statistical tests are valid in view of various baseline and inter-clinic discrepancies. The subjects were socially and ethnically heterogenous, the excess number of deaths in the tolbutamide group emanated from 3 clinics only, patients who discontinued or changed treatment were included with their original groups, and during the last year or so the difference in vascular deaths was no longer evident. Further, the 5 chief cardiovascular 'risk factors' were all more frequent **initially** in the tolbutamide-treated group than in the placebo group as follows: ECG abnormality 4% against 3% (astonishingly low), use of digitalis 7·6% against 4·5%, arterial calcification 19·7% against 14·3%, angina pectoris 7·0% against 5·0%, serum cholesterol > 300 mg/100 ml 15·1% against 8·6%. There was, however, less hypertension in the tolbutamide group.

The total death rates were not significantly different between the 4 groups, in fact there were fewer deaths from cancer in the tolbutamide group than in the placebo group—a difference which might be claimed as being 'significant'[2]—so that tolbutamide might even be considered beneficial in 'preventing' cancer.

Regarding the design of the trial, an outstanding error seems to us to be the use of a fixed dose of 1·5 g of tolbutamide for so many people throughout the whole study without reference to control of the diabetes or even apparently of symptoms. Since we know that tolbutamide fails initially to benefit some 30% of maturity-onset diabetics, and that the secondary failure rate at

the end of 5 years is around 50%,[3] such an empirical method of using tolbutamide appears to have little relation to clinical practice. (The same would seem to apply to the 10 - 16 units of insulin, given on fixed dose according to surface area—a new trial of homoeopathy, evidently.) Hence the lack of benefit to diabetics on this tolbutamide schedule, which is emphasized in the UGDP report, is hardly surprising to those of us who believe in at least reasonable control of the diabetic state.

Further criticism has been made of the change in definitions adopted by the study group between their initial report in 1968 and their final report in 1970.[4,5] In particular, originally 25% of the tolbutamide group were noted as having at least one major ECG abnormality at the time of entry to the trial, as against 15% of the placebo group. Yet in the 1970 report only 4% of the tolbutamide and 3% of the placebo group had major ECG abnormalities.

It is impossible to ensure perfection in important large-scale trials of this sort and it is always easy to point out errors after the event. There is no question that the physicians concerned in the trial acted in good faith and to the best of their ability. It seems to us, however, that their continued reliance on inadequate data and their refusal to admit the possibility of error are not in accordance with the best scientific ethics. Furthermore, it is difficult not to condemn the premature announcement and recommendations from both the FDA and the Committee of the American Diabetes Association, especially in their blanket condemnation of all oral drugs, without a shred of evidence against any but tolbutamide. At least it is pleasing to note that no other country appears to have been equally precipitate, and official recommendations for patients to continue oral drugs have been promulgated in several.

We must keep an open mind. Further work may indicate a true danger from tolbutamide and doctors must of course follow their own beliefs—any who believe that the dangers have been proved and that they exceed the benefits, will stop prescribing tolbutamide.

It is relevant to mention other studies that indicate either no danger from tolbutamide or even improvement in cardiovascular status. From the Bedford Survey, 248 'borderline' diabetics were randomly allocated to 4 different treatment schedules.[6] Analysis after 7 years revealed that fewer 'new arterial events' had occurred in the tolbutamide groups than in the placebo group. In Stockholm a 4-year study was made on 270 patients discharged from hospital after their first myocardial infarction.[7] Half were given tolbutamide and half placebo irrespective of the glucose tolerance. During the first 18 months the mortality was significantly lower in the tolbutamide group, though there was less difference by the end of the study. The glucose tolerance of the tolbutamide-treated group improved significantly when retested after the drug had been withheld for 60 hours. This investigation is worth careful study. In the Framingham study oral agents did not appear to differ from other modes of treatment with regard to incidence of cardiovascular disease,[8] and retrospective studies from the Joslin Clinic indicated no difference.[9]

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