Clinical Evaluation of Acetohexamide, A New Sulfonylurea Agent

James B. Field, M.D., and S. A. Tyroler, M.D., Bethesda

During the past six years many oral hypoglycemic agents have been studied in an effort to find an insulin substitute.[1] At the present time, three such drugs are commercially available, but each has its limitations. Although tolbutamide is associated with the least amount of toxicity, it is effective in a limited number of patients and the rate of secondary failure has been high.[2] Chlorpropamide is useful in a larger group of diabetics, but the incidence of toxicity, especially liver damage, is increased. Neither of the drugs has proven beneficial to most insulin-requiring diabetic patients. Phenformin may be helpful in some diabetics, but its usefulness is limited by the high percentage of side effects at a therapeutic dosage.

Since all of the available oral agents have their limitations, the search for an ideal drug continues. Ideally, a new oral drug should produce a response in all diabetic patients without the development of secondary failure. The incidence of side effects and toxicity should be minimal.

To determine whether acetohexamide, a new sulfonylurea derivative, offered any advantage over other sulfonylurea drugs, it was tested over a period of one year in a group of diabetic patients composed mostly of failures with the other oral agents. The formula of acetohexamide is given in figure 1. Animal experiments have indicated that the drug lowers the blood sugar when administered orally and is nontoxic.[3] Preliminary clinical trials suggested a maximum dosage of 2.0 gm. daily.[3] Since the drug is excreted slowly, the entire dose may be given at one time.

METHODS

Twenty nonketotic, diabetic patients, ages thirty-six to eighty-two, from the Georgetown University Diabetic Clinic were selected for evaluation of acetohexamide. Twelve of these patients were failures on prior sulfonylurea therapy according to the criteria listed below, while two others did not respond to phenformin. Two patients with diabetes of four and five years' duration, respectively, had received only diet therapy, and the remaining four patients were newly-discovered diabetics. Eighteen of the twenty patients were females. Twelve were moderately overweight, two were markedly obese, and six were of normal weight or thin.

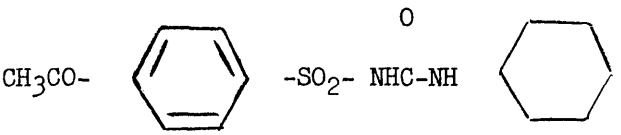

FIG. 1. Structural formula of acetohexamide.

Initially all the patients were seen weekly, but later at longer intervals depending on their response to the medication. Since a certain number of newly-diagnosed diabetics were included, all received placebo tablets for at least one month before treatment with acetohexamide was started. Only patients who had hyperglycemia during the placebo period were treated with acetohexamide. No attempt was made to modify the dietary habits of the patients, except newly-discovered diabetics were given standard American Diabetes Association diets aimed at obtaining their ideal weight.

Acetohexamide was started at a dosage of 250 mg. per day and gradually increased to a maximum of 2.0 gm. per day, if there was no satisfactory blood sugar response. If diabetic control was unsatisfactory while receiving 2.0 gm. per day, the drug was discontinued and the patient considered a primary failure. For the purpose of this report, a satisfactory response is considered to be an average fasting blood sugar of 150 mg. per 100 ml. or less (AutoAnalyzer, normal 65 to 110 mg. per 100 ml.). Although some patients demonstrated a decrease of 50 mg. per 100 ml. or more when taking acetohexamide as compared to placebo, such a fall was not considered satisfactory unless the average blood sugar was below 150 mg. per 100 ml. It is fully realized that this is an arbitrary classification but it appears to be less ambiguous than such terms as excellent, good, fair or poor. Many of these patients had been evaluated previously while on other oral

From the Department of Medicine, Georgetown University School of Medicine and the Diabetic Clinic, Georgetown University and Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

agents by criteria less strict than those listed above.[4]

A fasting blood sugar and a complete urinalysis were obtained at each visit. Hematocrit, total leucocyte and differential count, alkaline phosphatase and serum glutamic-pyruvate transaminase (SGPT) were determined at monthly intervals during both the periods of placebo and acetohexamide administration. Normal upper limits for the alkaline phosphatase and SGPT were considered to be 4.0 Bessie-Lowry units and 40 units respectively.[5] Although the normal value for alkaline phosphatase in this hospital was stated to be below 2.3 Bessie-Lowry units, this criterion was discarded since sixteen of the twenty patients had values above this while receiving placebo. There was no other evidence, either clinically or by laboratory tests, of underlying hepatic disease in these patients.

