Clinical and Pharmacological Effects of Substance BZ-55 in Diabetes

(p-Aminophenylsulfonyl Butylcarbamide)

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Two orally administered preparations having hypoglycemic action in the diabetic patient have been under study by a number of investigators in this country for the past year. The compound utilized in these studies has the chemical structure shown in figure 1 and has been given the generic name of carbutamide.

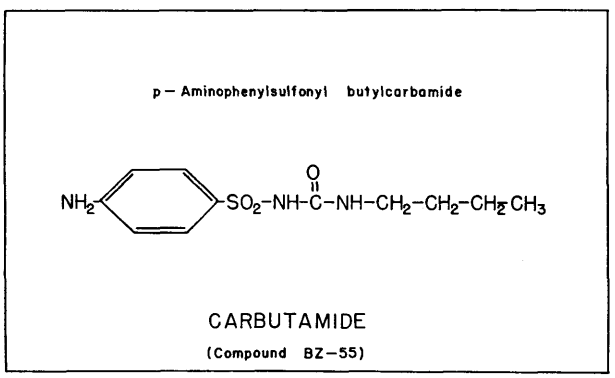

FIGURE 1

The hypoglycemic effect of sulfonamide derivatives is actually not a new observation since this action was first reported by Janbon[1] in 1942. He noted hypoglycemia while studying the antibacterial action of sulfonilamido isopropylthiodiazole. In 1944 Loubatieres[2] found that this same compound was without action in the depancreatized dog and postulated that hypoglycemia in the normal animal was probably the result of a stimulation of insulin secretion.

In 1946, Chen et al.,[3] showed that the cyclopropyl derivative lowered blood sugar profoundly in normal rabbits following 1- to 2-gm. doses orally, but in the alloxan diabetic rabbit a marked increase in blood sugar occurred. It was felt that these results were in agreement with Loubatieres' and perhaps indicated stimulation of insulin secretion.

In 1955 Achelis and Hardebeck,[4] Franke and Fuchs,[5] and Bertram, Bendfelt and Otto,[6] published experimental results with p-aminophenylsulfonyl butylcarbamide, designated compound BZ-55. They showed that the blood sugar could be lowered in normal animals and in certain diabetic patients. Franke and Fuchs[5] suggested on the basis of animal experimentation that the action of the drug might be due to an effect on the alpha cells of the pancreas with a resultant inhibition of glucagon production. Ferner[7] did not find that degranulation of alpha cells could be demonstrated in one patient given BZ-55.

The compound has been under study in this country since July 1955 and this report includes the results of acute and chronic toxicity in animals, of some of the effects of carbutamide in normal and diabetic animals, and a brief summarization of the effects in the treatment of diabetic patients.

ACUTE TOXICITY

The acute toxicity in normal animals is low. The LD_{50} of intravenously administered drug in mice is 1.9 gm./kg. Orally, the LD_{50} is 3.5 gm./kg.

Although some hypoglycemia occurred during the toxicity studies, death was not due to low blood sugar. Blood glucose levels were 104 to 122 mg. per cent just before death in rats; furthermore, the administration of

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glucose intraperitoneally 5 to 10 minutes before the intravenous dose of carbutamide did not alter the LD_{50} or change the toxic reaction.

Hypoglycemia can be produced in rabbits following single doses of 50, 100, and 150 mg./kg. intravenously, and with each increase in dosage, a fall in blood sugar of greater degree and duration is produced.

Carbutamide administered orally to rabbits varied greatly from one animal to another in its hypoglycemic effects. A single 500 mg./kg. dose may produce only a moderate fall in blood sugar in one animal, yet cause convulsions and prostration in another and require either glucagon or glucose to reverse the severe hypoglycemia.

In normal dogs doses up to 700 mg./kg. orally produce only a slight decrease in blood sugar. Seven hundred to 1,000 mg./kg. as a single oral dose caused vomiting and muscular weakness and twitching. Hypoglycemia did not develop and glucose did not relieve the symptoms.

