Improved Control of Non-insulin-dependent Diabetes Mellitus by Combined Halofenate and Chlorpropamide Therapy

E. ALAN KOHL, M.D., JAMES A. MAGNER, M.D., SCOTT T. PERSELLIN, M.D., GEORGE M. VAUGHAN, M.D., DAVID J. KUDZMA, M.D., AND SAMUEL J. FRIEDBERG, M.D.

Combined halofenate-chlorpropamide was evaluated for the treatment of NIDDM. Four subjects treated with 500 mg/day chlorpropamide were given 500–1000 mg halofenate daily for 48 wk or longer. Fasting plasma glucose fell from 210 ± 16 (±SEM) (11.67 ± 0.89 mM) to 107 ± 10 mg/dl (±SEM) (5.94 ± 0.55 mM), $P < 0.005$. Twelve additional subjects were entered into a 16-wk double-blind study testing chlorpropamide plus either placebo or halofenate. In the halofenate group, the mean fasting glucose fell from 227 ± 27 (±SEM) (12.61 ± 1.50 mM) and reached 107 ± 19 mg/dl (±SEM) (5.94 ± 1.06 mM) during the fourth month, whereas the placebo groups showed a decrease from 242 ± 22 (±SEM) to 208 ± 29 mg/dl (±SEM) ($P < 0.005$). In addition, halofenate reduced the height of postprandial glycemic excursions by lowering fasting plasma glucose. When halofenate was used as the only therapy, reduction in fasting plasma glucose was small [179 ± 12 reduced to 142 ± 8 mg/dl (±SEM); 9.94 ± 0.67 mM and 7.89 ± 0.44 mM], $P < 0.05$. DIABETES CARE 7: 19–24, JANUARY–FEBRUARY 1984.

Halofenate (2-acetoaminoethyl [4-chlorophenyl]-[3-trifluoromethylphenoxy] acetate) is an investigational agent known to lower triglycerides and uric acid.[1–5] In addition, it reduces platelet aggregation and it has been reported to potentiate the anticoagulant effect of warfarin without affecting protein binding.[1,6] However, halofenate may affect protein binding of thyroxin.[7]

Controlled studies conducted in many centers to evaluate the efficacy and safety of halofenate as a triglyceride-lowering agent involved over 900 patients (Merck, Sharp & Dohme Research Laboratories, West Point, Pennsylvania). In two participating institutions all of the patients were selected from diabetes clinics. In these two clinics, it was observed that marked reduction in fasting plasma glucose occurred in some patients. Jain, Ryan, and McMahon were the first to report that halofenate potentiates the action of sulfonylurea drugs and that this effect might be the result of displacement from protein binding sites.[8] From simultaneously obtained data we confirmed that halofenate potentiates the action of sulfonylurea drugs, particularly chlorpropamide, but does not augment the action of insulin.[9]

Because the potentiating effect of halofenate on sulfonylureas and possibly phenformin resulted in normalization of the fasting blood glucose in all of a small number of patients with NIDDM we chose to evaluate further the value of this agent for the treatment of this disorder; an agent that simultaneously reduces blood glucose, triglycerides, uric acid, and platelet aggregation, all of which are associated with vascular disease, might have singularly useful properties for the treatment of diabetes mellitus.

In order to address these issues, we report here on a long-term historically controlled study of 4 patients (minimum 48 wk) and on a shorter, 16-wk double-blind study of 12 patients. We also present data on the effect of halofenate alone on the fasting plasma glucose, and the insulin and glucose response to a glucose load in NIDDM.

METHODS

Subjects. Subjects were recruited from the diabetes clinics of the Robert B. Green Hospital (Bexar County Hospital District) and the Audie L. Murphy Memorial Veterans Hospital, San Antonio, Texas. Patients below the age of 65 with NIDDM were selected who were free from clinically significant micro- and macrovascular complications of diabetes (including amputations, previous myocardial infarctions, angina pectoris, proliferative retinopathy, nephropathy, and stroke). Subjects with a prior history of congestive heart failure, gastritis, peptic ulcer disease, or alcoholism and women capable of child-

bearing were excluded. Peripheral neuropathy was not a basis for exclusion. Written informed consent was obtained from each subject.

