HYPEROSMOLAR NON-KETOTIC HYPERGLYCAEMIA
DURING ORAL DIAZOXIDE THERAPY OF PROLONGED HYPERGLYCAEMIA IN INFANCY

J. M. SAVAGE, D.C.H., M.R.C.P. (U.K.),
Department of Child Health, Queen’s University, Belfast

C. SLATTERY, D.C.H., M.R.C.P.I.,
Consultant Paediatrician, Craigavon Area Hospital

SEVERE prolonged hypoglycaemia in infancy due to hyperinsulinism does not always respond to treatment with glucocorticoids or glucagon. Baker et al in 1967 suggested that diazoxide might be used as an alternative method of treatment.

Diazoxide is a benzothiadiazine derivative, chemically closely related to thiazide diuretics but lacking diuretic activity. Fajans et al (1968) have recorded this agent’s ability of suppress insulin release from normal and abnormal islet cell tissue. This property was exploited in the treatment of our patient, a 16 week-old infant with severe, prolonged symptomatic hypoglycaemia. Unfortunale adverse effects of the treatment included hyperosmolar non-ketotic hyperglycaemia and marked hirsutism.

CASE REPORT

A 16 week-old male infant was referred from a peripheral hospital for investigation following a convulsion during which his plasma glucose was unrecordable. He had been delivered normally at term after an uneventful pregnancy and weighed 3.5 kgs. There were no problems in the neonatal period. He was the second child of healthy unrelated parents with no family history of diabetes, epilepsy or unexplained infant deaths.

At the age of 4 weeks he had a brief hospital admission with an upper respiratory tract infection and at that time appeared developmentally normal. During the following months he was brought to his family doctor on several occasions with episodes which his mother called “colic”. During these attacks he screamed, became rigid and later appeared drowsy. She also reported that he was an exceptionally hungry baby demanding frequent large feeds of cow’s milk and cereal.

On admission he was at the 97th centile for height and weight (Tanner and Whitehouse, 1966) and his head circumference was on the 90th centile (Westrup and Barber, 1956). He was an obese hypotonic infant. There were no demonstrable tendon reflexes or response to stimuli other than pain. Complete head lag and palmar thumbing were noted but there were no localising neurological signs. The fundi were normal and there were no cataracts. The liver was palpable one finger breadth below the costal margin and there was no clinical evidence of visceromegaly and this was later confirmed by barium meal and intravenous pyelogram.
He continued to have focal left-sided convulsions after admission when his plasma glucose was found to be 0.5 mmol/l. Initial treatment was with a continuous intravenous infusion of 20 per cent dextrose with a total of 125 mls of 50 per cent dextrose given intermittently. This regimen maintained the plasma glucose between 1.0-1.5 mmol/l, reaching a peak of 2.0 mmol/l on one occasion.

Full investigations were performed during the first few days following admission but failed to establish evidence of hepatic disease or enzyme deficiency including galactosaemia and glycogen storage disease. Inborn errors of amino acid metabolism were excluded. EEG and all other neurological investigations revealed no abnormality. Endocrine studies other than insulin levels were normal. There was no response to a low leucine diet.

Intravenous dextrose was discontinued for 8 hours before measurement of plasma insulin. Inappropriate levels of 42 and 44 IU/ml (normal range 10-15 IU/ml) were found on 2 occasions when the plasma glucose levels were less than 1.0 mmol/l.

Satisfactory control of the hypoglycaemia was not achieved until diazoxide 50 mg. 3 times daily was introduced as therapy. Using this dose, his plasma glucose was initially maintained at a satisfactory level, but on the 10th day, this rose over a period of 24 hours to 24 mmol/l. Serum sodium was 154 mmol/l, urea 25 mmol/l and plasma osmolality was estimated as 352 milliosmols. Diazoxide was discontinued for 36 hours and osmolar correction was achieved using intravenous 0.45 per cent saline solution and a single dose of 4 units soluble insulin subcutaneously. Subsequently the diazoxide was recommenced at 90 mgs, (equivalent to 9 mg/kg per day) in 3 divided doses. The plasma glucose on this regimen was maintained at a satisfactory level and no further episodes of hyperglycaemia occurred.

A repeat EEG one month after admission showed a generalised slow wave abnormality in all regions. Salaam epilepsy developed and was controlled with clonazepam 0.5 mg twice daily. Unfortunately, despite adequate control of plasma glucose there was no neurological improvement prior to death. He remained hypotonic and unresponsive although he sucked well from a bottle. The head circumference diminished by 1 cm and was only 42 cm at 7 weeks.