RESULTS

Table 1 summarizes the data obtained from the twenty patients in this study. Of the four newly discovered diabetic patients, three had average fasting blood sugars of 114, 118 and 138 mg. per 100 ml. (cases 1, 2 and 4) respectively when maintained on diet and placebo medication, and therefore were not given acetohexamide. To date one newly discovered diabetic (No. 3) has demonstrated a satisfactory response to acetohexamide. Her blood sugar averaged 200 mg. per 100 ml. while taking placebo and 149 mg. per 100 ml. while receiving acetohexamide (1.0 gm. per day) over a ten-month period.

Fifteen of the sixteen patients with established diabetes were treated with acetohexamide after at least one

TABLE 1

Summary of patients used in evaluation of acetohexamide

Patient	Age	Sex	Year onset	Ht. in.	Wt. lbs.	Weight change during study	Average blood sugar values (mg. per 100 ml.) while receiving: Placebo	Aceto-hexamide	Duration of acetohexamide administration & maximum dose	Response to previous oral therapy†: Tolbuta-mide	Chlorpro-pamide	Phen-formin
(1) E.N.	46	M	1961	72	170	−16	118(3)*	‡	—	—	—	—
(2) E. Boy	36	F	1961	65	154	+ 7	114(5)	§	—	—	—	—
(3) M.Co.	59	F	1960	61½	160	−11	200(7)	149(16)	40 wks.; 1.0 gm.	—	—	—
(4) A.A.	47	M	1960	72	162	+12	138(4)	§	—	—	—	—
(5) A.S.	48	F	1957	59	148	− 2	254(4)	189(8)	23 wks.; 2.0 gm.	—	—	—
(6) D.R.	74	F	1956	64½	145	−14	159(14)	‖	—	—	—	—
(7) L.S.	39	F	1958	64½	270	− 1	350(5)	277(9)	12 wks.; 2.0 gm.	—	—	prim. fail.
(8) J.M.	62	F	1950	61½	136	+18	240(3)	237(8)	17 wks.; 2.0 gm.	—	—	poor
(9) J.H.	49	F	1960	64½	228	−17	317(4)	272(11)	27 wks.; 2.0 gm.	prim. fail.	—	—
(10) P.S.	56	F	1958	65½	166	+18	196(10)	229(8)	26 wks.; 2.0 gm.	poor	poor	fair
(11) L.B.	56	F	1958	60	125	+ 2	181(8)	186(4)	10 wks.; 2.0 gm.	good,	fair	—
(12) R.L.	67	F	1957	63¼	146	−11	255(3)	180(15)	43 wks.; 1.25 gm.	good	good	nausea
(13) L.H.	82	F	1956	63	122	− 9	247(3)	163(7)	20 wks.; 2.0 gm.	good sec. fail.	poor	—
(14) R.H.	37	F	1954	65¾	177	+ 4	257(4)	241(12)	17 wks.; 2.0 gm.		fair, sec. fail.	poor
(15) L.Mc.	38	F	1954	63	178	+ 2	179(6)	185(7)	28 wks.; 2.0 gm.	—	good	—
(16) R.R.	56	F	1953	60¼	139	− 2	283(4)	189(13)	22 wks.; 1.0 gm.	fair	good	poor
(17) M.S.	48	F	1950	63¾	170	+ 3	294(2)	268(8)	16 wks.; 2.0 gm.	fair	poor	poor
(18) M.T.	68	F	1942	61	138	− 1	378(3)	269(11)	30 wks.; 2.0 gm.	fair	good, sec. fail.	fair
(19) E.J.	47	F	1948	61¾	143	+ 2	177(3)	183(17)	40 wks.; 2.0 gm.	fair sec. fail.	prim. fair	fair
(20) A.M.	61	F	1945	65¼	161	+ 9	309(4)	213(18)	28 wks.; 2.0 gm.	prim. fair,	prim. fair	fair

*( )Number of determinations.
†Criteria listed in reference 4 and which were less strict than those chosen for present study.
‡Discontinued clinic attendance before acetohexamide was administered.
§Acetohexamide not administered since blood sugar values satisfactory while receiving placebo.
‖Developed myocardial infarction while receiving placebo. Insulin treatment commenced in hospital.