In the present investigation three studies were carried out:

Long-term efficacy of halofenate-chlorpropamide treatment. This was a controlled evaluation of the long-term efficacy of halofenate-chlorpropamide treatment in four subjects poorly controlled while receiving 500 mg chlorpropamide daily. Poor control was defined as fasting plasma glucose concentrations greater than 140 mg/dl on at least three consecutive clinic visits. All were followed initially for a 5-mo control period while continuing 500 mg chlorpropamide daily. In addition, specific directions were given to maintain constant body weight and not to change customary diet. During this period, subjects were seen every 2 wk for determination of fasting plasma glucose, urinalysis, and for complete blood count. A serum chemistry panel (SMA-12) was obtained at 9-wk intervals. Plasma glucose determinations were done on the SMA-12 multichannel analyzer using the hexokinase method. Each subject had an upper gastrointestinal x-ray series, an electrocardiogram, and a chest x-ray. Four-hour glucose tolerance testing with concomitant plasma insulin assays was done on an outpatient basis [100 g glucose given orally as Glucola (Ames Division, Elkhart, Indiana) at zero time]. In addition, the subjects were admitted for 1 day to a metabolic ward and were fed a standardized mixed diet (30 kcal/kg body wt; 35–48% carbohydrate, 14–18% protein, 37–47% fat, divided into three meals given at 8 a.m., noon, and 5 p.m.). Plasma was sampled hourly for glucose and insulin through an indwelling venous catheter beginning at 8 a.m. (fasting) and ending at 11 p.m. In addition, plasma was sampled 30 min after the beginning of each meal for a total of 19 plasma samples per patient per day. Urine was collected from 8 a.m. to noon, noon to 5 p.m., and 5 p.m. to 11 p.m. for quantitation of glucose excretion.

After the control period, 500 mg halofenate was administered orally once daily. If in the judgment of the investigators 500 mg/day did not result in a decreased fasting plasma glucose, the dose was increased to 1000 mg/day. Subjects were encouraged to maintain constant body weight. They were seen biweekly for a 16-wk period and then every 2–4 wk for a total of at least 48 wk. Pill counts were performed at every visit to assess compliance. Home monitoring for occult blood in the stool was carried out biweekly by means of Hemoccult slides (Smith Kline Co., Sunnyvale, California). Hemoglobin, hematocrit, fasting plasma glucose, and fasting urinalysis were obtained at every visit and the subjects were questioned about gastrointestinal symptoms. The SMA-12 was repeated every third visit. After 48 wk of combined treatment, a 4-h glucose tolerance test with concomitant measurement of plasma insulins was again obtained. The subjects were hospitalized as before for hourly plasma glucose and insulin measurements and for quantitation of urinary glucose excretion in response to the standardized mixed meals. Halofenate but not chlorpropamide was then withdrawn and follow-up was continued for at least 3 mo under the same conditions described above.

Sixteen-week double-blind study. This was a double-blind 16-wk evaluation of 500 mg chlorpropamide daily plus placebo versus 500 mg chlorpropamide daily plus 1000 mg halofenate daily. Twelve subjects with NIDDM, poorly controlled on 500 mg chlorpropamide daily, were recruited as described for the first study. Before randomization to placebo or treatment groups, they were admitted to a metabolic ward for 1 day for measurement of glucose and insulin responses to standard meals. Laboratory safety tests, including weekly stool guaiac, hemoglobin, and hematocrit determinations, were also obtained. One subject from the placebo group was dropped before completion of the study because of noncompliance. Follow-up details were analogous to those of the first study except that the subjects were seen weekly. Plasma glucose and urinalysis were obtained at each visit. Four-hour glucose tolerance testing was not done in this study. Glucose and insulin response to standard meals was carried out before drug allocation and during the sixteenth week of treatment as described above. Medication was supplied in numbered bottles with numbered tear-off coded labels. The contents were known by neither the patient nor the physician.

