Brief Notes and Comments

Severe Prolonged Hypoglycemia Following Tolbutamide and Carbutamide Treatment

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SUMMARY

Two elderly, nondiabetic patients with uremia, one of whom had received on the preceding day one gram of carbutamide per os and the other one gram of tolbutamide intravenously, had severe, prolonged hypoglycemic reactions. The reaction lasted for six days in the former patient and was so severe that daily administration of glucose was necessary. The patient died from uremia thirteen days after taking the drug. The other patient was markedly hypoglycemic until his death three and one-half days later. A fairly large benign adrenocortical adenoma was found at autopsy in each patient.

The same agents were also administered once to four severely uremic patients, but no significant depression of the blood sugar level was elicited. The cause of the prolonged hypoglycemia in some subjects remains undetermined. DIABETES *14*:606-08, September 1965.

Several unusually severe hypoglycemic reactions caused by oral hypoglycemic agents have been reported recently. These reactions have been characterized not only by the severity of the hypoglycemia but also by its duration greatly exceeding what is generally regarded as the expected duration of action of these drugs. Most of the earlier cases were attributed to chlorpropamide.[2,8,9] Later reports, however, have been concerned with reactions caused by tolbutamide: a total of eight cases in six reports.[1,6,7,10,11,13] No reactions of this type have been reported with carbutamide. However, this might well be because it is not used in America on account of its side effects, and almost all the reports cited above are from the United States.

The present paper describes two cases. One patient developed severe hypoglycemia lasting several days after the administration of peroral carbutamide. The other instance followed intravenous tolbutamide.

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CASE HISTORIES

Case No. 1. The patient was a white male farmer of seventy-five, who had a few months' history of fatigue and poor appetite. He had lost about 5 kg. in weight. On Oct. 7, 1963, he consulted his physician who incorrectly diagnosed diabetes and prescribed carbutamide tablets, one 0.5 gm. tablet twice daily (Alentin, R. Orion Oy, Helsinki). The patient took the agent as prescribed for one day, October 9, but then stopped because he felt it had a bad effect on him. On the following day, October 10, the patient had an attack of syncope and was again taken to his physician. He interpreted the condition correctly as hypoglycemic coma and gave him 20 cc. of 50 per cent glucose intravenously, whereupon the patient recovered immediately. The patient was then immediately hospitalized. On admittance about one hour later, he had again lost consciousness. His blood sugar was 25 mg. per 100 ml. He recovered briefly after another immediate intravenous glucose injection. During the same evening and ensuing night the patient received a total of 110 gm. of intravenous glucose in 5 and 30 per cent solutions. In spite of this, his blood sugar was only 22 mg. per 100 ml. on the following morning, October 11, and intravenous glucose infusion was continued. He received 100 gm. of glucose intravenously in the next twenty-four hours. It was difficult to feed him as he immediately became confused each time the infusion was discontinued. On October 12, his morning blood sugar was 53 mg. per 100 ml. Two-hundred and fifty grams of intravenous glucose was given during twenty-four hours and the patient began gradually to eat. Corticosteroid therapy was also instituted: 30 mg. of prednisolone per day. On October 13, blood sugar in the morning was 83 mg. per 100 ml. and 450 gm. of glucose was administered intravenously. On October 14, the morning blood sugar was for the first time over 100 mg. per 100 ml. viz. 150 mg. The patient received 200 gm. of glucose intravenously. On the days following he retained consciousness without intravenous infusions and his fasting blood sugar remained over 100 mg. per 100 ml.

The diagnosis first entertained was insuloma. Roentgenograms of the abdomen, thorax and skull revealed nothing indicative of tumor. Moreover, as the patient began, after a few days, to manage with peroral nutrition alone, the diagnosis of insuloma and the planned laparotomy were abandoned. On the other hand, the patient was found to have a creatinine

value of 10.7 mg. per 100 ml., his prostate was of considerable size, and there was retention, over one liter, in the urinary bladder.

On October 20, the patient again lost consciousness. His blood sugar was normal and intravenous glucose failed to resuscitate him. He died on October 22 in obvious uremic coma.

Autopsy (Dr. Aimo Helminen) on October 24 revealed in addition to the hypertrophy of the prostate and pyelonephritis a yellow cortical adenoma of 20 x 30 mm. enclosed by the cortex in the left adrenal gland. There was some fibrosis in the pancreas, the islets of Langerhans were fairly regular in appearance, the tissue was well preserved. The adrenal adenoma was limited to the cortex without signs of an invasive tendency. The size of the cells and the nuclei were relatively uniform.

