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Fred W. Whitehouse

John B. Bryan

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## QUESTIONS AND ANSWERS ABOUT TOLBUTAMIDE, THE ORAL HYPOGLYCEMIC AGENT

FRED W. WHITEHOUSE, M.D.\* AND JOHN B. BRYAN, M.D.\*

When insulin was found to be ineffective by mouth, attention was given to the development of an orally effective hypoglycemic agent. Many compounds have been tested over the years. Most have been too toxic for clinical use.

Janbon in 1942 first described the hypoglycemic action of sulfonamide compounds.<sup>1</sup> Recently, modified preparations have been studied intensively in Germany and the United States. One preparation, carbutamide, proved to be too toxic for general clinical use. Tolbutamide<sup>2</sup>, a closely related compound, has proven to be relatively safe and has been made available throughout this country for the treatment of diabetes mellitus.

This report summarizes our experience with this agent and attempts to clarify questions that have arisen with its use. Recent reports afford the interested reader a more detailed analysis of its pharmacology and clinical use and an excellent bibliography.<sup>2,3,4</sup>

Question: What is tolbutamide?

Answer: It is a sulfonylurea compound that has a significant hypoglycemic action when taken by mouth.

Question: How does tolbutamide act?

Answer: Current opinions suggest multiphasic activity. Insulin must be present for an effect. Experimental evidence indicates that tolbutamide (1) causes either a production of or a release of insulin from the beta cells of the pancreas, (2) inhibits anti-insulin factors (insulinase) in the liver, (3) slows the release of glucose from the liver. Tolbutamide has no effect on other endocrine organs nor does it increase glucose uptake by the individual cell. Its action is not inhibited by ablation of the pituitary, thyroid or adrenal glands. There is no toxic effect on the alpha cells of the pancreas. It must be emphasized that the final and possibly correct *modus operandi* of tolbutamide has not yet been established.

Question: Is there a hypoglycemic effect in all diabetics as is true with insulin?

Answer: No. Animals following total pancreatectomy or alloxanization show no hypoglycemic effect. In humans the percentage of patients with a significant hypoglycemic effect closely parallels the percentage of patients with insulin extractable from the pancreas. Those patients without extractable insulin do not respond to tolbutamide.

Question: Is tolbutamide effective in diabetic acidosis?

Answer: No. Neither is it effective in other acute complications of diabetes, including infections and surgical stress.

\*Division of Metabolism.

†Orinase R — Upjohn Company, Kalamazoo, Michigan.

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Question: What are the indications and contra-indications for its use?

Answer: Table 1 indicates our current opinion based on over a year's clinical experience. These indications are generally true, although there may be exceptions. They are to be used as a guide when applied to the individual patient.

Table 1

Indications	Contra-indications
Diabetes less than 10 years' duration.	Diabetes over 10 years' duration.
Onset of diabetes over age 40.	Onset under age 40.
Adult type diabetes.	Juvenile type diabetes.
Diabetes controlled with <i>less</i> than 30 units of insulin daily.	Diabetes controlled with <i>more</i> than 30 units of insulin daily.
Cooperative patient.	Uncooperative patient.
	Acute complications.
	Ketosis.

The presence of one contra-indication is sufficient to disqualify a patient for tolbutamide therapy. Tolbutamide is an insulin substitute clinically. It is not indicated in the obese diabetic patient before an adequate trial with undernutrition has been accomplished. Only if weight loss does not occur, or if not successful in controlling the diabetes, should tolbutamide be considered.

Question: What are the side-effects of tolbutamide?

Answer: We have seen one case of dermatitis and one case of nausea and vomiting, requiring cessation of the drug, in 150 cases treated with tolbutamide. There may be transient leukopenia, but no other hematologic complications have been encountered. Crystalluria does not occur. We have experienced no hepatic dysfunction. O'Donovan<sup>5</sup> reports three percent side-effects in over 7000 clinical cases. These have all been mild. There are no known deaths directly attributable to tolbutamide.

Question: How is a patient regulated with tolbutamide?