CHRONIC TOXICITY

At the end of five months, rats fed diets containing 0.25 per cent and 0.5 per cent carbutamide have all survived and have shown normal weight gain.

Deaths occurred in two out of ten rats fed 1.0 per cent in the diet after 33 and 121 days respectively. Blood carbutamide levels ranged between 30 and 60 mg. per cent. On a diet containing 2 per cent of drug, all animals were dead by 205 days. The first of this group died after

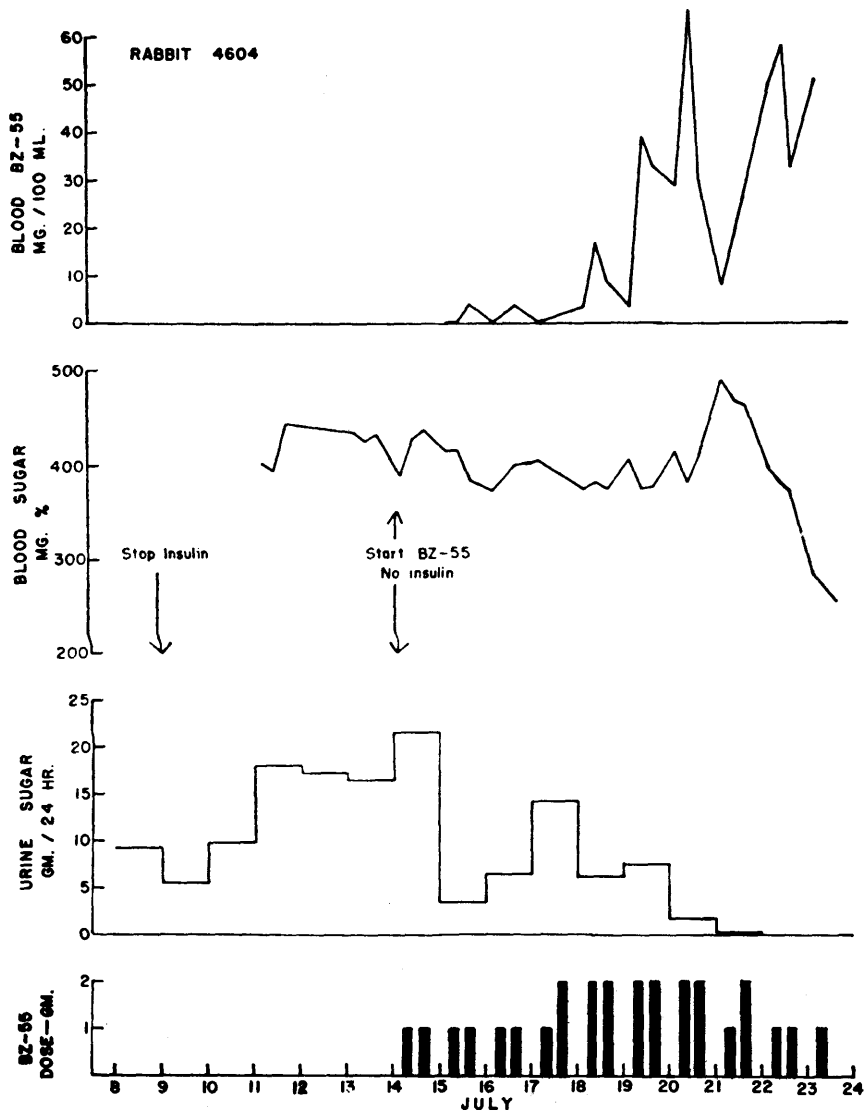

FIG. 2. Alloxan diabetic rabbit treated with carbutamide (BZ-55). The drug was administered by stomach tube twice daily in doses indicated by vertical bars. Progressive diminution of food consumption during treatment period contributed to the fall in blood sugar and glycosuria.

