Potentiation of Hypoglycemic Effect of Chlorpropamide and Phenformin by Halofenate

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SUMMARY

The potentiation of oral hypoglycemic drugs by the antilipemic agent halofenate is reported. Forty-seven diabetic patients were treated for 48 weeks with halofenate, clofibrate, or placebo. Five patients in the halofenate group were taking phenformin plus either chlorpropamide or tolbutamide. Their average initial fasting plasma glucose was 160 mg./dl. All five patients experienced a slow but substantial fall in fasting plasma glucose. The mean fasting plasma glucose for the five patients after 80 days of halofenate treatment was 63 mg./dl. As oral treatment for diabetes was reduced, the fasting plasma glucose returned to prehalofenate levels. In this study, we did not detect an effect of halofenate on the fasting plasma glucose of diabetic patients treated with insulin or on the fasting plasma glucose levels of patients treated with diet alone. DIABETES *26*:291-95, April, 1977.

Jain, Ryan, and McMahon[1] have recently reported their experience with halofenate (2-aceto-aminoethyl [4-chlorophenyl] [3-trifluoromethylphenoxy] acetate) a new investigational agent that has been shown to lower serum triglycerides[2-6] and uric acid.[2-4] These investigators found that halofenate potentiates the effect of oral hypoglycemic agents in patients with diabetes and that it has no effect on patients with diabetes treated by diet alone. Halofenate also increased serum tolbutamide levels and enhanced the hypoglycemic effect of tolbutamide in normal subjects.[1] The potentiation of oral hypoglycemic agents by a substance that simultaneously lowers triglycerides and uric acid might be clinically important. We, therefore, report our experience with halofenate and confirm the results of Jain, Ryan, and McMahon[1] and in addition provide data showing that halofenate does not lower plasma glucose in diabetic patients treated with insulin. The effect of halofenate on plasma glucose was not known to us a priori but was suspected by one of us (D.J.K.) when symptoms of hypoglycemia or low fasting plasma glucoses began to appear in several diabetic patients. These patients had previously been followed for extended periods in a diabetes clinic before selection for the halofenate study and were known to have high fasting plasma glucoses.

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Accepted for publication October 18, 1976.

METHODS

A double-blind randomized study of the effects of 48 weeks' administration of halofenate, 500-1,500 mg. once daily, clofibrate, 1,000 mg. twice daily, and placebo was carried out in patients with endogenous hypertriglyceridemia or hypercholesterolemia (TG 175 or >; chol. 274 or >). Fifty-five patients, selected mostly from a diabetes clinic, were randomly assigned to treatment with either halofenate (18 patients), clofibrate (18 patients), or placebo (19 patients). The number of patients with diabetes was 13 for the halofenate group, 18 for the clofibrate group, and 17 for the placebo group. Treatment data for diabetes mellitus for all patients are given in table 1. There was an eight-week pretherapy control period. Patients were seen every two weeks during the pretherapy control period and for the first two visits after randomization and introduction of double-blind treatment. Thereafter they were seen every four weeks for a total of 48 weeks. Patients were instructed to follow their customary diets. Thirteen patients in the halofenate group, 16 in

TABLE 1

Major therapy for diabetes during period covered by this report

	Number of patients		
	Placebo group	Halofenate group	Clofibrate group
Chlorpropamide	3	—	4
Chlorpropamide plus phenformin	1	4	2
Tolbutamide	1	2	4
Tolbutamide plus phenformin	—	1	—
Tolazamide	4	—	4
Tolazamide plus phenformin	3	—	2
Insulin	5	6	2
Insulin plus phenformin	1	—	1

the clofibrate group, and 15 in the placebo group completed 48 weeks of study. One patient in the halofenate group included in this study completed only 16 weeks. Fasting plasma levels of triglyceride, cholesterol, and glucose were measured at every visit. Laboratory safety tests were obtained at all pretreatment visits and at 2, 4, 12, 24, 36, and 48 weeks after randomization. The dose of clofibrate was 2 gm. per day, and the dose of halofenate depended on body weight (< 60 kg., 0.5 gm.; 60 to 110 kg., 1 gm.; > 110 kg., 1.5 gm. a day).

