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June 7, 1969

Professor Max Miller, M.D.
Lake~~side~~ Hospital, Dept of Medicine
Case Western Reserve University
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Dear Max:

This letter is written in answer to your request, received yesterday, for a brief statement of my position concerning Tolbutamide, and my reasons for this position. I am typing this at home, without benefit of carbon; I would appreciate it very much if you would send a copy of this back to me for my records, and another on to Chris. I'll try to keep the typing errors at a tolerable level.

As I stated in my letter to Chris just before the Williamsburg meeting, I believe that Tolbutamide is toxic; I believe that it increases the risk of death, through some action on the cardiovascular system. I think that the evidence supporting this belief is so strong that continuation of this treatment in the UGDP would be unethical.

The evidence for my conclusion is as follows (numbers in parentheses refer to page numbers in the Tolbutamide Report of May 9, 1969) :

a) There is a surplus of deaths in the Tolbutamide group, compared with the Placebo group (1).

b) The surplus of Tolbutamide deaths observed in the study is substantial, certainly large enough to be of clinical importance if real. The 8 year survival rate for Placebo is estimated at 90%, compared with only 78% for Tolbutamide (4) . The deaths due to "myocardial infarction and sudden death" are five-fold higher in the Tolbutamide group than in the Placebo group, 15 deaths to three (3) .

c) The observed differences in death rates between the Tolbutamide and Placebo groups are statistically reliable enough to suggest that they did not come about through chance allocation of higher risk patients to the Tolbutamide group. The difference in crude rates (1), the differences as displayed in the Monte Carlo analysis (2A) and the survival analysis (4) all indicate a difference between Tolbutamide and Placebo in the order of 1.5 standard errors, P approximately ~~=~~ 10% .

d) The observed difference in the occurrence of cardiovascular deaths is in the order of 2.3 standard errors (P approximately 2%) , whether analzed on the basis of crude rates (2) or by the matched pairs method (41A) . The difference is consistent over clinics.

e) Although the incidence of non-fatal events is very low, making statistically definitive comparisons impossible, The Tolbutamide group does show the

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worst experience of the four treatment groups, for four of the six events analyzed (24). The disturbing exception is myocardial infarction, as judged from the EEG.

f) It is true that the Tolbutamide-Placebo comparison is only one of six pairwise comparisons that could be made among the four treatment groups. However, when the Insulin Standard and Insulin Variable groups are brought under consideration, one finds that these two treatments perform consistently better than placebo, and markedly better than Tolbutamide. I feel that this strengthens the evidence against Tolbutamide. Statistical analysis of the difference between Tolbutamide and the Insulin Variable results shows the differences in death rates to be approximately 2 standard errors in magnitude, and the differences in cardiovascular death rates to be about 2.5 standard errors (1.4, 40C and 3.41C respectively). The differences are consistent across institutions.

g) Previous work published by Lazarow on animals, indicating possible toxicity in animals, contributes to the evidence against Tolbutamide but I don't think this has influenced me much.

In conclusion, the evidence convinces me that patients in this study who are continued on Tolbutamide would be subjected to higher risks than those on Placebo or Insulin. Surely there is negligible possibility of trends reversing themselves to the extent that final results would show Tolbutamide is better than Placebo. Hence I feel that it would be unethical to continue Tolbutamide medication in this study.

Of course it would be premature to assume that the toxicity of Tolbutamide would be reproducible in other studies or experience, involving different clinicians, different patient populations, and different treatment and management regimes. This important question demands further study, in the laboratory and clinically, retrospectively and, ultimately, in further randomized clinical trials.

Sincerely yours,

Byron Wm. Brown, Jr.
Biostatistician