29 days. Blood carbutamide levels were more than 70 mg. per cent.

Postmortem examinations of the twelve rats that died while on the drug revealed various lesions. Malnutrition was present in all animals. Crystalluria was found in four, and central necrosis of the liver was observed in only one. Hypertrophy of the thyroid of a slight degree was observed in half the animals which had received the 2 per cent diet.

In monkeys, daily doses of 250 mg./kg. by stomach tube were tolerated well and all animals maintained or gained weight. Blood carbutamide levels reached a peak of 45 to 65 mg. per cent two hours after each dose and fell to a trough value of 4 to 12 mg. per cent.

A fall in blood sugar was noted following each dose although the pattern was inconsistent from day to day.

Urinary excretion of the drug shows a species variation. Rabbits excrete the acetylated form to the greatest degree. Dogs excrete the free form for the most part and in man the excretion is intermediate, approximately 66 per cent of the free form and 33 per cent as the combined form.

EFFECTS ON DIABETIC ANIMALS

To study the response in experimentally induced diabetes, alloxan diabetic rats, rabbits and dogs, and depancreatized dogs were treated with carbutamide. Alloxan treated rats showed no improvement in the diabetic state when carbutamide was administered daily in doses up to 1 gm./kg. orally.

In an alloxan diabetic rabbit (figure 2) there was no decrease in blood sugar until the last few days, at which time the animal had stopped eating and was in poor physical condition. Urinary sugar excretion decreased slightly with decrease in food intake and fell off to zero when the animal stopped eating entirely.