The effect of halofenate alone. Six subjects with NIDDM and six nondiabetic control subjects were selected. The diabetic subjects had all been treated with a sulfonylurea compound. These were discontinued. Six to eight weeks later, the subjects were treated with 500 mg halofenate twice daily for 3 mo. Fasting plasma glucose concentrations were obtained three times before, five times during, and three times after the treatment period. Oral glucose tolerance tests were obtained before, after, and at 2 and 12 wk during the treatment period.

Plasma insulin was measured by BioScience Laboratories (Richmond, California). Plasma and urine glucose, other chemistries, and other radiologic and diagnostic testing were performed in the facilities of the Audie Murphy Memorial Veterans Administration Hospital or the Medical Center Hospital of the Bexar County Hospital District.

Observed changes in monitored parameters of treatment, such as fasting glucose concentrations, were analyzed for statistical significance by means of the two-tailed Student's *t* distribution, by the paired *t* test, and by an analysis of covariance adjusting for initial values.[10]

RESULTS

First study: long-term controlled study of chlorpropamide versus combined halofenate-chlorpropamide treatment of NIDDM. The mean fasting blood glucose concentrations during the 5-mo chlorpropamide control period ranged from 168 ± 15 to 244 ± 17 mg/dl (±SEM) (9.33 ± 0.84 and 13.56 ± 0.95 mM) for individual patients (seven to nine determinations). During the experimental period, which lasted from 50 to 74 wk, the four subjects experienced a mean plasma glucose fall ranging from 40% to 54% of the control values (18–24 determinations). Thus, during combined chlorpropamide-halofenate treatment the fasting plasma glucose ranged from 77 ± 10 to 122 ± 19

