Special Article

The UGDP Controversy

Clinical Trials Versus Clinical Impressions

*Prepared for the University Group Diabetes Program**
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Information concerning the relationship of blood glucose control and the development of vascular complications in patients with diabetes cannot be obtained by review of clinical records. There are many reasons why this is true. For example, patients with milder disease are likely to be better controlled than patients with more severe disease and it would be fallacious to conclude that the control of blood glucose prevented complications without reference to other facts about the metabolic defect. A true picture of this relationship can be obtained only with a controlled clinical trial. The facts that patients with adult-onset diabetes are usually not insulin-dependent, that they constitute a large majority of the patients seen in clinics and in private practices, and that these patients are subject to all of the severe vascular complications common to insulin-dependent patients made possible the study of the relationship of control to the development of vascular complications by the University Group Diabetes Program (UGDP).[1-4] The important design features of this cooperative, prospective study included the establishment of a common study protocol to provide for the collection of comparable data; random allocation of patients to the treatments under investigation; double-blind evaluation of the oral drugs under study; incorporation of a comparable placebo control group; long-term observation of patients; and central collection, editing, and monitoring of the observed data. Although the need for these basic safeguards is self-evident, it is surprising how many observations are brought up to challenge the results of the UGDP in which few, if any, of these design principles were observed.

A summary list of criticisms of the UGDP by Seltzer, which was published in the September issue of this Journal,[5] is to a large extent a rephrasing of the questions raised by Feinstein[6] and Schor,[7] many of which were carefully and thoughtfully answered by Cornfield.[8] Our review of the points listed by Seltzer[5] indicated that many of these are redundant and can be grouped under the following general headings:

I. Patient selection criteria.
II. Comparability of treatment groups at baseline.
III. Heterogeneous clinic populations.
IV. Use of fixed dose.
V. Treatment for conditions other than diabetes.
VI. Classification of cause of death.
VII. Questions concerning statistical analyses.
VIII. Clinical implications of the UGDP results.

Throughout this paper we will refer to the points listed in Seltzer's report by using the following code system: A-1 is the first point listed under the heading "A. Defects in Design"; A-2 is the second point under that heading; B-1 is the first point under the heading "B. Defects in Execution," etc. Seltzer's critique is concerned primarily with the reported results for tolbutamide therapy in the UGDP with only a few references to the preliminary report on phenformin results. Therefore, in our response we have also been concerned primarily with the reported results for tolbutamide. A detailed report on the results of phenformin therapy on mortality and nonfatal events is in preparation and will be published later.

I. PATIENT SELECTION CRITERIA

a. *Patients Admitted Who Had Some Evidence of Cardiovascular Disease (A-1)*

No attempt was made in the UGDP to exclude patients who already had signs of vascular disease since restriction of the UGDP patient population to patients free of cardiovascular complications would have made

*For a list of participating investigators and consultants, see The University Group Diabetes Program. DIABETES 19 (Suppl. 2): xii-xv, 1970.

them quite unrepresentative of newly diagnosed diabetics. The increased prevalence of hypertension in patients diagnosed as diabetic has been reported[9] and other studies have noted the presence of vascular complications at the time diabetes is diagnosed.[10-12] Inclusion of patients with evidence of vascular complications does not invalidate the treatment comparisons for mortality since patients were randomly assigned to one of the treatment groups. Furthermore, these patients could be observed for progression or regression of the identified complication as well as other abnormalities.

b. *Selection of Patients With Good Prognosis for Five-Year Survival (B-4, C-6, D-2, and D-6).*

