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Medical Memoranda

Liver Damage and Impaired Glucose Tolerance after Paracetamol Overdosage

Brit. med. J., 1966, **2**, 506–507

Paracetamol is a widely used and comparatively safe antipyretic analgesic (*Brit. med. J.*, 1965 ; *Drug and Therapeutics Bulletin*, 1966). In view of its increasing clinical use, the following case history is of interest.

Case History

A 54-year-old man weighing 7 st. 10 lb. (49 kg.) was admitted to the casualty ward at Woolmanhill, Aberdeen, on 11 September 1965, within two hours of consuming a bottle of beer and a number of paracetamol tablets, estimated at 70 by his wife. He had been taking the drug over a period of two years for low back pain of undetermined origin. There was nothing else of note in his past medical history, and, in particular, no history of liver disease or alcoholism. His mother was known to have had diabetes.

On admission he was drowsy, but no abnormal physical signs were elicited. The pulse rate was 78/min. and the blood-pressure 100/70 mm. Hg ; the extremities were warm. The stomach was washed out, and the aspirate was reported to contain a " small amount of paracetamol." The serum concentration of paracetamol on admission was 76 mg./100 ml.

As the patient was cooperative, treatment was started with forced oral fluids. A urine sample obtained three hours after admission contained 2% glucose, but was otherwise normal. Over the next 12 hours the glycosuria continued, and as his general condition was deteriorating he was transferred to Woodend General Hospital on 12 September. On arrival he was lethargic but aggressive when disturbed, was incontinent of urine and faeces, and complained of blindness. He lay with his eyes deviated to the right, and horizontal nystagmus was present. From lack of cooperation full assessment of the nature and extent of the visual defect was not possible. No other abnormalities were found on physical examination. The pulse rate was now 110/minute and the blood-pressure 150/100 mm. Hg.

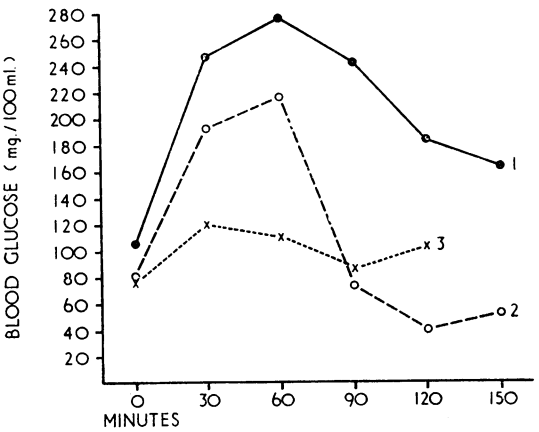
Investigations on 12 September showed: urine—glucose 1%, no acetone, bile, or urobilinogen ; serum urea 20 mg./100 ml., blood sugar 146 mg./100 ml. (glucose oxidase method) ; haemoglobin 13.7 g./100 ml., W.B.C. 8,200/c.mm., and E.S.R. 3 mm./hour (Westergren).

On 13 September an oral glucose-tolerance test with 50 g. of glucose was abnormal, with a fasting blood-sugar level of 106 mg./100 ml., rising to 276 mg./100 ml. at one hour and falling to 184 mg./100 ml. at two hours (see Chart, curve 1). A 2,000-calorie diet containing 200 g. of carbohydrate was therefore started on 14 September together with 100 mg. of chlorpropamide daily. With no other treatment his general condition improved, there was no further glycosuria, and his vision returned to normal.

On 17 September he was noticed to be icteric, and although the liver was not enlarged clinically, he complained of upper abdominal pain.

Investigations showed:—urine: bilirubin++, urobilinogen+++, no glucose or acetone ; serum: bilirubin 4.4 mg./100 ml., Van den Bergh+, glutamic oxaloacetic transaminase (S.G.O.T.) 216 units, glutamic pyruvic transaminase (S.G.P.T.) 124 units, sodium 137, potassium 3.7, chloride 96, CO_2 26.5 mEq/l., alkaline phosphatase 19 King-Armstrong units, proteins normal, urea 59 mg./100 ml., and fasting blood sugar 90 mg./100 ml.