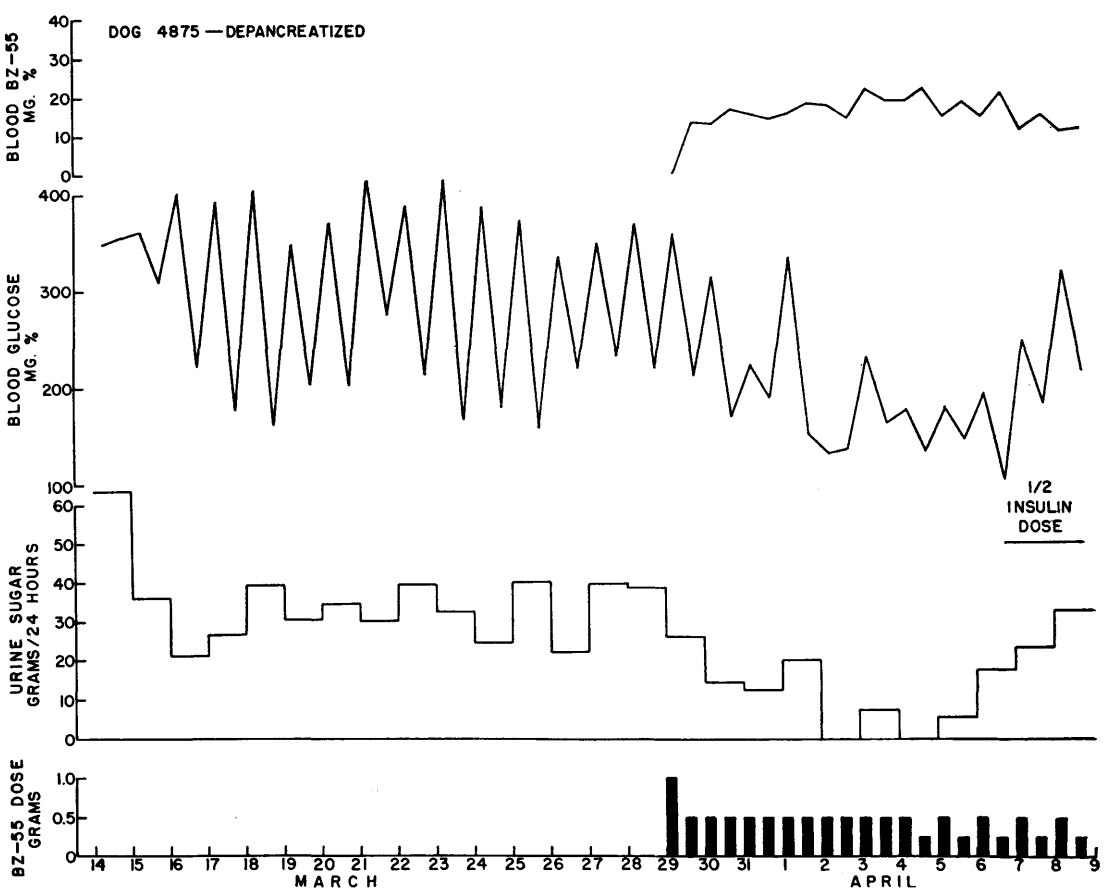

FIG. 3. Totally depancreatized dog poorly controlled on a constant dose of NPH insulin and a constant diet. Carbutamide was administered orally as indicated. With no change in insulin or diet there was a fall in blood sugar and glycosuria. During the last two days of the experiment the insulin dose was decreased by one-half with a return of glycosuria.

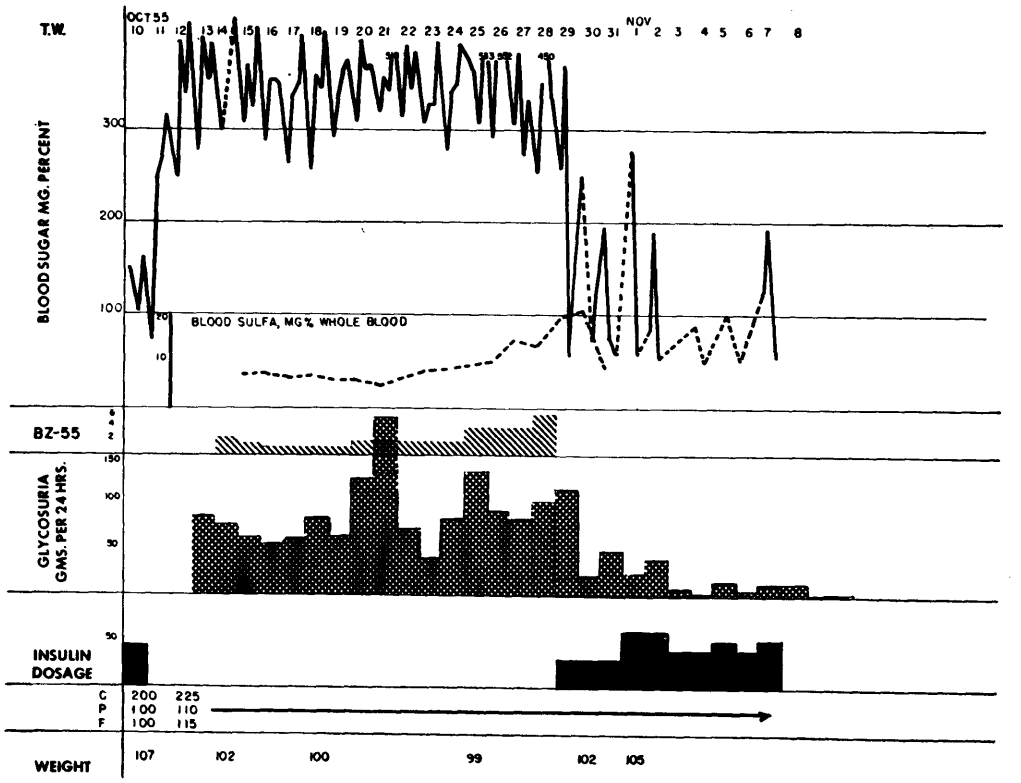

FIG. 4. Asthenic male patient age thirty - eight. There was a complete lack of response to carbutamide. Rapid improvement followed reinstitution of insulin therapy.