Case No. 2. The patient was a white male pensioner, aged sixty-seven, who had felt tired throughout the autumn, lost 10 kg. in two months and suffered thirst for the same period. He was admitted to hospital on Sept. 30, 1963. Uremia was diagnosed, creatinine was 6.0 mg. per 100 ml., hemoglobin 8.3 gm. per 100 ml., reticulocytes 4.9 per cent. ESR was 133 mm. per hour. The patient's prostate was hypertrophic and there was retained urine in the bladder. Blood sugar was 86 mg. per 100 ml. Despite the manifest renal disease, and as the patient's history displayed features that accorded well with diabetes, an intravenous tolbutamide test was performed; he was given 1.0 gm. of tolbutamide (Rastinon, R. Farbwerke Hoechst AG, Basel) intravenously on October 16 at 0800 hours. It lowered the blood sugar level in thirty minutes from 111 to 59 mg. per 100 ml. The patient went into coma on the following day around 1500 hours and was given intravenously 5 ml. of theophyllamine and 20 ml. of 50 per cent glucose. He regained consciousness during the injection, again went into a coma the same evening and regained consciousness after receiving the same doses of the same drugs. He was conscious until the morning of October 18 when his blood sugar was 31 mg. per 100 ml. He was given 250 gm. of glucose intravenously during the following twenty-four hours, but in the morning of October 19, his blood sugar was again only 30 mg. per 100 ml.; in the afternoon, however, it had risen to 57 mg. per 100 ml. Creatinine was 12.9 mg. per 100 ml. on the same day. The patient died in the evening of October 19, conscious until the last but having been anuric almost throughout his last day of life.

Autopsy (Dr. Aimo Helminen) on October 24 revealed in addition to the hypertrophic prostate and pyelonephritic nephrosclerosis a yellowish adenoma of 10 x 5 mm. enclosed by the cortex in the left adrenal gland. The adrenal glands were of normal size. Histologic examination showed a fresh infarct in the right kidney and also numerous nephrosclerotic changes. The adrenal adenoma was cortical and its growth distinctly benign. The pancreas was completely autolyzed and consequently impossible to study more closely.

DISCUSSION

Because both patients had severe renal failure while receiving the sulfonylurea drugs, control tests were carried out in which four other nondiabetic uremic patients (with creatinine values respectively of 4.5, 5.7, 11.1 and 17.0 mg. per 100 ml.) were given these drugs. One received 1 gm. of tolbutamide, another 1 gm. of chlorpropamide per os and two 1.0 gm. of tolbutamide intravenously. The blood sugar was followed at 0800 and 1500 hours on the pre-administration day, on the day of administration (at 0800 hour) and on the following day at 0755, 0830, 1100, 1500, and 1900 hours and at 0800 hours in the next two days. A drop in the blood sugar either in excess of normal or longer than normal was established in none of these patients.

Although the hypoglycemic patients received different drugs, one per os and the other intravenously, their response to the treatment was rather similar: Hypoglycemia reached such dimensions circa twenty-four hours after the administration of the drug that the patient went into a hypoglycemic coma which persisted severely for several days. The patients received a single dose or dosage limited to one day, so there could not be any kind of a cumulative phenomenon in question. It is possible that in one of the cases hypoglycemia had a direct role in a patient's death three and one-half days after the administration of the drug (cf. 12).

Common to both reported patients was that they were fairly old, nondiabetic men with severe renal failure. The majority of the tolbutamide reactions previously reported concerned patients over age seventy, three out of eight nondiabetic and another three out of eight with impaired renal function. However, it is questionable whether such a small series warrants conclusions as to the role of these factors in the causation of the reaction (cf. 3,5). It should be noted specifically that the advanced age of the patients may be due to the fact that it is generally the older diabetics who are treated with peroral drugs and that most of the nondiabetic patients had a history of Parkinson's disease which is also a disease of the aged.

The autopsy finding was rather interesting. Both patients had a fairly large adrenocortical adenoma which is a fairly uncommon finding in autopsy; e.g., an adenoma of over 3 mm. diameter in only 2.86 per cent of a total of 7,437 autopsies.[4] None of the patients with hypoglycemic reactions reported earlier in the literature was studied at autopsy.

