Henry Ford Hospital Medical Journal

Volume 7 | Number 1 Article 3

3-1959

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CURRENT STATUS OF CHLORPROPAMIDE IN MANAGEMENT OF DIABETES MELLITUS

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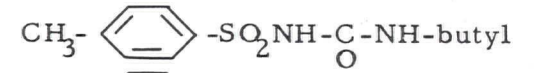
One year ago in this journal, we reported our experience with tolbutamide in the management of diabetes mellitus.[1] Spurred on by the successful clinical application and low toxicity of tolbutamide, pharmacologists tested a large number of closely related compounds, seeking one with similar innocuousness but with greater potency and broader clinical applicability. One such compound, N-propylparachlorobenzene-sulfonylurea (chlorpropamide) has demonstrated such activity. We began clinical trials with this drug in the spring of 1958. This report represents an appraisal of its clinical effectivity.

Chemically, chlorpropamide differs only slightly from tolbutamide. Figure 1 shows the comparative chemical structures. The altered chemical structure accounts for the greater potency of chlorpropamide. Tolbutamide, with a methyl radical on the benzene ring, is rapidly inactivated by the liver, while chlorpropamide with a chlorine atom in place of the methyl group passes through the liver unchanged and is excreted unaltered by the kidneys. This failure of inactivation by the liver permits higher and more prolonged blood levels with chlorpropamide than was possible with tolbutamide. Like tolbutamide, chlorpropamide is completely absorbed from the gastrointestinal tract. Its pharmacologic activity in no way differs from tolbutamide, acting primarily on the islets of Langerhans with an associated hepatic effect.

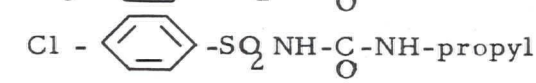
Our experience dates back nine months. Twenty-seven selected patients with diabetes have been given chlorpropamide. A good hypoglycemic effect occurred in twenty-three patients. In this group, twenty patients were over 50 years of age at initiation of oral therapy. Sixteen patients had known diabetes less than five years and twenty-one less than ten years. Chlorpropamide was used as an insulin substitute in fourteen patients, as a tolbutamide substitute in four patients, and as an insulin supplement in one patient. Chlorpropamide was the initial hypoglycemic agent in four patients. In the fourteen patients on insulin prior to chlorpropamide, thirteen had been maintained on less than 40 units per day and eight took less than 20 units per day. In the patient to whom chlorpropamide was given as an insulin supplement, one gram of the drug and 80 units of isophane (NPH) insulin controlled his diabetes as well as 200-250 units of insulin daily had previously. Chlorpropamide was substituted for tolbutamide in three cases for investigational purposes only, while in two patients it was used successfully after secondary failures with tolbutamide.

Figure 1 Comparative chemical structure

TOLBUTAMIDE



CHLORPROPAMIDE



*Division of Metabolism.

Four patients were unresponsive to chlorpropamide. Table 1 summarizes their data. The reader should note the long duration of diabetes and the relatively large daily insulin dosage required. Three patients had prior primary tolbutamide failures. None of our patients with primary tolbutamide failures has been successfully controlled with chlorpropamide. Generally speaking, all juvenile (growth-onset) diabetics are unresponsive to chlorpropamide.

Table 1 Chlorpropamide-Unresponsive patients

Patient	Age	Duration DM	Insulin/day	Tolbutamide
L.M.	55y	19y	100u	none
F.M.	30y	17y	50u	primary failure
I.M.	65y	3y	36u	primary failure
B.P.	46y	7y	50u	primary failure

Toxicity to tolbutamide is limited to the skin and gastrointestinal tract. The reactions are minor and reversible. Our experience with chlorpropamide has also been benign. One patient complained of nausea and epigastric pain which was relieved by decreasing the dosage of the drug. A second patient experienced giddiness on 1.0 gram per day which disappeared with a decrease to 750 mg per day. This singular central nervous system reaction occurs with normo — or hyperglycemia and is related to the size of the daily dose. It is definitely not due to hypoglycemia. Ataxia may also occur. The incidence of this reaction increases strikingly when more than 1.0 gram of chlorpropamide is given daily. A third patient noted unsteadiness and an intolerance to alcohol. His drug dosage was 750 mg per day. Complete symptomatic relief was afforded by the use of insulin. A fourth patient developed positive liver flocculation tests after six weeks of 250 mg per day. One month after cessation of the drug, further liver function studies were normal. No clinical evidence of liver disease ever occurred. This patient is currently well controlled on diet alone. Iezzoni[2] reports thirteen cases of jaundice in a group of over 5000 diabetics controlled with chlorpropamide. No deaths from hepatic failure have occurred. Specimens of liver obtained by needle biopsy show bile stasis and pericholangiolar round cell infiltration, reminding one of the hepatic changes following chlorpromazine and methyltestosterone. Two deaths in patients on chlorpropamide have occurred elsewhere from sustained hypoglycemia. Transient leukopenia may occur and one case of thrombocytopenic purpura has been reported. It is apparent that the spectrum of toxicity for chlorpropamide is broader than tolbutamide and falls somewhere between that drug and carbutamide, which was abandoned because of excessive toxicity.