Answer: Once a decision to use tolbutamide is made, initiation may be accomplished either in the hospital or with frequent office visits. Hospitalization is recommended if there is any question regarding the patient's likelihood of response. The following program has been generally adopted in our clinic:

1. Begin with 1 gram 3 times daily.
2. After 1-3 days, decrease to 1 gram twice daily.
3. Adjust the daily maintenance dosage with the help of frequent urine tests and blood tests for sugar.
4. If the patient is on insulin at the time of initiation,
  - a. omit insulin if less than 20 units per day.
  - b. If over 20 units daily, decrease the daily dose 25-50 percent initially, and then eliminate the insulin if the blood sugars so indicate.
5. Check the white blood count frequently at the beginning of therapy.

## Tolbutamide

Question: How long should one await a successful response?

Answer: Not longer than 7-10 days. If the degree of diabetic control deteriorates sooner, abandon the trial at once and start insulin. The development of ketonuria indicates failure. It is imperative that the patient be kept under close observation during this trial period.

Question: What is the average maintenance dose?

Answer: Table 2 records the maintenance dosage of 83 patients regulated on tolbutamide.

Table 2  
Maintenance Dosage of Tolbutamide

Grams per day	Number of patients
0.5	8
1.0	23
1.5	14
2.0	24
3.0	14

Question: Can tolbutamide and insulin be used together?

Answer: Yes, but there is little point in it. The only advantage of tolbutamide over insulin is its effectiveness by mouth. Theoretically, one might lower a very large daily dose of insulin to a more convenient level with the aid of tolbutamide. We have tried this twice without success.

Question: Should tolbutamide be used in the obese diabetic patient?

Answer: Tolbutamide, like insulin, is contra-indicated initially in the obese diabetic patient. Undernutrition should be tried first. If optimum weight is accomplished and still the diabetes is not controlled, then tolbutamide may be tried. If poor cooperation prevents weight loss, then tolbutamide probably should also be avoided.

Question: Can the diet be liberalized when tolbutamide is used?

Answer: No. If anything, it should be followed more closely.

Question: Once on tolbutamide, must the patient stay on it?

Answer: Like insulin, no. A patient with mild diabetes and good control may improve his glucose tolerance to the degree that diet alone will adequately control his diabetes.

Question: If the patient is regulated on tolbutamide, will insulin again be necessary?

Answer: Most patients on tolbutamide will require insulin if acute stress occurs. A few patients well regulated on tolbutamide at the beginning will gradually lose this good control. They must restart insulin.

Question: How is tolbutamide supplied?

Answer: Half-gram tablets, bottles of 50, \$6.75 per bottle, filled by prescription only.

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Question: Does tolbutamide have any antibacterial activity?

Answer: No.

Question: Has hypoglycemia been a problem?

Answer: No. We have seen no serious hypoglycemic reactions. There have been several mild reactions occurring during the first few days following initiation of tolbutamide therapy.

Question: What have been the failures?

Answer: Our failures with the use of tolbutamide include patients with diabetes and carcinoma of the pancreas (4 cases), steroid diabetes (1 case) and juvenile type diabetes. The basic nature of the diabetes appears to be the most important determinant in the individual response to tolbutamide.

Question: What theoretical danger exists with the use of tolbutamide?

Answer: Permanent diabetes can be produced in animals by chronic overstimulation of the beta cells of the pancreas. Tolbutamide is a beta cell stimulator. Will tolbutamide in time produce "total" diabetes in patients maintained on it?

A patient with diabetes well regulated with tolbutamide will lose this sensitivity in the presence of acute complications. This may make the patient more vulnerable to the rapid occurrence of ketosis and acidosis than a similar patient regulated with insulin.

### Summary:

The experience at the Henry Ford Hospital with tolbutamide is reviewed. Pertinent questions regarding its use are answered. The only advantage of tolbutamide over insulin is one of convenience — it is effective orally. The present and future health of the diabetic must not be compromised for mere convenience. The patients using tolbutamide must be carefully and thoughtfully selected.

We are grateful to Doctor C. J. O'Donovan of the Upjohn Company, Kalamazoo, for the generous supply of tolbutamide.

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