On the one hand, Seltzer comments that the clinical prognosis of many patients enrolled in this study was less than five years and on the other hand speculates that the mortality was too low in all treatment groups except the tolbutamide and phenformin groups. The placebo-treated group as well as both insulin-treated groups had observed mortality rates which were lower than would be expected for a general population of the same age, race, and sex composition.[8] These data suggest that the investigators did an excellent job of selecting patients who had a good prognosis for a five-year survival. Selection of patients for clinical trials with a better than average prognosis has been observed in other intervention studies. The National Diet Heart Feasibility Study reported an annual incidence of new coronary heart disease of 0.5 per cent compared with an expectation of 1 per cent for a comparable general population.[13]

c. *Diabetes at Time of Entry (B-1, B-2, and C-1)*

The inclusion of patients accepted as having diabetes on clinical grounds, but who did not meet the diagnostic criteria adopted by the study a few months after patient recruitment had started, does not detract from the conclusions concerning the efficacy of the oral agents. The arbitrary exclusion of these patients after they had been enrolled in the study would be harder to defend than including the results for these patients. This was brought out by Feinstein[6] who commended the UGDP statisticians for including the sixty-nine patients under question since as he noted "the subsequent comparison of the death rates for the smaller denominators in the PLBO and TOLB groups would have magnified the existing differences in these rates."

Duration of diabetes was taken into account by enrolling only patients who were known to have had the diagnosis of diabetes established during the twelve-month period immediately preceding the patient's date of entry into the UGDP. We are unaware of other methods which could be used to ascertain the duration of diabetes prior to the actual recognition or diagnosis of the disease.

II. COMPARABILITY OF TREATMENT GROUPS AT BASELINE

a. *Statistical Significance of Observed Differences (A-4, A-5, A-6, A-7, B-3, B-6, D-1, D-2, D-3, D-7, and E-1)*

The UGDP is unique with respect to the amount of detailed information which was presented to describe the characteristics of the patients in each treatment group prior to the initiation of treatment.[1,2,4] In addition to mean values, detailed frequency distributions for each treatment group for a large number of baseline variables were presented to provide the reader with an opportunity to evaluate the comparability of the treatment groups at baseline. Missing values for certain baseline characteristics occurred as a result of technical problems or failure to perform the indicated examination within the time limits specified by protocol, but Seltzer's statement concerning the number of missing values is incorrect. Careful review of the results for the fourteen baseline variables considered as cardiovascular risk factors did not identify any variable with 123 missing observations (see table 6 of UGDP II[2] and table 2 of UGDP IV[4]). Extensive analyses of these results indicated that there was no evidence that the observed differences in baseline composition among the four treatment groups, placebo, tolbutamide, insulin standard, and insulin variable, were any greater than would be expected by chance in groups of this size nor were these minor differences found to be of any significance in explaining the significant cardiovascular mortality observed among patients treated with tolbutamide.[2,8] As pointed out by Seltzer in D-3, mortality was higher in the tolbutamide-treated group than in the placebo-treated group among the individuals without cardiovascular risk factors at baseline, for example, patients with cholesterol levels $<$ 300 mg. per 100 ml., patients without significant ECG abnormalities, and patients not classified as having definite hypertension.[2,3]

Concern about the amount of information available to describe the characteristics of patients at the time of entry into the study and the distribution of these baseline characteristics among the treatment groups would seem to indicate a failure to appreciate the purpose and power of randomization. As Cornfield[8] has noted, the major function of randomization is to achieve approxi-

mate comparability with respect to all variables whether observed or not and there is no reason to believe that randomization was not effective in doing so in the UGDP.

b. *Changes in Definitions or Lack of Definitions (A-5 and C-2)*

Seltzer's comments regarding changing definitions are a vestige of an earlier attempt at disputation by innuendo and have been adequately answered by Cornfield: "definitions of baseline factors, including ECG abnormality, were used by the Coordinating Center to classify study patients in the hope of further elucidating the cause for the elevated eight-year cardiovascular mortality for those receiving tolbutamide. But this finding depended only on the brute facts of the UGDP experience and was beyond the ability of anyone to influence by manipulating definitions of baseline characteristics."[8]

III. HETEROGENEOUS CLINIC POPULATIONS

a. *Two "Pools" of Patients (A-2 and C-3)*

The fact that phenformin was administered in only six of the twelve UGDP clinics is not relevant for the evaluation of the tolbutamide results. Each of the twelve clinics contributed approximately the same number of patients to the tolbutamide group as it contributed to the placebo, or insulin standard or insulin variable groups.