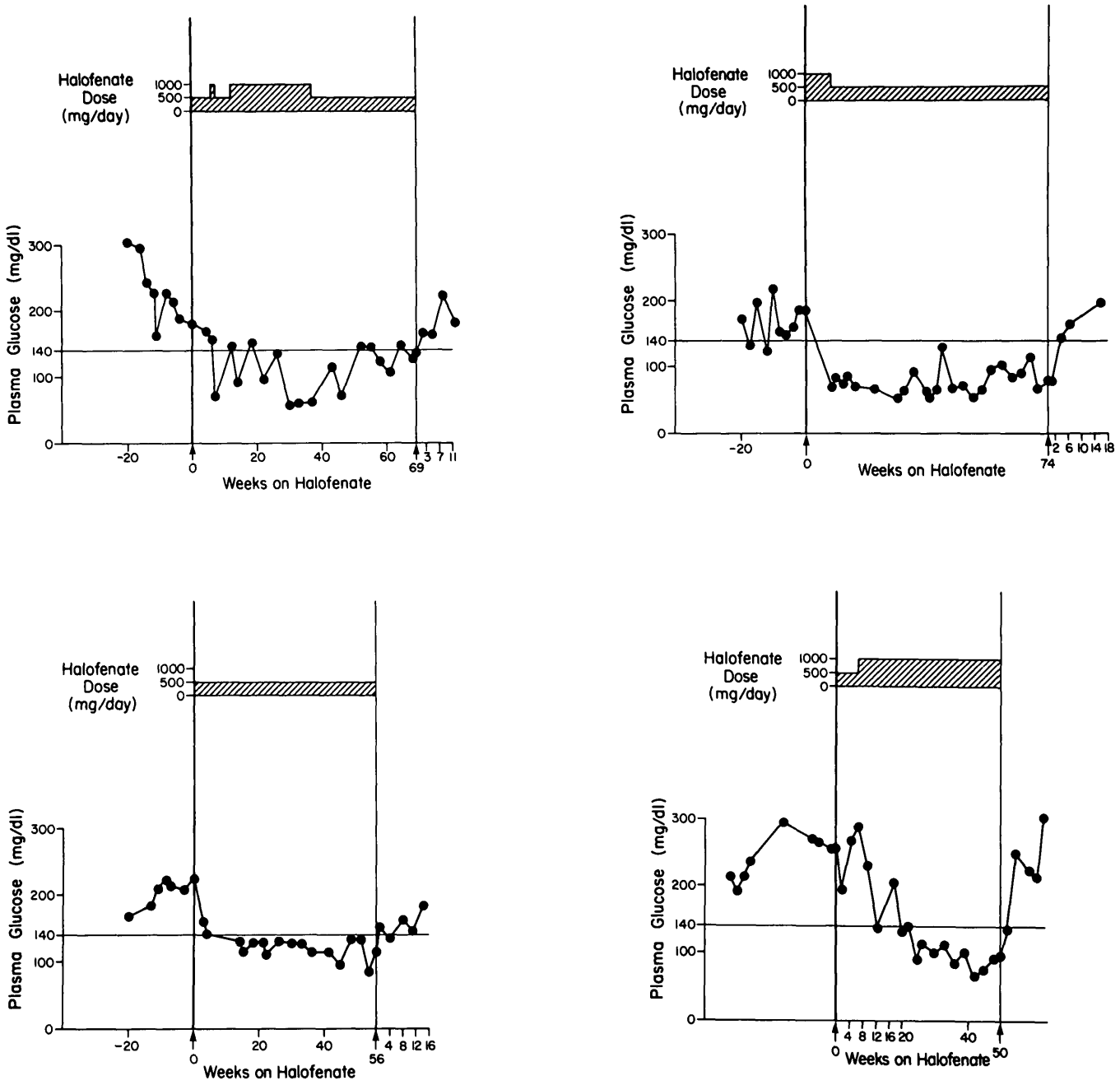

FIG. 1. The effect of combined halofenate-chlorpropamide treatment on mean fasting plasma glucose in four subjects. Chlorpropamide, 500 mg/day, was administered before, during, and after halofenate. The upper limit of normal for fasting plasma glucose is 100 mg/dl. To convert glucose values to mmol/L multiply by 0.056.

mg/dl (4.28 ± 0.56 to 6.78 ± 1.03 mM) in individual subjects (Figure 1). The halofenate effect lasted for the entire treatment period. In three of the four subjects it was possible to lower the dose of halofenate to 500 mg, half the dose necessary for achieving maximum triglyceride-lowering effect.[1-3] None of the subjects developed symptomatic or chemical hypoglycemia, adverse drug reactions, weight change, symptomatic polyuria, or fasting glycosuria while on the combined drug regimen during the study period. Plasma glucose concentrations after a 100-g oral glucose challenge were lower at all times in each subject treated with the combined regimen compared with chlorpropamide alone (Figure 2). This effect was apparently entirely the result of a lowering of the fasting plasma glucose levels since postprandial glucose excursions were not reduced by the combined regimen. Moreover, the insulin response and the glucose concentration

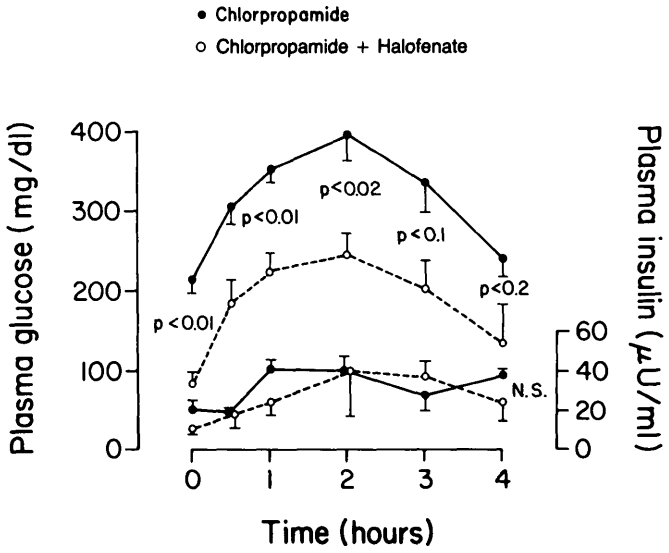

FIG. 2. The effect of added halofenate on glucose tolerance and plasma insulin concentrations in four subjects receiving 500 mg/day chlorpropamide. Each data point is the mean of four values ± SEM. To convert to mmol/L multiply by 0.056. (Two upper lines: glucose concentrations; two lower lines: insulin concentrations; solid line: chlorpropamide alone; dashed line: chlorpropamide plus halofenate.)