Hirsuitism was first noticed after 2 weeks treatment with diazoxide and was severe after 4 weeks.

Death occurred from an intercurrent chest infection at the age of 7 months. Permission for a post mortem could not be obtained.

DISCUSSION

Hyperinsulinism was the cause of hypoglycaemia in this case. A comprehensive review of the causes of hypoglycaemia was published by Pagliara et al in 1973. Histological and histochemical studies were suggested, when one wishes to distinguish between pancreatic B-cell tumours, islet cell hyperplasia, nesidioblastosis and functional disorders causing hyperinsulinism. However, in our patient a laparotomy was not considered justifiable as irreversible cerebral
damage had occurred before adequate plasma glucose levels were established and no improvement was seen in his intellectual development when these were maintained.

The use of diazoxide in the management of hypoglycaemia of infancy is now established (Baker et al, 1967; Erlich and Martin, 1969; Marks and Samols, 1968). The condition remains, however, extremely difficult to treat satisfactorily. Early correction of the plasma glucose remains of major importance in preventing severe brain damage. Diazoxide is perhaps the agent most likely to achieve this. Drash et al (1968) report many complications of diazoxide including hyperglycaemia, ketosis, hirsutism, hyperuricaemia and electrolyte abnormalities. They do not record the hyperosmolar condition described here but this has been reported in adults (Charles and Danforth, 1971). Correction of this hyperosmolar state is not difficult if diazoxide is withdrawn and adequate intravenous fluids administered, insulin was probably not essential in our patient. The possibility of this potentially lethal complication requires regular monitoring of the serum electrolytes and plasma glucose during the early days and weeks of treatment. Prevention depends on the use of minimum effective dose of diazoxide which is probably 7.5 to 12.5 mg/kg per day. Hirsutism is an unfortunate but unavoidable complication.

SUMMARY

A 16 week-old infant presented with severe prolonged symptomatic hypoglycaemia resistant to the treatment with intravenous dextrose. The aetiology of the condition was established as hyperinsulinism and treatment was initiated with diazoxide 15 mg/kg per day, in 3 divided doses. This was shown to be successful in correction and maintainance of plasma glucose levels initially but led to the development of a hyperosmolar non-ketotic hyperglycaemic state on the 10th day of treatment.

This was readily corrected by discontinuing diazoxide administration, intravenous infusion of 0.45 per cent saline solution and subcutaneous insulin. Subsequent reduction of diazoxide therapy to 9 mg/kg per day prevented recurrence of this dangerous complication.

Residual cerebral impairment due to the initial prolonged hypoglycaemia led eventually to the child's death.

REFERENCES

1. BAKER, L. and KAYE, R., (1967). Diazoxide treatment of idiopathic hypoglycaemia of infancy. Journal of Pediatrics, 71, 494-505.

2. CHARLES, M. A. and DANFORTH, M. D. Jr. (1971). Nonketo-acidotic hyperglycaemia and coma during intravenous diazoxide therapy in uremia. Diabetes, 20, 501-503.

3. DRASH, A., KENNY, F., FIELD, J., BLIZZARD, R., LANGS, H. and WOLFF, F., (1968). The therapeutic application of diazoxide in pediatric hypoglycaemic states. Annals of New York Academy of Science, 150, 337-355.
4. EHRICH, R. M. and MARTIN, J. M. (1969). Diazoxide in management of hypoglycaemia in infancy and childhood. *American Journal of Disease of Children*, 117, 411-416.

5. FAJANS, S. S., FLOYD, J. C. Jr., THIFFAULT, C. A., KNOPF, R. F., HARRISON, T. S. and CONN, J. W., (1968). Further studies on diazoxide suppression of insulin release of normal and abnormal islet tissue in man. *Annals of New York Academy of Science*, 150, 261-280.

6. MARKS, V. and SAMOLS, E., (1968). Diazoxide therapy of intractable hypoglycaemia. *Annals of New York Academy of Science*, 150, 442-454.

7. PAGLIARA, A. S., KARL, I. E., HAYMOND, M. and KIPNIS, D. M., (1973). Hypoglycaemia in infancy and childhood, (I & II), *Journal of Pediatrics*, 82, 365-379 and 558-577.

8. TANNER, J. M., WHITEHOUSE, R. H. and TAKAISHI, M., (1966). Standards from birth to maturity for height and weight. *Archives of Disease in Childhood*, 45, 755.

9. WESTRUPP, C. K. and BARBER, C. R., (1956). Standards for head circumference. *Journal of Neurology, Neurosurgery and Psychiatry*, 19, 52.