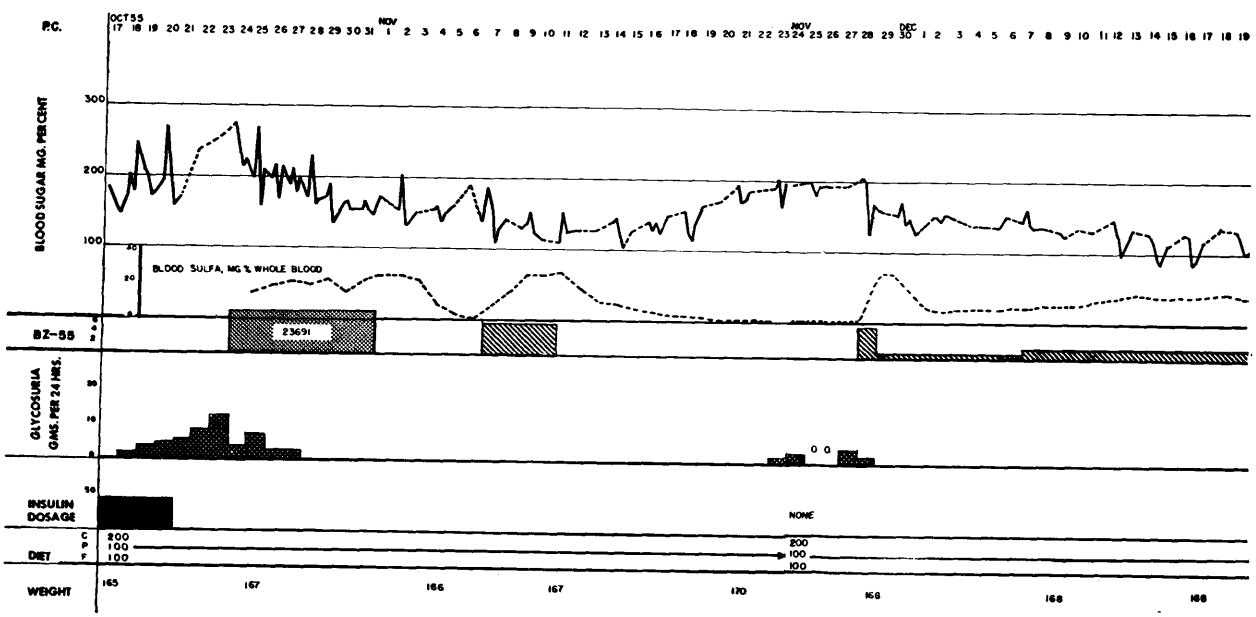

FIG. 5. Obese female patient age fifty-nine previously well controlled on 40 units of insulin daily. A gradual lowering of blood sugar is demonstrated following the use of sulfonamide derivatives. She continues to be well controlled on 2 gm. daily and no insulin.

A totally depancreatized dog, maintained on unmodified insulin, showed a drop in blood sugar when carbutamide was given orally, eighteen hours after the last dose of insulin. This same animal showed no response when carbutamide was given sixty-six hours after the last insulin dose. Apparently some unmodified insulin still remained in the animal's tissues after eighteen hours.

It seems clear that insulin or functioning islet tissue must be present if a hypoglycemic response to carbutamide is to be expected.

Data which indicate that there may be an effect on insulin activity are demonstrated in the following experiment (figure 3).

A totally depancreatized dog on a constant, weighed diet and receiving suboptimal doses of insulin, showed a reduction in daily excretion of glucose when carbutamide was added to the regimen. Indications are that approximately one-half the dose of insulin was replaced in this particular animal.