curves remained abnormal (Figure 2). In addition to the response to an oral glucose load, plasma glucose concentrations after defined mixed meals, during a single 1-day period from 7 a.m. to 11 p.m., were markedly reduced with halofenate-chlorpropamide combined treatment compared with chlorpropamide alone. During treatment with chlorpropamide alone the mean plasma glucose concentration was 250 ± 42 (14 ± 5 mM) versus 144 ± 8 mg/dl (±SEM) (8.1 ± 0.5 mM). Mean quantitative glucose excretions were 10.2 and 1.13 g for the control versus the treatment period, respectively. The primary effect of the combined regimen was to lower fasting plasma glucose levels and, although the highest postprandial glucose concentrations attained during the combined regimen were lower, this effect was the result of lower initial fasting levels. The dynamics of glucose disposal were unaltered and remained abnormal.

Patient no. 1 was treated for a period of 2 yr with 0.5 g halofenate and 500 mg chlorpropamide. After an acute episode of gouty arthritis he was given indomethacin, a known ulcerogenic drug. One week later the patient was hospitalized because of symptoms of gastritis and gastrointestinal bleeding. Endoscopy revealed multiple superficial gastric ulcerations. After cessation of all medication the patient made an uneventful recovery. Treatment with halofenate was not resumed.

Second study: short-term double-blind studies of halofenate-chlorpropamide versus chlorpropamide-placebo combined regimen. Figure 3 and Table 1 detail the results of these studies. The mean fasting blood glucose concentrations were 242 ± 22 and 227 ± 27 mg/dl (±SEM) (13.44 ± 1.2 and 12.61 ± 1.50 mM) for the placebo and treatment groups, respectively. The mean fasting blood glucose fell during placebo treatment and then rose somewhat. This was due to a substantial sudden fall in fasting plasma glucose in one subject for unknown reasons and a more modest fall in another. In the treatment group the fasting blood glucose gradually fell to a mean value of 112 ± 19 mg/dl (±SEM) (6.22 ± 1.06 mM) during the third month of treatment and to 107 ± 24 mg/dl (±SEM) (5.94 ± 1.33 mM) during the fourth month. In the placebo group corresponding values for the same periods were 200 ± 31 and 208 ± 30 mg/dl (±SEM) (11.11 ± 1.72 and 11.56 ± 1.67 mM), respectively. Comparison of the fasting plasma glucose concentrations of the halofenate group with those of the placebo group during the fourth month by analysis of covariance adjusting for initial values gave $P < 0.005$.[10]

The results of combined halofenate-chlorpropamide on the mean insulin response to standard mixed meals was not significantly different in the placebo versus the treatment group. In fact, the halofenate-chlorpropamide group as a whole had slightly lower plasma insulin concentrations. In these studies mean plasma insulin levels were determined from replicate assays obtained from mixing equal aliquots of plasma from 19 hourly samples drawn from 8 a.m. to 11 p.m. Thus, mean plasma insulin during eight standard meal tests in four subjects from the placebo group was 41 ± 7 versus 45 ± 5 μU/ml (±SEM) in seven subjects from both the long- and short-term studies before halofenate was administered. When halofenate had lowered fasting plasma glucose to its nadir in these seven subjects, the mean plasma insulin was 29 ± 4 μU/ml (±SEM). These differences are not statistically significant to an oral glucose load obtained during the long-term study (first study).