The analytic problems posed by this aspect of the UGDP design for the evaluation of the phenformin results were discussed in the preliminary report on phenformin[4] and will be considered in more detail in a definitive report on phenformin results which is in preparation.

b. *Homogeneous Population Required for a Clinical Trial (A-3, B-5, C-4, and E-8)*

The heterogeneous patient population studied in the UGDP is a strength not a weakness of the study. First of all, the heterogeneity of the patient population makes it more difficult to discern treatment differences than would be the case for a patient population of comparable size recruited from a single clinical center. Secondly, the more widely the general diabetic population is sampled, the greater the ability to generalize the findings to the total diabetic population. The converse is true when the results are obtained from a single highly selected homogeneous population.

c. *Mortality Differences Among Clinics (C-4 and E-5)*

It is not surprising that the observed differences among clinics in the total number of reported deaths can be explained to some extent by the variation among clinics in the distribution of baseline characteristics thought to be predictive of death. However, that fact per se is not pertinent to the evaluation of the tolbutamide-placebo comparisons of the number of deaths. It is the distribution of baseline risk factors among treatment groups within each clinic that is important for the evaluation of treatment effects. The results for the four clinics (Birmingham, Boston, Cincinnati, and Minneapolis) which account for most of the excess cardiovascular mortality observed in the tolbutamide treatment group were examined. Analysis of the results for these clinics indicated that the observed differences in baseline characteristics among the treatment groups within this subgroup of clinics did not account for the observed excess cardiovascular mortality for patients treated with tolbutamide.[8]

If one considers the mortality rates for each of the four treatment groups in each of the twelve clinics as separate experiments, one finds that the per cent dead from cardiovascular causes for patients treated with tolbutamide exceeded the per cent dead for patients treated with insulin variable, insulin standard, or placebo in twenty-three of the thirty-six possible pair-wise comparisons involving tolbutamide.[2]

IV. USE OF FIXED DOSE (A-9, B-7, B-8, E-3, and E-4)

The prescribed dosage level for tolbutamide in the UGDP was the level most commonly used in clinical practice.[1] More important, the increased mortality experience in patients treated with the oral agents cannot be explained by the use of fixed dose. This is readily demonstrated in several ways. Inspection of the fasting blood glucose response over time reveals that placebo-treated patients had worse control than tolbutamide-treated patients but a better mortality experience. Tolbutamide- and insulin standard-treated patients had similar fasting blood glucose responses over time but insulin standard-treated patients had significantly lower cardiovascular mortality. It should also be noted that the distributions of baseline characteristics in these two groups were almost identical.[14] Thus, a fixed dose of insulin did not result in the same mortality trend as observed for patients treated with a fixed dose of tolbutamide in spite of the similarity of fasting blood glucose response over time.

The protocol provided that the assigned study medication was to be modified or temporarily discontinued if this appeared medically indicated. If symptoms of hypoglycemia were reported, the assigned treatment dosage was to be reduced to avoid repetition of such

episodes. The number of reported episodes of hypoglycemia was highest for patients in the insulin variable and insulin standard treatment groups (forty-nine for IVAR, twenty-six for ISTD, six for TOLB, and two suspect episodes for PLBO).

Dosage adjustments of the study medication were not permitted on the basis of elevated blood glucose levels alone except for patients assigned to the insulin variable treatment group. The protocol specified that an increase of at least two units of insulin was required for patients in the insulin variable-treated group if the fasting blood glucose value was greater than 110 mg. per 100 ml. and the one-hour value was greater than 210 mg. per 100 ml. As a result the mean fasting blood glucose level for patients in the insulin variable-treated group remained very close to 110 mg. per 100 ml.[3] The mean fasting blood glucose levels for the other treatment groups all tended to increase with the length of follow-up. Patients treated with a fixed dose of insulin were no better controlled than patients treated with a fixed dose of tolbutamide or a fixed dose of phenformin.[2,4] In spite of differences in blood glucose response, there were no differences in mortality for the insulin variable-treated group compared to either the group treated with a fixed dose of insulin or the placebo-treated group.