RESULTS

An initial comparison of the results of plasma glucose determinations for the placebo, halofenate, and clofibrate groups revealed a significant fall in plasma glucose for the entire halofenate group (18 patients) (figure 1). These changes were significant from the pretreatment level ($p < 0.05$) at 12 and 24 weeks. A further analysis revealed that only patients receiving phenformin plus either chlorpropamide or tolbutamide experienced a significant fall in plasma glucose from pretreatment levels. Table 2 shows that halofenate produced a marked fall in fasting plasma glucose in four patients receiving chlorpropamide plus phenformin and in one receiving tolbutamide plus phenformin ($p < 0.001$ at 18 and 12 weeks, and $p < 0.02$ at 24 weeks as compared with the placebo-treated group). Three subjects receiving chlorpropamide plus phenformin and one receiving tolbutamide plus phenformin had been previously poorly controlled in spite of near maximal doses of oral agents. Halofenate administration resulted in normalization of the fasting plasma glucose and even mild hypoglycemia in these individuals and required reduction in oral drug treatment for diabetes. By the end of the 48 weeks of the study, however, the fasting plasma glucose had returned to the pretreatment levels. In order to evaluate these results, the 48 weeks of the study were divided into three periods showing obvious trends in fasting plasma glucose levels. These changing patterns were compared with the average dose of oral hypoglycemic agents administered for a given period expressed as a percentage of the average initial dose of medication for diabetes. Three periods were identified (figure 2). The first period was associated with gradually decreasing blood glucose levels over a period of six to 12 weeks and an average dose of 500 mg. of chlorpropamide and 55 mg. of phenformin daily. The second period was characterized by a slight rise in the average fasting plasma glucose level and a progressive reduction in oral treatment for diabetes. The third, or last, period was characterized by a rise in fasting plasma glucose to prehalofenate levels and a further decrease in the total dose of oral antidiabetic treatment. One patient was lost to follow-up at 16 weeks but was included in the results because the halofenate effect was evident. In this group of patients, which had a significant reduction in plasma glucose, there were no changes in body weight that could have been responsible for the effect. In addition, halofenate produced an average 30 to 40 per cent fall in serum

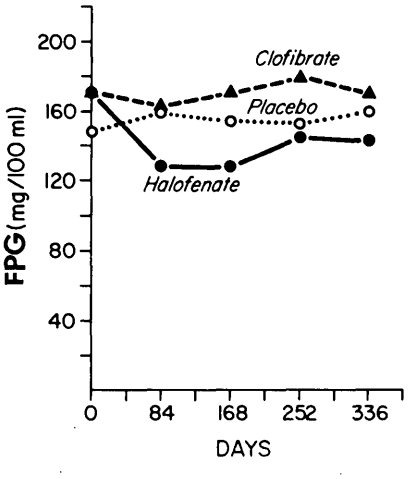

FIGURE 1

Effect of halofenate, clofibrate, and placebo on fasting plasma glucose levels in 55 patients.

TABLE 2

Effect of halofenate on fasting plasma glucose levels in five patients with diabetes mellitus treated with oral hypoglycemic agents

Day	Patient no. 1		Patient no. 2		Patient no. 3		Patient no. 4		Patient no. 5		Mean	S.E.M.	P value compared with placebo group
	*FPG	Treatment	FPG	Treatment	FPG	Treatment	FPG	Treatment	FPG	Treatment			
0 (Mean of all pre-treatment values)	81	†C 500 †P 50	182	†T 1,500 P 50	179	C 500 P 75	235	C 500 P 75	153	C 500 P 50	166	26.4	—
57 (8th week)	57	C 500 P 50	61	T 1,500 P 50	91	C 500 P 75	63	C 500 P 75	76	C 500 P 50	70	7.0	<0.001
85 (12th week)	68	C 500 P 50	60	T 1,500 P 50	62	C 500 P 75	62	C 500 P 75	—	—	63	1.7	<0.001
169 (24th week)	50	C 500	100	T 500 P 50	76	C 500 P 75	132	C 500	—	—	90	17.5	<0.02
253 (36th week)	138	—	108	T 500	270	—	136	C 250	—	—	163	36.3	—
330 (48th week)	167	C 125	175	—	162	C 250	172	C 250	—	—	169	2.9	—

All doses are in milligrams per day, and all fasting plasma glucose levels are in mg./dl.
*FPG—fasting plasma glucose.
†P—phenformin, C—chlorpropamide, T—tolbutamide.

triglyceride concentrations. This fall was not significantly different in the group of patients that experienced substantial reduction in fasting plasma glucose concentrations.