CLINICAL STUDIES

Up to the present time, fifty patients have been treated with carbutamide at the Lilly Laboratory for Clinical Research and the Indianapolis General Hospital Outpatient Diabetic Clinic. Twenty-two of this group were started directly in the outpatient clinic and were not hospitalized for stabilization.

Following earlier questionable results in patients with long standing, severe diabetes, a better selection of the group to be treated was accomplished and success in lowering blood sugar and reducing glycosuria was obtained in the majority of patients.[8]

Generally, this latter group of patients have had diabetes of the maturity-onset type, which is relatively mild, and have either required no insulin in treatment or have taken a small daily dose.

Exceptions to this general classification have been found, which is doubtless the experience of all who have tested the drug.

Initially, six grams per day of carbutamide was used, a dose far higher than necessary. Later the dose was lowered to that recommended by the German investigators, namely, 2.5 gm. the first day, 1.5 gm. the second and 1 to 2 gm. daily thereafter. If a patient does not respond to this dosage, it is unlikely that a higher dose will be effective. Blood carbutamide levels have ranged from 4 to 17 mg. per cent and there does not seem to be good correlation between blood level and clinical response. Many patients showing good blood sugar lowering effects have had consistently low blood carbutamide levels.

Certain patients respond poorly or not at all to carbutamide. Figure 4 demonstrates graphically an example of a total failure. This patient, a thirty-eight-year-old, asthenic male who had been in acidosis and coma several times showed immediate deterioration of his diabetic status as soon as insulin was stopped and carbutamide started. He responded promptly when insulin therapy was reinstituted.

Patients who respond may follow one of two patterns of hypoglycemic effect. First there may be a quite rapid lowering of blood sugar to normal levels, most commonly seen in newly discovered diabetics or in patients who have never received insulin. The second pattern is a slower lowering of blood sugar over a period of days as demonstrated in figure 5. This patient first received the propyl analogue of carbutamide but later received carbutamide itself. Since her release from the hospital she has continued to do well on the drug as an outpatient.

This next example is that of a patient in whom a good hypoglycemic response was obtained but in whom toxic effects were observed (figure 6). Thirty-one days after the initiation of therapy the patient complained of a rash and was found to have a depressed white cell count. It was felt that perhaps high dosage may have contributed to the development of the sensitivity since she had received six grams of the drug daily on two different occasions and had shown a maximum blood carbutamide level of 35 mg. per cent. Symptoms disappeared rapidly when the drug was stopped. It is imperative that all patients have regular periodic white blood counts and if any evidence of agranulocytosis or other abnormality of the blood develops, the drug should be stopped immediately. Patients started on carbutamide in the outpatient clinic have had weekly white blood counts until they are stabilized on dosage. Later they are seen at monthly intervals and repeat counts are routine. Undesirable side reactions do exist and they must be guarded against.

Two points of chief interest are now receiving maximum attention. Firstly, how hypoglycemia is achieved and whether the diabetic is actually benefited by this action, and secondly, whether deleterious effects result from long-term administration of the compounds.

Since alpha cells and glucagon had been implicated, a group of six mild diabetic patients who showed a blood sugar response to carbutamide were given glucagon tolerance tests before and after receiving carbutamide. These same patients also were given glucose and insulin tolerance tests before and after carbutamide. These results are shown graphically (figure 7).