V. TREATMENT FOR CONDITIONS OTHER THAN DIABETES (A-8, B-8, and E-4)

The main objective of the UGDP was to evaluate the efficacy of hypoglycemic treatments in the prevention of vascular complications of diabetes and not to evaluate the effects of lipid-lowering agents or treatment of other conditions. The approach to the control of lipids or other conditions was the same for patients in all five treatment groups and thus is not a factor in the evaluation of the hypoglycemic treatments included in this study.

VI. CLASSIFICATION OF CAUSE OF DEATH (B-9, C-7, D-2, D-5, D-6, and E-5)

The differences observed among the treatment groups in the percentage of patients who were hospitalized or autopsied was no greater than would be expected for numbers this small and there is no evidence that the definition of cardiovascular deaths varied by treatment group.[8] It is important to recall that the final judgment concerning the principal cause of death for each deceased patient in this study was made by a special review team without knowledge of the treatment group to which the patient had been assigned.

In this study a death was classified as a sudden death if "death occurred within three hours of the onset of symptoms in an otherwise clinically stable patient and in a manner consistent with a cardiovascular event."[2] Thus, the best estimate of death due to coronary heart disease would be the total number of deaths classified as sudden death, myocardial infarction, and other heart disease. Viewed in this way there were four deaths in placebo, seven in insulin standard, and seven in insulin variable which would be attributed to coronary heart disease compared to nineteen in the tolbutamide-treated group. The number dead from all cardiovascular causes in the placebo-treated group was nearly the same as the number dead in each of the two insulin-treated groups (ten in placebo, thirteen in insulin standard, and twelve in insulin variable).[2] Twenty-six cardiovascular deaths were reported in the tolbutamide-treated group.[2]

Seltzer has noted in D-5 that there was a higher mortality among patients having a myocardial infarction for patients in the tolbutamide-treated group than for patients in the placebo, insulin standard, or insulin variable treatment groups. Palmer and co-workers[15] have shown an ionotropic effect in human heart muscle on cardiac contractions and an increase in cardiac irritability due to tolbutamide and other sulfonylurea drugs at concentrations which would be attained clinically. This may be the explanation of the observed results in the UGDP, but the causes of cardiovascular deaths in the tolbutamide- and phenformin-treated groups have not been positively identified.

The difference in cancer deaths for the tolbutamide-placebo comparison was not statistically significant (P value greater than 0.15) while the tolbutamide-placebo comparison for cardiovascular deaths was significant (P value less than 0.005).[2,8] This may be a demonstration of the principle of competing risks, that is, the patient must survive cardiovascular disease in order to die from cancer or some other cause.

VII. QUESTIONS CONCERNING STATISTICAL ANALYSES

a. *Use of Life Table Procedures (C-5, D-8, and E-6)*

Cumulative survival rates are not calculated on calendar time but on time under observation. Rates obtained in this way will not be the same as the results based on calendar time because patients entered the study at different times. The cumulative annual mortality rates for cardiovascular causes in tolbutamide-treated patients exceeded the rates recorded for the other three treatment groups beginning with the fourth year of follow-up. This difference increased with the length of follow-up (see UGDP II, figure 1[2]). A pro-

gressive increase in the tolbutamide-placebo difference in the cumulative number of cardiovascular deaths was apparent in the graph of the results by calendar time (see UGDP II, figure 2[2]). The observed mortality and resulting trends for the tolbutamide-treated group can hardly be regarded as a "data-dictated" endpoint.