month of placebo administration. One patient developed myocardial infarction while receiving placebo and was subsequently treated with insulin. Although seven of these had a significant fall (greater than 50 mg. per 100 ml.) in blood sugar, none achieved a level below 150 mg. per 100 ml. These, therefore, were not considered as having satisfactorily regulated diabetes. One of these patients (A.M.) was unable to maintain the early decrease in blood sugar and the average of the last three determinations (346 mg. per 100 ml.) was higher than that recorded on placebo despite the continuation of 2.0 gm. of acetohexamide daily. Eight patients manifested no change in blood sugar while receiving up to 2.0 gm. per day of acetohexamide for periods as long as forty weeks.

There was no apparent correlation between response to the drug and weight change during the period of observation. Although the only patient who achieved satisfactory blood sugar control with acetohexamide lost eleven pounds, there were four other patients with weight loss of ten pounds or more. One of these received placebo and diet and maintained an average blood sugar of 118 mg. per 100 ml. Another patient lost eleven pounds, and her average blood sugar fell from 255 mg. per 100 ml. (while on placebo) to 180 mg. per 100 ml. while receiving 1.25 gm. of acetohexamide daily. Despite a seventeen-pound decrease in weight, another patient had only a slight fall in blood sugar. Weight changes were inconstant in the other patients who demonstrated a significant decrease in blood sugar while receiving acetohexamide.

Responsiveness to previous oral drugs as evaluated by Moss, DeLawter and Canary[4] did not influence the results obtained with acetohexamide. The only patient who achieved satisfactory blood sugar values was a newly discovered diabetic. Seven other patients had a significant fall in blood sugar but still were not considered as satisfactorily controlled diabetics. One (A.S.) of these had had diabetes for four years but had never received oral drug therapy. Three others (R.L., R.R. and M.T.) demonstrated either good or fair responses to tolbutamide and chlorpropamide although one of them (M.T.) later was classified as a secondary failure while receiving chlorpropamide. One patient (L.S.), who had not received sulfonylurea drugs, had failed to respond when treated originally with phenformin. Another patient (A.M), who made an initial but unsustained response to acetohexamide, was considered a primary failure to both tolbutamide and chlorpropamide. Her response to phenformin had been fair. Initially one patient (L.H.) exhibited a good response to tolbutamide with subsequent secondary failure. Most of the patients who derived no benefit from acetohexamide had likewise either been primary or secondary failures to the other sulfonylurea compounds. Their response to phenformin had been variable.

During the study, one patient (R.L.) complained of symptoms suggestive of hypoglycemia several hours after the ingestion of 1.5 gm. acetohexamide daily. Blood sugar values below normal were never obtained, and her average blood sugar while receiving 1.25 gm. per day of the drug was 180 mg. per 100 ml. At this dose symptoms did not recur. Elevations of the blood alkaline phosphatase and SGPT levels, without jaundice or other evidence of hepatic dysfunction, were rather common findings during this study (table 2). If 2.3 Bessie-Lowry units had been accepted as the upper limit of normal, then most of the patients at one time or another would have had abnormal values, either while receiving placebo or acetohexamide. As described in the section on Methods, we have arbitrarily used a value above 4.0 Bessie-Lowry units as abnormal. By this criterion one patient (R.R.) had two or more abnormal determinations during administration of placebo. In this patient, the SGPT was also consistently elevated and the alkaline phosphatase tended to become more abnormal during acetohexamide therapy. The drug was discontinued despite a significant fall in the blood sugar and subsequently the alkaline phosphatase has returned toward normal (4.0 B-L. units). Three other patients had two or more abnormal alkaline phosphatase determinations while receiving acetohexamide. In these three patients, normal values were interspersed with the abnormal ones, despite the continuation of the acetohexamide, and the SGPT levels remained normal. All but one of these patients had

TABLE 2

Tabulation of abnormal liver function tests in patients receiving acetohexamide

	Results of tests while receiving			
	Placebo		Acetohexamide	
Patient	Alkaline phosphatase	SGPT	Alkaline phosphatase	SGPT
16. R.R.	6.9, 5.3	60	2.9, 7.8, 5.1, 7.9, 6.4, 8.3, 8.6	60, 60, 55, 60, 80
18. M.T.	Normal	Normal	3.7, 4.5, 4.8, 3.7, 3.4	Normal
19. E.J.	Normal	Normal	5.0, 3.8, 6.0, 4.2	Normal
20. A.M.	Normal	Normal	5.1, 3.3, 4.0, 3.4, 5.5	Normal

received prior sulfonylurea treatment without abnormalities in liver function tests. No evidence was obtained indicative of hematologic, renal or dermatologic toxicity during this study.

