TOLBUTAMIDE OVERDOSAGE AND IRREVERSIBLE CEREBRAL DAMAGE

A CASE REPORT

J. E. COSNETT, B.Sc., M.B. (RAND), M.R.C.P. (LOND.), *Edendale Hospital, Pietermaritzburg*

Irreversible cerebral damage due to prolonged hypoglycaemia is a well-known result of insulin overdosage. Since the discovery of oral hypoglycaemic agents the possibility has existed that similar effects could be caused by these drugs. Experimental evidence, however, tends to negate this possibility.

In most laboratory animals the hypoglycaemic action of tolbutamide is qualitative rather than quantitative. Large doses do not proportionately increase the degree of hypoglycaemia. There is, however, a difference in the sensitivity of various species. The threshold dose in the dog is one-tenth of that in the rabbit.[1] In dogs prolonged dosage in excess of 100 mg. per kg. causes death from acute hypoglycaemia.[2]

In human diabetics large doses of sulphonylurea derivatives do not significantly increase the response, though there have been reports of severe hypoglycaemia in diabetic patients who have appeared to be unduly sensitive to therapeutic doses of these drugs. McKendry[3] recorded the case of an 84-year-old diabetic man who twice developed hypoglycaemia while on normal doses of tolbutamide. On the second occasion the blood sugar was reduced to 26 mg. per 100 ml. and he succumbed to irreversible brain damage. Coates and Robbins[4] described 'hypoglycaemic shock' in an 88-year-old woman whose blood sugar was reduced to 8 mg. per 100 ml. by therapeutic doses of chlorpropamide. Camerini-Davalos *et al.*[5] recorded 2 patients in whom moderately severe hypoglycaemic reactions resulted from therapy with carbutamide. Seidler *et al.*[6] had 3 patients in whom hypoglycaemia occurred during therapy with carbutamide or tolbutamide. One of these became unconscious. A feature of these reported cases is that all of the hypoglycaemic reactions developed comparatively early in the course of treatment with oral hypoglycaemic agents. It appears also that the tendency to hypoglycaemia may continue for several days following cessation of treatment.

There have been no published reports of the effects of excessively large doses of these drugs in humans. Dr. Henry Dolger of the Mount Sinai Hospital, New York, had a diabetic patient who took 25 g. of tolbutamide in one day and apparently suffered no untoward effects apart from asthenia.[7] The effects of a massive dose of tolbutamide on a healthy subject have never been reported. The following case is probably unique.

CASE REPORT

A 30-year-old Indian woman was brought to the casualty department at Edendale Hospital on a Sunday evening in October 1959. She was deeply unconscious. Relatives stated that she had taken an overdose of tablets which had been supplied to her diabetic mother at this hospital. At this stage the tablets were not identified. The patient's stomach was washed out and she was given 40 ml. of a 50% glucose solution intravenously without any effect on her state of consciousness. She remained deeply comatose and was admitted to hospital at 10.30 p.m. when an intravenous infusion of 5% glucose in water was started. She was a well-nourished woman of average weight. Her blood pressure was 120/80 mm. Hg. There was no cyanosis and respiration was regular and normal. Her pupils were dilated and did not react to light. The tendon reflexes were normal. No other evidence of physical disease was found. The urine was normal.

During the night, because at that stage barbiturate poisoning was considered possible, she was given intravenous injections of bemegride and amiphenazole. Her coma lightened slightly and next morning she responded to painful stimuli and her pupils were smaller and reacted sluggishly to light, but she did not speak. Atropine and penicillin were given because there was excess bronchial secretion. Later methylamphetamine was administered intramuscularly in doses of 15 mg. 8-hourly. On the morning after her admission to hospital her blood sugar was 103 mg. per 100 ml. Her cerebrospinal fluid, serum electrolytes (sodium, potassium and chloride) and blood urea were normal.

She never regained consciousness although she survived for

6 months. Evidence, reconstructed from that gleaned from the patient's relatives and the hospital records, yielded the following story: The patient's mother was a middle-aged diabetic who was being treated with tolbutamide in a dose of 0·5 g. (1 tablet) twice daily. On the Thursday before her daughter's admission she had attended the outpatient department and received a month's supply of 60 tablets. She began using these tablets on that day. She lived with her son and daughter (the patient). Following an unhappy marriage the patient had been deserted by her husband who had taken their children away with him. As a result she had become depressed and had threatened suicide several times.