Two patients, each taking 500 mg. per day of tolbutamide (figure 3), experienced no fall in plasma glucose during halofenate administration.

Six patients who were not ketosis-prone were taking insulin and received halofenate. These patients experienced no significant fall in plasma glucose (figure 4), and the average dose of insulin was unchanged during the study, results that are in agreement with those reported by Jain et al.,[1] who noted no fall in plasma

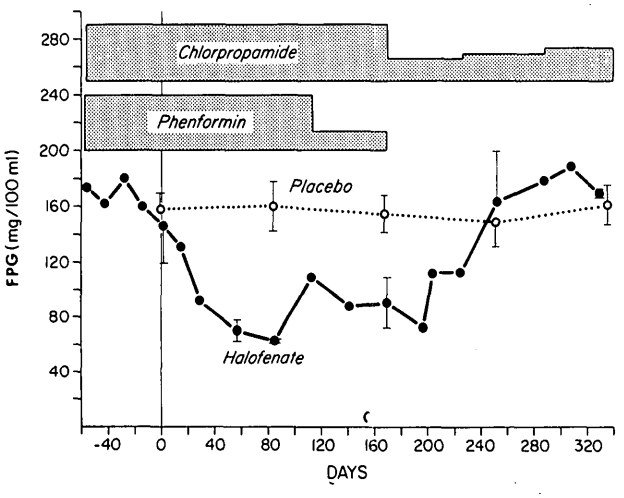

FIG. 2. Effect of halofenate and oral hypoglycemic agents on mean fasting plasma glucose. Four patients received phenformin and chlorpropamide. One patient received phenformin and tolbutamide. The mean relative chlorpropamide and phenformin doses for the halofenate-treated patients are indicated by the width of the horizontal bars. The mean initial doses for chlorpropamide and phenformin were, respectively, 500 and 55 mg. per day. One patient received 1,500 mg. tolbutamide and 50 mg. phenformin per day.

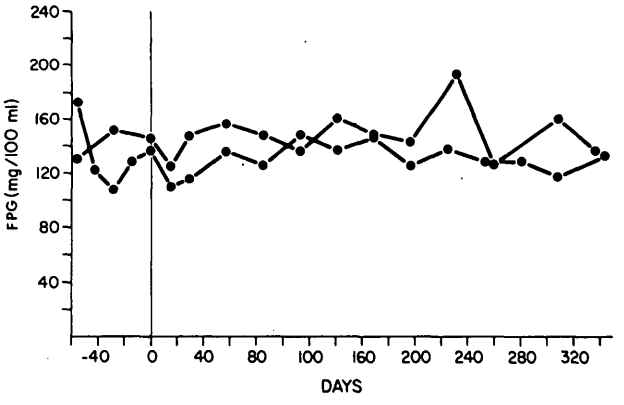

FIG. 3. Effect of halofenate on mean fasting plasma glucose in two diabetic patients treated with tolbutamide.

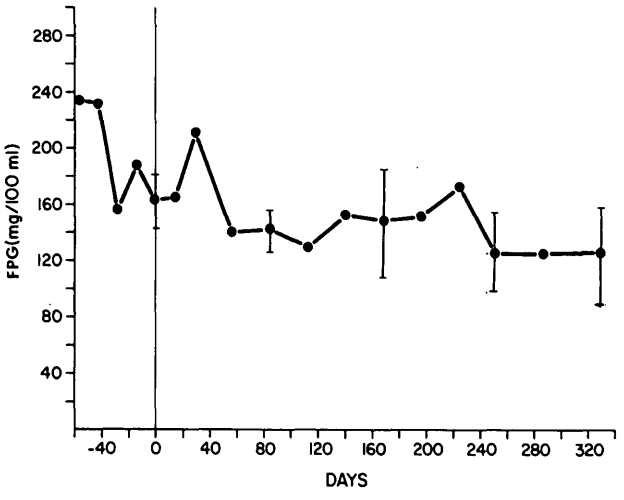

FIG. 4. Effect of halofenate on mean fasting plasma glucose in six diabetic patients treated with insulin.

glucose in two patients receiving halofenate and insulin.