DISCUSSION

These preliminary results suggest that acetohexamide is no more effective than the sulfonylurea drugs now commercially available. Only one patient of the sixteen who received the drug maintained an average fasting blood sugar below 150 mg. per 100 ml. She was a new diabetic who also had an eleven-pound weight loss during the study so that it is possible that the drug was not the only factor in her response. In a group of fourteen patients who were inadequately controlled according to the present criteria while using other oral drugs, administration of acetohexamide did not result in a single patient's maintaining a fasting blood sugar below 150 mg. per 100 ml., although seven had a significant fall of at least 50 mg. per 100 ml. One of these seven patients was unable to maintain her response despite the continued administration of 2.0 gm. acetohexamide daily. All but one of the patients were given 2.0 gm. daily for at least one month before it was concluded that the drug was ineffective. This is the maximum dose recommended by the manufacturer.

Diabetics unresponsive to currently available oral drugs were specifically chosen for this study, but the results would indicate that in these patients acetohexamide offers no advantage. Although some patients did demonstrate a fall in blood sugar, these were usually patients who also had responded partially to other sulfonylurea compounds.

This study again points out the importance of using placebo medication in the evaluation of any new agent. Had acetohexamide been started initially in all of these cases, the satisfactory response obtained by diet and placebo in three other new diabetics might have been attributed to the drug.

The finding of abnormal levels of the blood alkaline phosphatase suggests a possible deleterious effect on the liver. Diabetes per se is not usually associated with abnormal liver function unless the metabolic defect is poorly controlled.[6] All of these patients demonstrated hyperglycemia but none of them had acetonuria, and they were usually free of diabetic symptoms. Many had received previous sulfonylurea treatment, and a recent study has indicated a high incidence of focal granulomatous lesions in the livers of such patients.[7] Three of the patients given acetohexamide developed abnormalities of the alkaline phosphatase without other evidence of liver disease. It is difficult to be certain that these findings were attributable to the drug, since values below 4.0 were intermingled with values above 4.0 while acetohexamide was being given. Nonetheless, if this drug is to be used in the treatment of diabetes, its possible hepatotoxicity must be kept in mind.

SUMMARY

Sixteen nonketotic diabetics have been treated with acetohexamide, a sulfonylurea compound, following a placebo period. Only one newly-discovered diabetic demonstrated a satisfactory response. None of fourteen patients, inadequately controlled with other oral agents, had satisfactory diabetic control with acetohexamide. However, seven did show a fall in blood sugar of at least 50 mg. per 100 ml. Elevations in alkaline phosphatase were present in four patients while receiving the drug. In one patient, abnormal values obtained during the placebo period were accentuated while acetohexamide was being administered. In view of the lack of effectiveness of acetohexamide in patients unresponsive to presently available oral agents and its potential hepatic toxicity, it is concluded that acetohexamide offers little advantage in the treatment of this type of diabetic.

SUMMARIO IN INTERLINGUA

Evalutation Clinic de Acetohexamido, un Nove Agente Sulfonylurean

Dece-sex diabeticos non-cetotic esseva tractate con le composito sulfonylurean, acetohexamido, post un curso initial de placebo. Solmente un del patientes, con recentemente discoperite diabete, manifestava un satisfacente responsa. Nulle de dece-quatro patientes, in qui (secundo nostre criterios) le uso de altere agentes oral non habeva producite un satisfacente stabilisation del diabete, obteneva un tal stabilisation con acetohexamido, ben que septe monstrava un declino del sucro de sanguine de al minus 50 mg per 100 ml. Elevationes in le phosphatase alcalin esseva presente in quatro del patientes durante que illes recipeva le pharmaco. In un patiente, le anormalitate del valores obtenite durante le periodo a placebo esseva accentuate durante le curso de acetohexamido. Viste le facto que le pharmaco es inefficace in patientes qui non responde al currentemente disponibile agentes oral e in vista de su potential de toxicitate hepatic, il es concludite que acetohexamido offere pauc avantage in le tractamento de iste typo de diabetico.