Table 2 outlines our current indications for the use of chlorpropamide. Any patient responding to tolbutamide is a favorable candidate for chlorpropamide. However, from a practical standpoint, we are using chlorpropamide only when oral therapy is desirable and tolbutamide is ineffective. This attitude is reasonable and based

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Chlorpropamide (Diabinese) was generously supplied through the courtesy of Dr. Dominic Iezzoni of the Chas. Pfizer Co., Brooklyn, New York.

upon the comparative toxicity of the two drugs. Chlorpropamide may also be tried in patients with insulin resistance, in an attempt to lower the daily insulin dose. Any acute stress eliminates the consideration of chlorpropamide. Chlorpropamide is in no way a substitute for a good diet, carefully followed. Dietary indiscretions will rapidly bring about loss of good control. Because of the hepatic side effects, we do not advise the use of chlorpropamide in patients with known liver disease.

Table 2 Indications for Use of Chlorpropamide

Diet alone insufficient for good control
Oral therapy desirable
Maturity-onset (adult type) diabetes
Absence of stress
Tolbutamide failure

Chlorpropamide is supplied under the trade name, Diabinese, in 100 and 250 mgm tablets. Initiation of therapy is much the same as with tolbutamide except that an initial loading dose is unnecessary. No test of its effectiveness prior to its use is available. An initial daily dose of 100 to 500 mg is given. In four to seven days, the daily dose is increased or decreased by 100 to 250 mg. We have never used more than 500 mg initially nor more than 1000 mg as a daily maintenance dose. The initial dose should correspond roughly to the degree of estimated insulin deficiency. Depending upon the clinical and laboratory response, this change in daily dosage is repeated until a final maintenance dose is reached. Table 3 indicates the average maintenance dose of 23 successfully controlled patients. When insulin is being replaced, it is discontinued if less than 20 units per day is used. Otherwise, the insulin dose is halved until an effect from chlorpropamide is noted; then the insulin is stopped. If a large insulin dose is replaced, one can expect a higher maintenance dose of chlorpropamide. During the period of initiation, serial white blood cell counts are done. Our practice also includes a serum alkaline phosphatase determination at bimonthly intervals. The clinician must also be aware of hypoglycemia. Contrary to tolbutamide, chlorpropamide can result in severe hypoglycemia which may be prolonged. This is a potent hypoglycemic agent. Fortunately we have not experienced this, though just recently our patient taking a combination of insulin and chlorpropamide arrived in the Emergency Room comatose with a blood sugar of 40 mg.%. Prompt response following glucagon occurred.

Table 3 Average maintenance dose (23 patients)

100 mgm.	3*
250 mgm.	7
500 mgm.	6
750 mgm.	6**
1000 mgm.	1

*—one patient now controlled on diet alone
**—one patient now controlled on insulin

Chlorpropamide in Diabetes Mellitus

Chlorpropamide is an active hypoglycemic agent and can be used when oral therapy is desirable. As with tolbutamide, the theoretical disadvantage stemming from chronic islet cell stimulation is present. Our experience in 27 *highly selected* diabetics has been good. Twenty-three patients are well controlled (preprandial normoglycemia and aglycosuria). Toxicity has prevented its use in only two patients. It was disappointing to find that three patients with primary tolbutamide failures were unsuccessfully regulated with chlorpropamide. This indicates essentially that chlorpropamide gives the clinician greater depth with the use of oral agents but only a slight increase in breadth. The long duration diabetic and the growth-onset diabetic still are denied oral therapy. The diabetic under acute stress is denied oral therapy. The importance of dietary therapy and the miracle of insulin is reaffirmed.

REFERENCES

1. Whitehouse, F.W., and Bryan, J. B.: Questions and answers about tolbutamide, Henry Ford Hosp. M. Bull. 5:179-182, Sept. 1957.

2. Iezzoni, D. Personal commication.