The remaining patients in the group who were not taking oral agents or insulin experienced no fall in plasma glucose.

Evaluation of the fasting plasma glucose trend in patients receiving clofibrate and chlorpropamide suggests that clofibrate may lower plasma glucose in this group of patients (figure 5). The effect, if any, appears to be transient. The clofibrate group as a whole, however, showed no fall in plasma glucose (figure 1).

No fall in plasma glucose was observed in the placebo group. Nine of these patients were taking chlorpropamide, phenformin, or both.

DISCUSSION

In this study, four diabetic patients received chlorpropamide and phenformin. All four had a quantitatively significant and gradual fall in fasting plasma glucose when treated with halofenate. A similar effect was noted in another patient receiving phenformin and tolbutamide. The effect was absent in patients treated with diet alone, insulin, or tolbutamide. It is not clear, however, whether both chlorpropamide and phenformin are necessary for maximal effect. Jain et al.[1] observed a substantial effect of halofenate on the blood glucose of patients receiving chlorpropamide alone. It is also pertinent to our investigation that their two patients who received halofenate and phenformin alone experienced only slight improvement in fasting hyperglycemia.

In the last third of the 48-week period, during which our four patients were taking reduced quantities of chlorpropamide, the plasma glucoses returned to the prehalofenate levels. It is, therefore, not known whether or not there was an escape from the halofenate effect. During this period of time, however, the patients were receiving no phenformin and the average dose of chlorpropamide was half of the pretreatment dose. It is possible that the fasting plasma glucose levels might have risen to levels exceeding the prehalofenate levels if the patients had not been taking halofenate along with the reduced dose of oral hypoglycemic agents.

The mechanism by which halofenate potentiates the hypoglycemic effects of sulfonylureas and possibly of phenformin or of a combination of the two is not clear. A similar effect has been reported from clofibrate administration[7] and in the present study the possibility of a slight effect is suggested. The studies of Jain et al.[1] show that halofenate appears to decrease the rate of excretion of intravenously injected tolbutamide in normal individuals. This effect was accompanied by a potentiation of the hypoglycemic effect of tolbutamide. Consequently, these workers suggest that the observed increase in serum tolbutamide might be due to tolbutamide displacement from protein-binding sites by halofenate, which is known to have a strong affinity for plasma proteins.[2,5]

Other drugs can potentiate the hypoglycemic action of sulfonylureas, particularly certain monoamine oxidase inhibitors.[8,9] The monoamine oxidase inhibitors, unfortunately, are not useful in the treatment of diabetes. Halofenate, however, is of interest because it normalized the fasting plasma glucose in patients who

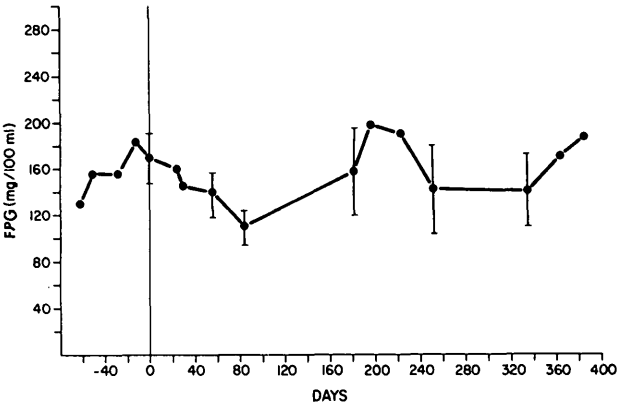

FIG. 5. The effect of clofibrate on mean fasting plasma glucose in six diabetic patients receiving chlorpropamide.

were poorly controlled in spite of maximal doses of chlorpropamide and phenformin. Furthermore, the concomitant effect of halofenate in lowering serum triglycerides and uric acid might be particularly useful in the treatment of diabetes, since diabetics commonly have hypertriglyceridemia and hyperuricemia.

Additional studies on a larger group of patients treated with chlorpropamide and halofenate are clearly needed.

ACKNOWLEDGMENT

This work was supported by a grant from Merck, Sharpe and Dohme.

The authors gratefully acknowledge the assistance of Mrs. JoAnne Kudzma, nurse-practitioner, coordinator; Mrs. Anne Heifetz; Mrs. Constance Stahl; and Miss Susan Pfeiffer in carrying out this project.

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