b. *Procedures for Handling Dropouts and Nonadherers (D-4)*

Analysis of the results for all patients originally assigned to each treatment group regardless of level of adherence is conservative and dilutes whatever treatment effects may be present. However, if the analysis is restricted to patients with high adherence it will be noted that the excess mortality for patients treated with tolbutamide not only persists but is intensified.[8] Cardiovascular mortality for patients with high adherence was four times greater in the tolbutamide-treated group than in the comparable placebo-treated group (P value = 0.001). In fact for this subgroup of patients the tolbutamide-placebo comparison based on overall mortality would also be regarded as statistically significant at the 5 per cent level (P value = 0.014).

VIII. CLINICAL IMPLICATIONS OF THE UGDP RESULTS (C-6, C-7, E-2, E-7, and E-8)

A definite increase in cardiovascular mortality of approximately 1 per cent per year was apparent for patients treated with tolbutamide in the UGDP. The observed mortality from all causes and from cardiovascular causes for patients in the phenformin-treated group was higher than that observed in any of the other treatment groups. This increased risk of mortality in patients treated with these oral agents could not be explained on the basis of baseline differences or on the basis of known cardiovascular risk factors. Moreover, there was no evidence that phenformin or tolbutamide was more effective than any of the other treatments in preventing the occurrence of nonfatal vascular complications associated with diabetes. In the absence of beneficial effects it was considered unethical to continue patients on what might be a harmful treatment.[16]

Results from studies by Keen[17] and Paasikivi[18] have been contrasted with the findings of the UGDP. An independent review[19] of these studies states, "Compared to the UGDP both of these were less well designed and less adequately controlled. The study by Keen on borderline diabetes did not find excess cardiovascular mortality in patients treated with tolbutamide; the report by J. Paasikivi in post-coronary patients is contradictory in its data and can more profitably be interpreted as supporting the findings of the UGDP."

Although it is difficult to view with equanimity the possibility that present efforts in the treatment of adult-onset diabetes may not alter the overall morbidity or mortality for patients, the results of the UGDP are not really surprising. An exhaustive search of the literature by Knowles[20] indicated that the evidence to support the hypothesis that good blood glucose control delays or prevents the vascular complications of diabetes is largely conjectural. Viewing the problem of mortality of diabetes more generally, it is disturbing to find that there has been a large percentage increase in mortality of patients with diabetes on a global basis when death rates between 1951-1953 are compared to those for 1961-1963.[21] This increase may or may not be related to the excess use of oral agents during this time period but it cannot give us great comfort that our present therapeutic measures are highly successful.

The results from the UGDP have given little hope thus far that the degenerative complications of diabetes are preventable by simple control of blood glucose levels. No differences in mortality or nonfatal events were seen between groups of patients controlled as well as possible in a clinical setting on diet and variable quantities of insulin and those treated with diet alone but without any hypoglycemic agent. The review of the UGDP by an ad hoc committee of the ADA[22] pointed out that "the real lesson of the UGDP is that if diet plus insulin does not reduce mortality experienced with diet alone, it is highly improbable that oral hypoglycemic agents will do so."

Whether the mortality results for tolbutamide in the UGDP can be extended to other populations and other similar hypoglycemic agents is a matter of individual judgment in the present state of knowledge. In making this judgment, however, one should be reminded of the fact that the findings reported by Palmer and co-workers[15] demonstrated similar effects of several sulfonylurea drugs on cardiac contraction and cardiac irritability. If one accepts the possibility that there may be inherent dangers in the use of one of the drugs in the sulfonylurea family, it would be difficult to justify the use of other oral sulfonylurea agents without due consideration of the possible risks even though they remain unproven. The same must be said for the biguanides.

The UGDP findings and their implications cannot be dismissed on the basis of clinical impressions. As Cornfield[8] has noted, they could only be rejected if "a large body of scientifically defensible evidence against them, not now available, has been accumulated, and not because of continued exegesis of current results."

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