

## Hypoglycaemic coma with chlorpropamide

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MILD hypoglycaemic reactions are well recognized as a complication of chlorpropamide therapy, and have been estimated as occurring in 7% of all cases (Stowers & Bewsher, 1962). Severe hypoglycaemic coma due to this drug seems, however, to have been infrequently recognized, and we have been able to find only four isolated reports of this condition in the literature (Coates & Robbins, 1959; Bloch & Lenhardt, 1959; Sackner & Balinn, 1960; Lindeman, 1960). We have admitted five patients with severe hypoglycaemic reactions after taking chlorpropamide, one of whom died, during the first 6 months of last year. None of the cases that occurred at home was diagnosed before admission, and all were considered to have suffered some sort of cerebro-vascular accident. Several, indeed, showed abnormal neurological signs. We have had the opportunity to study the four surviving cases to see if there were any reasons for the severe reactions, and if there are any factors that merit special consideration when using this drug.

### Case reports

#### Case 1

A.S., a 76-year-old woman, was found to be diabetic in 1964, and was treated with chlorpropamide, 250 mg o.d. This dose was doubled in December 1966 because of glycosuria. In February 1966 she was admitted in congestive cardiac failure, and treated with diuretics and digoxin. The dose of chlorpropamide was maintained at 500 mg o.d. On 5 February she was found unrousable at 05.00 hours. She was deeply unconscious, with no abnormal neurological signs. The blood sugar was 37 mg/100 ml and she recovered after intravenous glucose. She required further injections over the next 36 hr for recurrent hypoglycaemia. She is now controlled on 250 mg of chlorpropamide a day.

#### Case 2

G.S., a 72-year-old woman, presented in 1962 with a mild peripheral neuropathy. She was found

to be diabetic and started on chlorpropamide 250 mg o.d. The drug was discontinued in 1965 but restarted in January 1966. A week later she was admitted deeply unconscious with some meningism, exaggerated deep reflexes and bilateral extensor plantar responses. The blood sugar was only 27 mg/100 ml and she recovered with intravenous glucose. She relapsed into coma after 24 hr and required further therapy. All the abnormal signs disappeared and she is now controlled on diet alone.

#### Case 3

T.W., a 77-year-old man, was admitted in 1965 with a mild and transient right hemiparesis. He was found to be diabetic and treated with chlorpropamide 250 mg o.d. The blood urea at the time was 95 mg/100 ml. In March 1966 he became confused at home and his doctor stopped the chlorpropamide. Over the next 2 days he deteriorated and developed signs of a right hemiparesis. He was then admitted unconscious, and the blood sugar was found to be 5 mg/100 ml. The hypoglycaemia was corrected with some difficulty by continuous infusion of glucose, and, although the hemiparesis slightly improved, he died 2 days later. The blood urea on this admission was 109 mg/100 ml. At necropsy the brain was normal, with no evidence of haemorrhage or infarction to explain the hemiparesis.

#### Case 4

M.M., a 60-year-old woman, was admitted in September 1965 with pulmonary fibrosis. Diabetes was discovered and she was discharged taking chlorpropamide 500 mg o.d. and prednisone, reducing from 25 mg q.d.s. In May 1966 phenformin 25 mg q.d.s. was added because of glycosuria. A few days later she was admitted semi-conscious. Apparently she had been getting progressively drowsy and disorientated over the past few days with weakness of her limbs and difficulty in swallowing. On examination she appeared to have an extensive muscular weakness, was unable to move any limbs, to speak, or to swallow. The reflexes were diminished and the plantar responses flexor.

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The blood sugar was 46 mg/100 ml and she recovered after several injections of glucose. She is now stabilized on chlorpropamide 250 mg o.d.

#### Case 5

J.S., a 72-year-old man, was found to be diabetic in March 1965 and was treated with chlorpropamide, 100 mg o.d. In May 1966 he increased his dose to 200 mg o.d. Over the next 3 weeks he complained of recurrent attacks of confusion and difficulty in speaking, and was finally admitted severely confused with a right facial weakness and dysphasia. The blood sugar was 50 mg/100 ml. He made a full recovery with repeated injections of intravenous glucose. His diabetes is now controlled by diet alone.

The following investigations have been performed on the four surviving cases: renal function has been assessed with a creatinine clearance, hepatic function with a bromsulphthalein excretion test, and the ability to utilize hepatic glycogen by the response to intravenous glucagon (0.02 mg/kg). The patient's sensitivity to the action of the sulphonylureas has been tested by the response to intravenous tolbutamide (20 mg/kg). The results are summarized in Table 1.

TABLE 1  
Tolbutamide test

Patient	Blood sugar (mg/100 ml), minutes after injection						
	0	15	30	45	60	90	120
A.S.	108	108	108	98	80	74	70
G.S.	88	62	38	32	34	50	60
M.M.	264	260	260	246	240	234	234
J.S.	112	104	96	90	92	86	86

#### Glucagon test

Patient	Blood sugar (mg/100 ml), minutes after injection					
	0	10	20	30	60	75
A.S.	149	167	188	200	198	185
G.S.	84	122	132	136	116	104
M.M.	142	165	186	228	220	224
J.S.	130	150	160	172	186	172

#### BSP test

Patient	Percentage retention, minutes after injection		
	0	25	45
	A.S.	70	24
G.S.	60	4.5	1.1
M.M.	36	4	3
J.S.	66	12	5

#### Creatinine clearance

Patient	Creatinine clearance (ml/min)
A.S.	27
G.S.	54.1
M.M.	81
J.S.	51

## Discussion

There are several points of interest arising from the clinical features shown by these cases.