A practical conclusion to be drawn from these cases may perhaps be the need always to take into account hypoglycemia when looking for the cause of comatose episodes in patients given peroral diabetes drugs. The present cases also suggest that the performance of the intravenous tolbutamide test, hitherto regarded as completely harmless, on patients other than those under observation in hospital might be risky.

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ABSTRACTS

Alp, Haluk; and Recant, Lillian (Nutrition Research Lab. of the Dept. of Preventive Med. and the Dept. of Medicine, Washington Univ. Sch. of Med., St. Louis, Mo.): STUDIES OF THE INSULIN-INHIBITORY EFFECT OF HUMAN ALBUMIN FRACTIONS. J. Clin. Invest. *44*:870-83, May 1965.

The authors report findings that confirm the basic observations of Vallance-Owen that there is an inhibitor of insulin associated with the plasma albumin fraction. Fractions of human plasma albumin were prepared by both the Debro procedure and the method 6 of Conn. Both of these preparations demonstrated significant insulin-inhibitory activity when tested in vitro with rat diaphragm muscle. Albumin preparations were made from normal subjects, diabetic patients, and pregnant nondiabetic women in the third trimester of pregnancy. Albumin prepared from normal subjects and used in a concentration of 3 to 3.5 per cent demonstrated significant inhibition of insulin action. In concentrations of 2 per cent or less no significant degree of insulin inhibition was observed. Albumin preparations from diabetic patients were used in a concentration of 1.25 per cent to 2.5 per cent. Throughout this range of concentration there was highly significant inhibition of insulin action. Albumin prepared from pregnant nondiabetic women and used in a concentration of 2.5 per cent or less also demonstrated significant insulin inhibition. The mechanism of insulin inhibition appeared to be competitive. At higher concentrations of insulin, the inhibitory effect of the same concentration of albumin was decreased. The competition of inhibitor with insulin did not appear to be manifested by an impairment of binding of insulin to the diaphragm. Studies were done that demonstrate that the inhibition is not quantitatively related to free fatty acid content of the albumin. The authors point out that it is not possible to say whether the inhibitor is albumin itself or some molecule associated with the albumin. J.D.B.

Antoniades, Harry N.; Huber, Agnes M.; Boshell, Buris R.; Saravis, Calvin A.; and Gershoff, Stanley N. (Protein Foundation Labs., Jamaica Plain, Mass.; Dept. of Med., Harvard Med. Sch., Dept. of Nutrition, Sch. of Public Health, Harvard Univ. Boston, Mass.; the Dept. of Med., Univ. of Alabama Med. Center, Birmingham, Ala.): STUDIES ON THE STATE OF INSULIN IN BLOOD: PROPERTIES OF CIRCULATING "FREE" AND "BOUND" INSULIN. Endocrinology 76:709-21, April 1965.

The immunologic reactivity of "free" and "bound" insulins with guinea pig anti-insulin antisera, their electrophoretic mobilities on Pevikon block and their chromatographic behavior on Sephadex were examined. Bound insulin was obtained from pooled sera on Dowex resin columns; acid ethanol extracts of this insulin were prepared. The "free" insulin was found to correspond to Crystalline Insulin in its physicochemical, immunologic and biological properties. The "bound" form of insulin exhibited a higher molecular weight, slower electrophoretic mobility and was unreactive to insulin antisera. The acid ethanol extraction procedure increased the reactivity of "bound" insulin with insulin antisera as demonstrated by the inhibition of the biological activity of the extracts of "bound" insulin on epididymal adipose tissue by antisera. Identification of the chemical nature of "bound" insulin remains to be elucidated. C.R.S.

Aronson, Stanley M.; and Aronson, Betty E. (Dept. of Path., State University of New York, Downstate Med. Center; and the Inst. of Path., Kings County Hosp. Center, Brooklyn, N.Y.): Arch. Neurol. *12*:390-98, April 1965.

From the autopsy records of 9,223 cases studied at Kings County Hospital Center from 1953 to 1963, the incidences of certain types of brain tumors found in diabetic patients were compared with those found in the nondiabetic population. There was a notable decrease in the frequency of gliomas and metastatic cancers in the 1,011 cases designated as diabetic. The frequencies of meningioma, neurinomas and pituitary