

before recovery, and Henderson and Psaila's patient was moribund until nalorphine was given.

The use of nalorphine is vital in all cases of diphenoxylate hydrochloride poisoning. It undoubtedly saved the lives of our patient and of Henderson and Psaila's, and there can be fewer more dramatic drug responses in the field of clinical pharmacology. There are no clear rules about dosage, timing, and duration of nalorphine administration, but this drug must be given if respirations become abnormal in a suspected case of diphenoxylate poisoning and repeated frequently if necessary. Some caution is advised because nalorphine itself can cause respiratory depression in normal patients. The average dose is from 0.25 mg for the newborn to 10 mg for the adult.

The manufacturers of 'Lomotil' mention in their reference manual the dangers of narcosis and respiratory depression in accidental overdose, particularly in children. The case reported above and the 3 others in the literature underline this advice. We stress the importance of emptying the stomach as soon as possible, hospital admission, continuous observation of the patient for at least 48 hours, and the prompt and repeated administration of nalorphine if respiration is threatened.

### Summary

A 2-year-old child swallowed an unknown quantity of diphenoxylate hydrochloride (Lomotil) tablets. Many hours later she developed severe respiratory depression which responded to nalorphine. The dangers of this poisoning in children and its appropriate therapy are discussed.

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R. WHEELDON and H. J. HEGGARTY

*Paediatric Department, Northern General Hospital, Sheffield.*

Correspondence to Dr. R. Wheeldon, Children's Hospital, Western Bank, Sheffield S10 2TH.

## Hyperglycaemia Due to Phenytoin Toxicity

Neurotoxicity due to phenytoin overdose is well recognized but it has also been reported to

cause hyperglycaemia. We report a case of a child presenting with neurotoxicity found to have temporary hyperglycaemia and an abnormal glucose tolerance test with raised insulin levels.

### Case Report

An 11-year-old boy with post-traumatic epilepsy was admitted to a paediatric ward with a history of ataxia, headache, vomiting, and drowsiness. 2 weeks before admission he first had difficulty in walking. His ataxia worsened and about a week later he began to have severe headaches and vomiting. He became increasingly drowsy and admission was requested when he was found to be unrousable. He had a 3-year history of *grand mal* convulsions after a skull fracture. He had last been seen in the neurological outpatients department 3 weeks previously. Because of increasingly frequent fits his dose of phenytoin was increased from 200 to 300 mg daily. Primidone 250 mg daily and nitrazepam 5 mg at night were continued as before. There was no evidence that these drugs were not taken as prescribed.

On admission he was stuporose but rousable and had a normal temperature. The only abnormal findings on examination were in the nervous system. His speech was slurred and he was ataxic with tremor and marked nystagmus. Tone and reflexes were variable but showed no localizing features. The clinical picture was suggestive of phenytoin overdose.

Plasma anticonvulsant levels were estimated by gas chromatography and found to be: phenobarbitone 0.3 mg/100 ml; primidone 0.2 mg/100 ml; phenytoin 4.4 mg/100 ml. The therapeutic level of phenytoin is stated to be between 1.0 and 2.0 mg/100 ml in the plasma (Kutt and McDowell, 1966).

Glycosuria was noted and plasma glucose estimated as 280 mg/100 ml. A glucose tolerance test showed a diabetic curve (Fig. 1) with plasma rising from a fasting level of 72 mg/100 ml to 214 mg/100 ml at 1½ and 2 hours and only falling to 190 mg/100 ml at 2½ hours. Insulin levels were estimated (Fig. 1) and were found to be raised.

Phenytoin was discontinued and the level was 2.2 mg/100 ml in the plasma at 5 days and undetectable at 10 days. The neurological signs returned to normal over 3 days and he remained free from convulsions taking primidone 250 mg daily.

A repeat glucose tolerance test was normal one month later (Fig. 2), with a fasting level of 84 mg/100 ml rising to a maximum of 170 mg/100 ml at 1 hour and falling to 56 mg/100 ml at 2½ hours.