All the patients were elderly and four were over the age of 70.

Four of the patients showed abnormal neurological signs, which improved to a large extent after recovery from the hypoglycaemia. Persistent neurological damage due to chlorpropamide hypoglycaemia has previously been recorded in one case (Sackner & Balian, 1960) and it seems possible that the effects of hypoglycaemia are most marked in those parts of the brain already suffering from ischaemia. In the patient that died (Case 3), although the signs of a hemiplegia persisted to some degree, there was no gross evidence of a vascular accident to account for this at autopsy. It is interesting that his transient ischaemic attack 1 year previously had involved the same side. In Case 5 the recurrent attacks of speech difficulty were probably due to hypoglycaemia and he eventually presented with a right facial weakness. The abnormal neurological features in several of the cases suggested at first a less remediable condition, and a routine 'Dextrostix' test is clearly of value in all cases presenting with a neurological deficit if there is any question of the administration of hypoglycaemic drugs or if there is no history available. Only because of this was an early diagnosis made in the four surviving cases in this series.

The recurrence of severe hypoglycaemia within 48 hr of the initial episode compares with previously reported cases, and is a feature that should always be expected in these patients.

In considering the factors responsible for the prolonged hypoglycaemia, a brief mention of the pharmacology of chlorpropamide is relevant. The drug is rapidly absorbed from the gastro-intestinal tract; in the serum it is bound to protein, and the half-life in the plasma has been estimated at 33 hr. It is excreted by the kidney and 70–80% of <sup>35</sup>S-labelled chlorpropamide has been found unchanged in the urine after 72 hr (Johnson *et al.*, 1959).

The possible aetiological factors that might have contributed to the severe reactions in our cases are therefore: (1) abnormal metabolism or transport of the drug causing it to have a more profound effect; (2) potentiation of the usual hypoglycaemic response by other factors; (3) failure of the compensatory glycogenolysis from the liver in response to hypoglycaemia; (4) failure of adequate renal excretion; and (5) overdosage of the drug, or a combination of several of these factors. In order to assess the effects of the sulphonylureas on our patients, we have measured the effects on the blood sugar of an intravenous

injection of tolbutamide in the four surviving cases. Case 2 (G.S.) showed a rather severe fall in blood sugar for a diabetic subject, with a drop of over 50% after 45 min. It is possibly significant that she was only a latent diabetic and her response more closely resembles that of a non-diabetic subject. The other three patients show a fairly normal response for diabetics, with no exaggerated fall in blood sugar to suggest that they might be especially sensitive to the effects of the drug.

It has recently been recognized that the administration of leucine can potentiate the hypoglycaemic effects of tolbutamide (Jarrett & Butterfield, 1964). We have not studied leucine tolerance in our patients, but a careful history has not revealed any change in their dietary intake in the period preceding the hypoglycaemic episode, and it seems unlikely that this mechanism was of much significance in the present series.

Failure of compensatory release of glucose from the liver may be responsible for prolonged hypoglycaemia. Reduced glycogen stores in the liver may result in failure or delay in adequate glycogenolysis, and a reduced rise in blood sugar after an injection of glucagon has been demonstrated in patients with liver disease (Van Itallie & Bentley, 1955; Dall & Melrose, 1964). Although one of our patients (A.S.) had a slightly abnormal BSP test, all showed a rise in blood sugar of at least 50 mg/100 ml after intravenous glucagon, and in the case that died there was no evidence of hepatic disease.

Failure of renal excretion of the sulphonylureas has been suggested as a cause of protracted hypoglycaemia (Bolinger, Tu & Kendall, 1960). It is possibly significant that in the present series three patients showed reduced creatinine clearance, and the man that died had a persistently raised blood urea.

It is, finally, possible that some of these cases were receiving too high a dose of the drug and it is of interest, in this respect, that in two cases the dose of chlorpropamide had been raised shortly before the hypoglycaemic episode, in a third patient phenformin had just been added, and in a fourth case the drug had only recently been restarted. It is also significant that all the surviving patients have since been adequately maintained on a reduced dose of chlorpropamide, with no further trouble.

It is probable that several factors have contributed to the severe reactions in these cases, but the evidence suggests that chlorpropamide should be given with caution to the elderly, especially over the age of 70, and if there is any evidence of renal or hepatic impairment. These

patients should be maintained on as small an amount as possible of the drug and the dose should only be increased with caution, if there is very good reason, and not on the evidence of an occasional blood or urine sugar reading. It would also seem advisable to review the position from time to time and see if the dose of chlorpropamide could be reduced.

### Summary

Five cases are reported of severe hypoglycaemic reactions due to chlorpropamide. All presented within a 5-month period, and one patient died. Several of the cases showed abnormal neurological signs, which appeared to be due to the hypoglycaemia. An attempt has been made to elucidate some of the mechanisms responsible for the severe hypoglycaemia in these patients.

It is concluded that chlorpropamide should only be given with great caution to patients over the age of 70, especially if there is renal or hepatic impairment. Care should be taken to maintain these people on the lowest possible dose of the drug necessary to control their diabetes.

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