CHLORPROPAMIDE,* A NEW DRUG FOR DIABETES MELLITUS: CLINICAL STUDIES

A Preliminary Report

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SINCE 1942, when sulfonylurea derivatives were found to have hypoglycemic action, a large number of related compounds have been developed and are being used in diabetic patients. The most recent of these is chlorpropamide.*[1-7]

The basic molecular structure of chlorpropamide is similar to that of other sulfonylureas, but the addition of a chlorine atom has made the action of the drug more prolonged. In man, the plasma concentration of chlorpropamide has decreased by one half in approximately 36 hours,[8, 9] whereas that of tolbutamide has decreased by one half in four hours.[10] As a result, considerably smaller doses of chlorpropamide will achieve concentrations of blood sulfonylurea and hypoglycemic action similar to that of tolbutamide.

This report is a summary of clinical studies during the last six months of 1958 of 53 patients with diabetes mellitus.

Material and Methods

Our clinical study of 53 diabetic patients consisted of three parts: trial of chlorpropamide in (1) 31 adult patients with stable diabetes, (2) four elderly patients with unstable diabetes, and (3) 18 young patients with diabetes.

Adult, stable diabetics. The 31 patients were selected for chlorpropamide therapy because they were candidates for tolbutamide therapy. They all had the so-called "stable" (onset at maturity) diabetes. They were between 32 and 81 years of age. Sixteen patients previously were well maintained on daily doses of from 10 to 52 units of insulin. Eight patients previously had received tolbutamide therapy up to 2 gm. daily, but in two, there was primary, and in six, secondary failure to respond to that therapy. Seven patients previously had followed a careful dietary program without obtaining adequate control of the hyperglycemia.

Adult, unstable diabetics. Four patients, from 30 to 64 years of age, had unstable diabetes. In them, minor changes in insulin dosage brought about rapid development of hyperglycemia and ketosis.

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Young diabetics. Eighteen patients were young diabetics; the average age was 11 years, in a range of four to 17 years.

Results

Adult, stable diabetics. Of the 31 patients, the chlorpropamide treatment was successful in 28: primary failure occurred in two patients, and secondary failure in one patient. For 23 patients the control of diabetes was considered to be excellent; in those patients the blood sugar values were—fasting, less than 140 mg., and postprandially, less than 160 mg. per 100 ml. In five patients the results were good: there was no glycosuria, but the blood sugar values were higher than the above-mentioned values, although less than 190 mg. per 100 ml. fasting or postprandially. The average follow-up is more than three months, in a range of one to seven months. The average maintenance dosage of chlorpropamide was 285 mg. daily, in a range of 100 to 750 mg. per day.

Adult, unstable diabetics. Of the four adult patients with unstable diabetes, chlorpropamide therapy brought about a decrease in insulin requirement in one patient, and no change in the other three. One patient believed that he was better able to anticipate insulin reactions, although there was no objective change in their frequency or severity. In two patients the administration of chlorpropamide had to be stopped because of severe abdominal pain when the dose was greater than 1 gm. per day.

Young diabetics. In six of the 18 patients the insulin dosage could be decreased and satisfactory blood sugar values still could be maintained. In two patients, normal blood sugar content was maintained for eight weeks without any supplemental insulin. Insulin was then restarted because of increasing hyperglycemia in association with poor adherence to the diet. A third patient has maintained excellent control of glycemia for 22 weeks without supplemental insulin.

Comment

It is our experience that the same daily dosage of chlorpropamide must be maintained for from five to seven days in order to ascertain its full hypoglycemic effect. The therapeutic dosage of chlorpropamide usually decreases significantly with prolonged therapy during the course of weeks or months.

The only side effects were observed when the dosage of chlorpropamide was raised to more than 1 gm. per day. They consisted of abdominal pain, lethargy, somnolence, drowsiness, and ataxia. The neurologic symptoms resembled those of hypoglycemia, although the blood sugar values were not hypoglycemic.

Summary

Fifty-three patients with diabetes mellitus were treated with chlorpropamide (average daily dose of 285 mg.) for from one to seven months. The drug therapy was effective in 28 of 31 adult patients with stable diabetes. It was effective in a number of these patients in whom diabetes was not well controlled with tolbuta-

mide. Of four adult patients with unstable diabetes, one patient obtained a decrease in insulin requirement; the other three patients were unaffected by chlorpropamide therapy. With this drug therapy, temporary control was obtained in six of 18 young diabetic patients, and normal glycemia has been maintained in one of them without insulin administration. Severe side effects occurred only in the two patients who required more than 1 gm. of chlorpropamide daily.

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