ADDENDUM

After submission of this manuscript, our attention was called to the report of Camerini-Davalos, R., Lozano-Castaneda, O., and Marble, A., "Five Years' Experience with Tolbutamide," DIABETES, Vol. 11, Supplement, 74-80, 1962. These authors report that there was a statistically significant elevation of the alkaline phosphatase levels but not of BSP excretion values in a group of patients who had been on long-term tolbutamide therapy. This observation would suggest that the elevations of alkaline phosphatase observed in our patients receiving acetohexamide might be more related to sulfonylurea drugs in general and not unique for acetohexamide. In all four of our patients the alkaline phosphatase values returned to normal after acetohexamide therapy was discontinued.

ACKNOWLEDGMENT

The authors are indebted to Drs. James M. Moss and DeWitt DeLawter for their helpful comments and suggestions during the course of this study.

This work was supported in part by Contract S.A. 433-ph-3044 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and a grant from Eli Lilly and Company.

REFERENCES

[1]Marble, A.: Critique of the therapeutic usefulness of the oral agents in diabetes. Amer. J. Med. *31*:919, 1961.

[2]DeLawter, D. E., Moss, J. M., Tyroler, S., and Canary, J. J.: Secondary failure of response to tolbutamide treatment. JAMA *171*:92-1786, 1961.

[3]Kirtley, W. R.: Personal communication.

[4]Moss, J. M., DeLawter, D. E., and Canary, J. J.: The results of the treatment with tolbutamide of 200 diabetic patients. A discussion of secondary failure. Ann. Intern. Med. 50:1407, 1959.

[5]Futterweit, W.: Serum alkaline phosphatase activity in infectious mononucleosis. Arch. Intern. Med. *108*:253, 1961.

[6]Cohen, N. N., Potter, H. P., Jr., and Bowers, G. N., Jr.: An evaluation of isocitrate dehydrogenase in liver disease. Ann. Intern. Med. *55*:604, 1961.

[7]Bloodworth, J. M. B., Jr. and Hamwi, G.: Histopathologic lesions associated with sulfonylurea administration. Diabetes *10*:90, 1961.

Body Composition of Infants Born to Diabetic Mothers

An appreciable percentage of newborn infants born to diabetic mothers show rather striking abnormalities. As a group, these infants are more frequently affected by congenital anomalies, and have a distinctly higher death rate than normal. They also present a rather characteristic physical appearance. They are large, overweight, plethoric, frequently have hepatosplenomegaly and cardiomegaly, and often suffer from respiratory distress. Hypoglycemia is more commonly encountered than in the normal newborn. This situation has been reviewed in detail by H. C. Miller (Advances in Pediatrics *8*:137, 1956). Of even greater theoretical interest is the fact that these characteristic abnormalities are sometimes seen in infants born to prediabetic mothers, that is, women who do not have diabetes mellitus at the time of delivery, but who are destined to develop the disease in subsequent years.

The clinical picture manifested by these infants is sufficiently characteristic to permit the diagnosis to be made at a glance by the experienced clinician. One question often raised is: Do these infants differ from normal in terms of body composition, and if so, how do they differ? For example, is the large size of these infants due to edema of the tissues, or are they merely fat?

An attempt to answer this question has been made recently. M. Osler and J. Pedersen (Pediatrics *26*:985, 1960) have applied some of the newer technics for estimation of body composition to a series of such infants, and have compared the data derived to those obtained with normal babies.

Three groups of newborn infants were studied. Two groups consisted of 122 infants born to diabetic mothers and an equal number (control infants) born at the same gestational age (thirty-six to thirty-eight weeks) to normal mothers. In addition, a number of normal full-term infants and normal prematurely born infants were also studied. Certain specialized determinations were made in some of the infants in each group.

Infants born to diabetic mothers were, on the average, 550 gm. heavier and 1.5 cm. longer than the control infants. An attempt to assess skeletal maturity was also carried out. The maximum diameters of the ossification centers of the inferior femoral epiphysis and superior tibial epiphysis were measured on roentgeno-

(*Continued on page 261*)