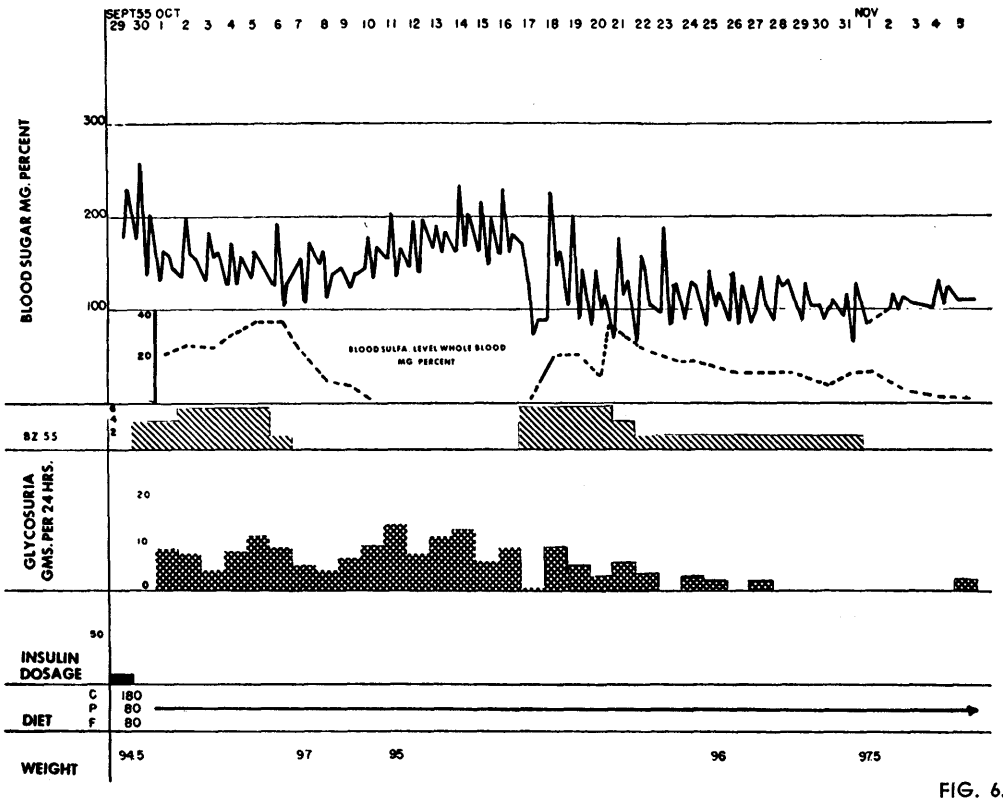

FIG. 6. (Above) Asthenic female patient age fifty-four with mild diabetes requiring 10 units of insulin daily. She showed stabilization on 2 gm. of carbutamide daily after two previous poor responses to 6 gm. daily. Patient was found to have a rash and leukopenia at the thirty-first day of regimen, and the drug was stopped.