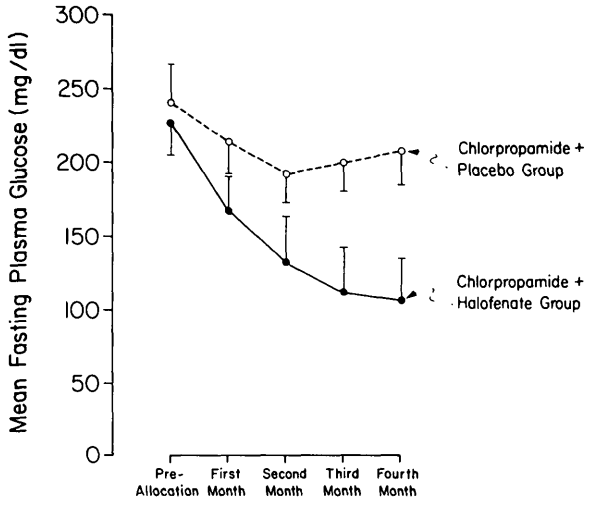

FIG. 3. Mean monthly fasting plasma glucose obtained from 12 subjects treated with 500 mg/day chlorpropamide. Six patients were allocated to 500 mg/day chlorpropamide plus placebo and six to 500 mg/day chlorpropamide plus 1000 mg/day halofenate. The error bars represent the SEM. To convert to mmol/L multiply by 0.056.

TABLE 1
The effect of chlorpropamide plus placebo versus chlorpropamide plus halofenate on fasting plasma glucose in a 16-wk double-blind study

	Fasting plasma glucose (mg/dl)		
	Pretreatment	Mean for treatment months three and four	Range
Halofenate group (subject no.)			
1	186	99 (8)*	54–183
2	340	196 (7)	130–315
3	239	78 (2)	61–95
4	249	117 (8)	105–141
5	199	73 (4)	66–78
6	151	72 (5)	48–97
Mean	227	105	
Placebo group (subject no.)			
7	181	228 (6)	178–286
8	230	166 (8)	144–190
9	323	287 (4)	244–315
10	249	233 (4)	225–260
11	190	117 (7)	93–130
12	281	258† (3)	250–262
Mean	242‡	206§	

*Number of determinations during period.
†This subject was dropped after the fifth week. The fasting plasma glucose at week 5 was 262 mg/dl.
‡Calculated for six subjects.
§Calculated for five subjects.

Third study: the effect of halofenate alone upon fasting plasma glucose and on glucose tolerance in subjects with NIDDM and nondiabetic control subjects. For the six diabetic subjects, mean fasting plasma glucose before and after halofenate was 179 ± 12 (9.94 ± 0.67 mM) versus 181 ± 12 mg/dl (SD) (10.05 ± 0.67 mM). During halofenate therapy the mean fasting glucose was reduced to 142 ± 9 mg/dl (SD) (7.89 ± 0.48 mM), $P < 0.05$. The characteristic diabetic shape of the glucose tolerance curves and plasma insulin concentrations were unaltered by halofenate therapy.

The results of the oral glucose tolerance tests were evaluated by measuring the incremental area under the glucose tolerance curves corrected for the fasting plasma glucose. For each subject, the two determinations obtained without halofenate and the two determinations obtained during halofenate treatment were averaged. The paired data for each of the six diabetic subjects during treatment revealed a mean decrease in area of 23% [446 ± 39 (SEM) versus 342 ± 32 mg-h/dl], $P < 0.05$. The control group of six nondiabetic subjects showed no lowering of fasting plasma glucose while taking halofenate and no change in glucose tolerance.

DISCUSSION

The efficacy of combined halofenate-chlorpropamide therapy in reducing ambient, integrated plasma glucose over time is demonstrated by the data presented. This effect could be important since some evidence suggests that hyperglycemia is responsible for the microvascular complications of diabetes, and that glycemic control may prevent or reverse these complications.[11] To date, in 15 consecutive subjects treated with halofenate-chlorpropamide combined therapy, there was marked reduction of the fasting plasma glucose in all 10 subjects in this study and 5 from a previous study.[9] We have yet to encounter a patient with NIDDM with an elevated fasting glucose receiving 500 mg chlorpropamide daily who has failed to respond with a decrease in fasting glucose when halofenate was added to the regimen. In contrast to these findings, raising the dose of chlorpropamide above 500 mg usually does not result in improvement and increases the incidence of side effects.[12] In our hands halofenate-chlorpropamide has proved to be an effective method for the treatment of NIDDM.