### Comment

Phenytoin was first found to produce hyperglycaemia during studies on the effect of electroshock seizures on blood sugars in rabbits (Belton, Etheridge, and Millichap, 1965). An average rise of 130 mg/100 ml was noted in animals pretreated with phenytoin, while control animals, given no anticonvulsant, had an average post-shock rise of

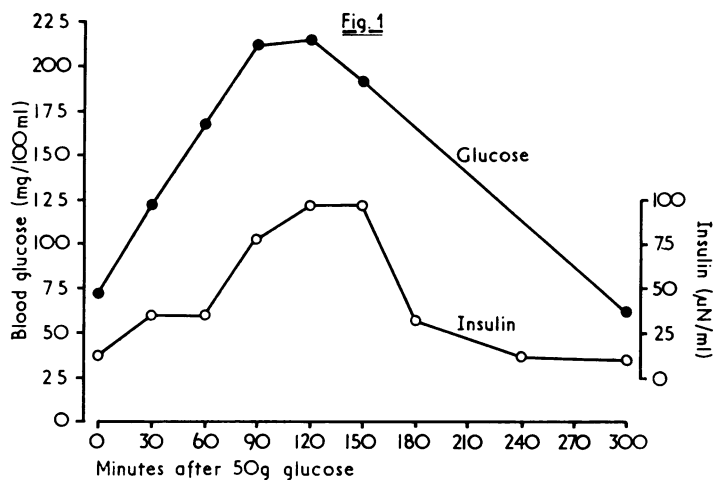


FIG. 1.—Glucose tolerance test on admission.

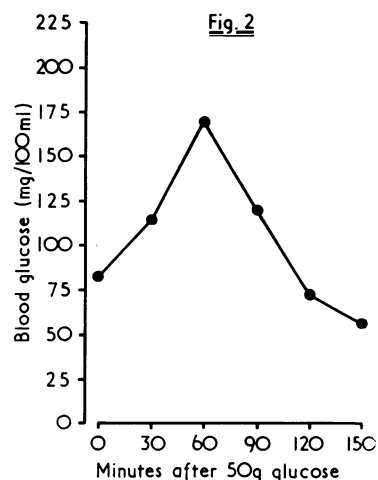


FIG. 2.—Glucose tolerance test 1 month later.

50 mg/100 ml. Further studies showed that phenytoin alone in doses of 70 mg/kg produced an average rise in blood sugar of 118 mg/100 ml, and this hyperglycaemic effect has since been shown in dogs (Goldberg and Sanbar, 1969).

Abnormalities of glucose metabolism with phenytoin toxicity have been reported in 6 cases where hyperglycaemia was thought to be due to this drug (Klein, 1966; Dahl, 1967; Said, Fraga, and Reichelderfer, 1968; Goldberg and Sanbar, 1969; Peters and Samaan, 1969). In particular, Peters and Samaan found a diabetic glucose tolerance curve in a patient with a plasma phenytoin of 6.5 mg/100 ml. The test subsequently returned to normal.

The raised insulin levels measured in our case rule out pancreatic suppression as the cause of the hyperglycaemia observed.

The reason for the high plasma levels of phenytoin while taking 100 mg t.d.s. is uncertain. A higher dose than was prescribed may have been taken, as in other cases reported (Klein, 1966; Dahl, 1967). Phenytoin is metabolized by parahydroxylation in the liver and it has been shown that in some subjects there is a relative defect in the enzymatic factor involved (Kutt *et al.*, 1964). Progressively rising plasma levels were found on an oral dose of phenytoin 300 mg daily. The increase from 200 to 300 mg daily in this patient may have created the same effect by exceeding his ability to metabolize the drug.

### Summary

A case is reported of a child who developed neurotoxicity due to phenytoin therapy associated

with abnormality of glucose tolerance test and raised insulin levels. After cessation of phenytoin therapy, the glucose tolerance test reverted to normal.

We would like to thank Dr. P. R. Evans for permission to publish the case, and Dr. L. Stimmler and Dr. G. Snodgrass for measuring insulin levels and for their helpful advice.

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T. TREASURE and P. A. TOSELAND

From the Department of Clinical Chemistry, Guy's Hospital, London S.E.1.

Correspondence to Dr. T. Treasure, Accident Service, Addenbrooke's Hospital, Cambridge.