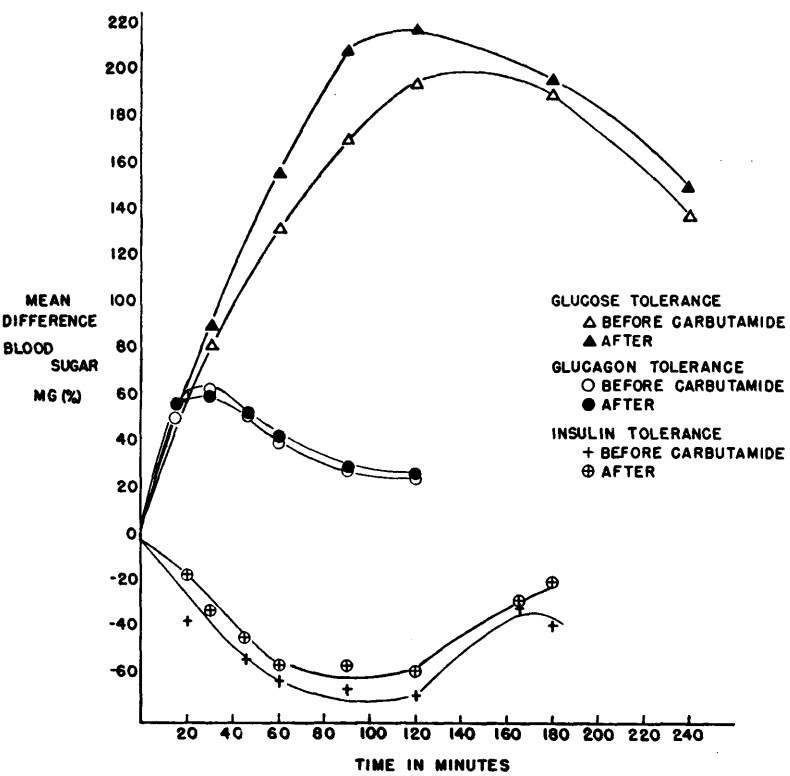

FIG. 7. Glucose, glucagon, and insulin tolerance tests in six mild diabetic patients who showed hypoglycemic response to carbutamide. No significant differences in the curves before and after carbutamide therapy were demonstrated.

These data have been subjected to statistical analysis and it is concluded that by the methods utilized, no significant differences could be found attributable to the carbutamide.

Because of evidence in animals indicating possible undesirable effects on thyroid, renal, and liver function, groups of patients taking a therapeutic dose of carbutamide have been investigated to determine if significant effects are present in patients as well.

Thyroid function as measured by I^{131} uptake, protein bound iodine determinations and basal metabolic rate, has remained normal in ten cases. Forty of the group have had serum transaminase studies as a liver function test while on the drug and there was no evidence of liver damage. All other tests of liver and renal function have remained within normal limits. Not a single example of crystalluria has occurred. White blood counts have remained unchanged in all but one patient who showed a transient leukopenia.

SUMMARY

Carbutamide and related compounds will lower blood sugar in normal animals and in normal and diabetic patients. In addition, glycosuria is diminished in diabetic subjects.

Experimentally, it has been shown that endogenous (or exogenous) insulin must be present for a blood sugar lowering effect to occur. Clinically, the best response to carbutamide can be anticipated in the obese patient with mild diabetes of short duration. Juvenile patients with diabetes of several years standing and severe, easily decompensated patients respond poorly or not at all.

Although toxicity in normal animals is low, there is suggestive experimental evidence that thyroid, renal, and liver function may be altered. Clinically, such effects have not been demonstrated in this study.

Sensitivity reactions such as skin rash and leukopenia, although infrequent, occur relatively early in the course of therapy. In our opinion, these reactions are definite indications for stopping the drug. Nothing as yet is known of the effects of long-range chronic administration of this compound.

So far, no single theory of mechanism of action is completely satisfactory in explaining all reported effects of these substances on carbohydrate metabolism.

SUMMARIO IN INTERLINGUA

Effectos Clinic e Pharmacologic de p-Aminophenylsulfonyl-Butylcarbamido (Substantia BZ-55) in Diabete

Carbutamido e compositos affin reduce le nivello del sucro sanguinee in animales normal e in patientes normal e diabetic. In plus, illos reduce glycosuria in subjectos diabetic.

Il ha essite demonstrate experimentalmente que le occurrentia de un reduction del sucro sanguinee require le presentia de insulina endogene (o exogene). Le melior responsa clinic a carbutamido es a expectar in patientes obese con leve diabete de breve duration. Patientes con diabete juvenil de plure annos de duration e patientes con sever grados de diabete que es facilemente discompensate responde pauco ben o non del toto.

Ben que le toxicitate in animales normal es basse, il ha datos experimental que suggere que le functiones thyroide, renal, e hepatic es possibilemente alterate. In le presente studio tal effectos ha non essite demonstrate clinicamente. Reactiones de sensibilitate—per exemplo eczema cutanee e leucopenia—esseva infrequente e occurreva relativemente tosto in le curso del therapia. In nostre opinion, tal reactiones es definitivemente indicationes pro le discontinuation del administration del droga. Nulle informationes es disponibile a iste tempore in re le effectos de chronic administrationes a longe durantia.

Usque nunc nulle theoria individual del mechanismo del action del droga es completemente satisfactori, i.e., nulle theoria individual pote explicar omne le reportate effectos de iste substantias super le metabolismo del hydratos de carbon.

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