In terms of side effects, previous extensive clinical trials with the use of halofenate as an agent for lowering plasma triglycerides uncovered a potential ulcerogenic risk that was greater in the group receiving halofenate than in any other groups receiving control drugs or placebo. All other untoward reactions were minor, were about equally common in the control groups, and usually consisted of vague epigastric discomfort. Symptomatic or chemical hypoglycemia did not occur in any of the 28 subjects exposed to halofenate. The risk of ulcer must be evaluated in comparison with the ultimate risk to longevity of having diabetes mellitus treated with currently accepted modes of therapy. This risk is possibly greater than the risk of peptic ulceration. Of the 28 subjects exposed to halofenate in our studies, one, concurrently exposed to indomethacin, developed frank upper gastrointestinal bleeding from superficial ulcerations. Whether or not the incidence of peptic ulceration or gastrointestinal bleeding can be reduced by excluding patients with prior history of peptic ulcer, reducing the dose of medication, avoiding the concurrent use of other ulcerogenic drugs, or giving the medication in divided doses after meals with antacids or cimetidine remains to be demonstrated. We have already shown in the present study that effective lowering of fasting plasma glucose can be achieved in some patients with 500 mg halofenate daily, half the dose previously used and recommended for lowering plasma triglycerides. The efficacy of still lower doses has not been evaluated.

ACKNOWLEDGMENTS: This work was supported in part by a grant from the Merck, Sharp & Dohme Research Laboratories, West Point, Pennsylvania, and by an institutional biomedical research support grant (RR 05654) from the National Institutes of Health.

From the Division of Endocrinology and the Department of Medicine, The University of Texas Health Science Center, the

Audie L. Murphy Veterans' Administration Hospital, San Antonio, Texas, and the Albert Einstein College of Medicine, New York, New York.

Address reprint requests to Samuel J. Friedberg, M.D., Division of Endocrinology and the Department of Medicine, The University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

REFERENCES

[1] McMahon, F. G., Jain, A. K., Ryan, J. R., et al.: Some effects of MK-185 on lipid and uric acid metabolism in man. Univ. Mich. Med. Ctr. J. 1970; 36:247–48.

[2] Morgan, J. P., Bianchine, J. R., Hsu, T. H., et al.: Hypolipidemic uricosuric and thyroxine-displacing effects of MK-185 (halofenate). Clin. Pharmacol. Ther. 1971; 12:517–24.

[3] Aronow, W. S., Harding, P. R., Khursheed, M., et al.: Effect of halofenate on serum lipids. Clin. Pharmacol. Ther. 1973; 14:358–65.

[4] Dujovne, C. A., Azarnoff, D. L., Huffman, D. H., et al.: One-year trials with halofenate, clofibrate, and placebo. Clin. Pharmacol. Ther. 1975; 19:352–59.

[5] Jain, A., Ryan, J. R., Hague, D., et al.: The effect of MK-185 on some aspects of uric acid metabolism. Clin. Pharmacol. Ther. 1970; 11:551–57.

[6] Hucker, H. B., Stauffer, S. C., and White, S. C.: Effects of halofenate on binding of various drugs to human plasma proteins and on the plasma half-life of antipyrine in monkeys. J. Pharm. Sci. 1972; 61:1490–92.

[7] Ryan, J. R., Jain, A. K., Maha, G. E., et al.: The effect of MK-185 on thyroid function. Clin. Pharmacol. Ther. 1971; 12:464–67.

[8] Jain, A. K., Ryan, J. R., and McMahon, F. G.: Potentiation of hypoglycemic effect of sulfonylureas by halofenate. N. Engl. J. Med. 1975; 293:1283–86.

[9] Kudzma, D. J., and Friedberg, S. J.: Potentiation of hypoglycemic effect of chlorpropamide and phenformin by halofenate. Diabetes 1977; 26:291–95.

[10] Snedecor, G. W., and Cochran, W. G.: Statistical Methods, 6th edit. Ames, Iowa, Iowa State University Press, 1967.

[11] Brownlee, M., and Cahill, G. F., Jr.: Diabetic control and vascular complications. *In* Atherosclerosis Reviews. Paoletti, R., and Gotto, A. M., Jr. New York, Raven Press, 1979:29.

[12] St. Whitelock, O. V., Furness, F. N., Ressner, P., and Goldner, M. G., Eds.: Chlorpropamide and diabetes mellitus. Ann. NY Acad. Sci. 1959; 74:621–1028.