Placebo-Controlled Trials in Type 2 Diabetes

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Papers published by U.S. Food and Drug Administration (FDA) employees are required to state that the opinions expressed do not necessarily represent the official position of the FDA. With respect to the ethics of placebo-controlled trials, it is fair to say that my views are almost completely the opposite. Through letters to newspapers (1,2) and medical journals (3), I have attempted to point out the very problem that David S.H. Bell has identified in his letter to Diabetes Care (4). My personal view is that trials of new drugs should try to mirror the conditions in which the drugs will actually be used. Patient volunteers should not be expected to accept a standard of care that would be unacceptable in other settings. If the scientific situation requires that patients be willing to accept additional risk or discomfort, the proposition should be put to them by someone other than the physician on whom they are dependent. Although straightforward enough to me, these views have received little support from the people who run FDA.

An explanation—of what might be considered the FDA position—can be found in the writings of Dr. Robert Temple. His major argument is that placebo-controlled trials are necessary to prove efficacy in conditions whose natural history is variable. Placebo-controlled trials are ethical, even for conditions where effective treatment already exists, provided that patients are not harmed and are fully informed (5,6). With respect to type 2 diabetes, it is difficult to prove that patients are actually harmed by withholding or withdrawing active treatment for short periods of time. Uncontrolled hyperglycemia may be unpleasant, but in the absence of permanent harm, why should a federal agency restrict the right of a patient to participate in a clinical trial?

Most recent approvals for drugs to treat type 2 diabetes have depended on placebo-controlled trials in which active agents were withdrawn with the intent of worsening the hyperglycemia that the new drugs were designed to treat (7–9). Protocols have specified that glucose values up to 400 mg/dl could be tolerated. FDA medical officers have been discouraged from reviewing consent forms, thus allowing that major omissions may be overlooked. In one case, I was able to document that patients were not informed that active treatment was being withdrawn to make them eligible to participate in the study, but FDA was unwilling to take any action (2). Of equal importance is that patients are almost never informed that physician-investigators are paid to recruit patients.

The recent tendency for institutional review boards (IRBs) to be replaced by commercial review boards is also disturbing. A well-functioning IRB can act as the moral compass of an institution. But commercial review boards are more likely to act as rubber stamps for the drug companies that pay them.

As reported recently in Science, FDA’s views of the ethics of clinical trials differ from those of the international community (10). The new Bush administration faces the task of trying to find ways to reconcile these differences. But given the large amount of money involved in drug development and the paucity of opposition in Congress, I see little to prevent exploitation of patient volunteers. It might even get worse.

The simple reason that we continue to have placebo-controlled trials is that without them, the pharmaceutical industry would be forced to find better drugs rather than just more drugs. It may be risky to try to show that a new drug is better than drugs currently available. It is much safer for pharmaceutical companies to test new drugs against placebos. Why risk trying to be better than something when all you need to show is that you are better than nothing?

Unless the new Commissioner of the FDA is willing to lock horns with the people who currently set policy, I see little possibility that the FDA will require trials comparing new drugs to drugs already marketed. But even now, it should be possible to design clinical trials in which patient volunteers are not required to accept poor clinical care. The trial of metformin in pediatric patients with type 2 diabetes illustrates my point (11). This was a placebo-controlled trial in which patients were enrolled if their fasting plasma glucose (FPG) did not exceed 240 mg/dl. Patients were withdrawn if their FPG exceeded 230 mg/dl at 2 weeks, 180 mg/dl at 4 weeks, and 140 mg/dl at 6 weeks and beyond.

The results of the trial, shown in Table 1, look very much like the data obtained from standard trials, except that the mean FPG and HbA1c levels did not change much in the placebo group. Not surprisingly, significantly more patients in the placebo group (65%) were withdrawn for persistent hyperglycemia than in the metformin group (9%). The proportion of patients withdrawn because of lack of efficacy provided a means of distinguishing metformin from placebo that was as valid clinically and statistically as reduction in FPG or HbA1c.

An additional feature of this study was that placebo patients who were withdrawn because of hyperglycemia received “rescue” therapy with metformin. Metformin was also given to the placebo pa-
tients when the trial was ended. The effectiveness of metformin in these placebo patients was approximately the same in the patients randomized to metformin originally. Thus, efficacy data were obtained on all randomized patients and no patient was required to forego effective treatment.

Early rescue of nonresponders is an ethically acceptable way to conduct a placebo-controlled trial of new drugs for many conditions, not just type 2 diabetes. I hope that this idea will be embraced by the pharmaceutical industry and the FDA as a way of reconciling the desire to bring more drugs to market and the need to protect the interests of patient volunteers.

### Table 1 — Trial of metformin in adolescents with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metformin</th>
<th>Difference</th>
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<tbody>
<tr>
<td><strong>HbA1c(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.9</td>
<td>8.2</td>
<td>-1.2* (P &lt; 0.001)</td>
</tr>
<tr>
<td>Last†</td>
<td>8.9</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td><strong>FPG (mg/dl)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>192</td>
<td>163</td>
<td>-64* (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Last†</td>
<td>207</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Required rescue</td>
<td>65%</td>
<td>9%</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

*Based on ANCOVA using baseline as covariant; †mean value at 16-week end point or last value (11).

### References

7. Medical officer's review of the new drug application for Avandia. Rockville, MD, Food and Drug Administration, 1999
8. Medical officer's review of the new drug application for Actos. Rockville, MD, Food and Drug Administration, 1999