During that week-end the patient had been alone at home from Saturday afternoon at about 4.30 p.m. until she was discovered unconscious more than 24 hours later. Her mother and brother were closely questioned on several occasions regarding the possible causes of her unconsciousness. Their first and sustained belief was that she had consumed an overdose of the tablets which her mother took for diabetes. This belief was strengthened by the fact that the tablets had been available to her, and that only 12 tablets remained in the container after she was discovered in coma. Efforts were made to establish the possibility of any other form of poisoning. It appeared that the usual kinds of household remedies were present in the house. These included laxatives, aspirins, vitamin pills and potassium permanganate crystals. None of these was missing, nor did the patient's condition suggest poisoning by any of them. There was no insulin in the house. No fire had been burning.

Subsequent Course

During the first 48 hours after admission to hospital the patient's coma lightened slightly, she responded to painful stimuli, her pupils reacted to light and her deep reflexes were brisk and equal. She did not speak, nor did she make any response to questions. Blood-sugar estimations gave normal results. She was incontinent of urine and faeces, and was fed with a gastric tube. It became obvious that she had suffered irreversible cerebral damage. From the first week onwards she lay curled up in bed grinding her teeth and uttering periodic unintelligible shrieks without provocation. Chlorpromazine and later phenobarbitone were used as sedatives. In many respects her condition resembled that of a severe grade of mental defective.

As the months passed she lost much weight despite efforts to maintain her food intake through the gastric tube. She gradually developed a quadriplegia with exaggerated deep reflexes and bilateral ankle clonus. Her pupils retained their reaction to light but it appeared that she had some impairment of vision. She continued to menstruate fairly regularly. Examination of the cerebrospinal fluid 4 months after admission to hospital showed a slight excess of globulin but no other abnormality. She died, after 6 months of progressive intellectual and neurological deterioration, in April 1960.

Postmortem Findings

At the postmortem examination (performed by Dr. P. Matthews) the body weighed 63 lb. There were flexion deformities of the limbs and superficial ulcers over both hips. There was a chronic ulcer, measuring 2 cm. by ½ cm., in the anterior wall of the upper third of the oesophagus. This was presumably caused by the gastric tube. The heart, liver and kidneys were atrophic, being about half their expected size. The bladder showed signs of chronic infection. The brain was oedematous and the lateral ventricles were slightly dilated but there was no other gross lesion. Dr. J. Suskin reported that sections of the brain showed neuronal degeneration and gliosis. These changes are not specific, but would be expected following prolonged anoxia or hypoglycaemia with survival for some time after the accident. Other organs showed no significant changes.

DISCUSSION

Though there is no definite proof that this patient took an overdose of tolbutamide, the circumstantial evidence points strongly to the conclusion that she consumed 20 g. or more of the drug about 24 hours before she was brought to hospital. This represents a dose of approximately 330 mg. per kg. body weight. (Her weight on admission was estimated to be 60 kg.) There can be no doubt that she suffered irreversible cerebral damage with permanent depression of higher cerebral function and diffuse damage to the pyramidal tracts. It is difficult to escape the conclusion that this was due to prolonged hypoglycaemia though, unfortunately, blood was not taken for glucose estimation before intravenous glucose was administered. The clinical and pathological features of the case resembled those of cerebral damage caused by anoxia or hypoglycaemia.

Some animal experiments tend to contradict the conclusion that tolbutamide was responsible, but it appears that different species vary considerably in their response to sulphonylurea drugs. The few recorded cases of severe hypoglycaemia due to therapeutic doses of sulphonylurea drugs indicate that there must also be an individual variation in response to these drugs. Since the action of tolbutamide depends partly on the integrity of the pancreas and its ability to secrete insulin, it is possible that large doses in healthy subjects would have a quantitatively different action to that in diabetics who show a response to the drug. Furthermore it appears that the hypoglycaemic effect is maximal after the first few doses; this is probably due to liberation of insulin from the pancreas in excessively large amounts. It is therefore likely, in the light of present knowledge, that the cerebral damage in this previously healthy patient was caused by an overdose of tolbutamide, probably by means of prolonged hypoglycaemia.

SUMMARY

A case is described in which irreversible brain damage apparently followed a massive overdose of tolbutamide, taken with suicidal intent. Severe hypoglycaemia has occasionally been reported after therapeutic doses of sulphonylurea compounds. There is no previous record of the effect of an overdose in a healthy person.

ADDENDUM

Since this report was submitted for publication, Locket and Brown[8] have described 2 cases of coma which were apparently caused by oral hypoglycaemic agents. In 1 case a non-diabetic woman deliberately took an overdose of tablets and died after being comatose for 96 hours.

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