Over the next four days the jaundice gradually faded and by 4 October the serum alkaline phosphatase was 11 units, the S.G.O.T. 46 units, and the S.P.G.T. 51 units. A repeat oral glucose-tolerance test showed considerable improvement (Chart, curve 2). The chlorpropamide was discontinued on 8 October, and a normal ward diet introduced on 16 October with no recurrence of the glycosuria. A third glucose-tolerance test on 28 October was normal (Chart, curve 3). Apart from persisting back pain which necessitated his transfer to an orthopaedic ward, his progress thereafter was uneventful.



Glucose-tolerance tests on 13 September (1), 4 October (2), and 28 October 1965 (3).

Comment

The remarkable lack of reported side-effects of paracetamol suggests that it is comparatively safe when used in normal therapeutic doses. There is no doubt that this patient had taken and absorbed a large quantity of the drug. The high serum concentration of 76 mg./100 ml. is compatible with the estimated intake of 70 tablets (35 g.), as after ingestion of 2 g. of paracetamol, serum concentrations of up to 5 mg./100 ml. may be expected in normal subjects (Prescott and Conney, unpublished data).

Apart from the blindness (which we cannot explain), the presenting clinical features were unremarkable. It was not until six days after the paracetamol was taken that jaundice appeared ; and had it not been for the initial finding of glycosuria the patient might well have been discharged home on the second or third day with the liver damage unrecognized. The results of the liver-function tests suggest hepatocellular damage rather

than cholestasis. Until recently there have been no clinical reports of liver damage associated with administration of paracetamol. However, Davidson and Eastham (1966) have now recorded two cases of liver necrosis ascribed to overdosage of paracetamol. Both patients had hypoglycaemia and neither survived. In addition, we know of two other unpublished cases of liver damage after intake of large amounts of paracetamol. A 13-year-old girl died with "massive toxic necrosis of the liver" five days after taking at least 15 g. of the drug, and a woman aged 32 developed hepatocellular jaundice four days after ingestion of 17.5 g. of paracetamol, but subsequently recovered. In experiments on rats, Boyd and Bereczky (1966) noted the delayed onset of hepatic necrosis after feeding large doses of paracetamol, and in some animals this was accompanied by glycosuria. Although chlorpropamide has been associated with liver damage (Popper *et al.*, 1965) we feel that it is unlikely to be responsible in this case, since jaundice was present after only 200 mg. of the drug had been taken, and liver-function tests showed a return to normal despite continued administration of chlorpropamide.

The cause of the transient impairment of glucose tolerance observed in the present case is not clear. Paracetamol has no known diabetogenic action, and the duration of the abnormality makes a direct drug-effect most unlikely. Both hyperglycaemia and hypoglycaemia are known to occur with parenchymal liver damage (Leevy *et al.*, 1952 ; Sherlock, 1963), and it is tempting to postulate that the hyperglycaemia was related to the hepatic injury. On the other hand, there was a family of diabetes, and an undoubtedly stressful situation may have unmasked a latent diabetes. Unfortunately the patient has been unwilling to return for further glucose-tolerance studies. Since both cases described by Davidson and Eastham (1966) had hypoglycaemia (presumably due to massive hepatic necrosis), it is important that a close watch be kept on the blood sugar levels of patients who have taken large amounts of paracetamol.

We should like to thank Dr. D. S. Short for permission to publish the details of this case and for helpful criticism. Our thanks are also due to Dr. J. E. G. Pearson, of Frenchay Hospital, Bristol, and Dr. J. A. Shrigley, of Birch Hill Hospital, Rochdale, for permission to mention the unpublished cases ; and to Bayer Products Ltd. for drawing them to our attention.

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Hypokalaemia of Unknown Aetiology Complicating Hodgkin's Disease

Brit. med. J., 1966, **2**, 507–508

In the following case Hodgkin's disease was associated with abnormal urinary potassium loss of unknown pathogenesis.

CASE REPORT

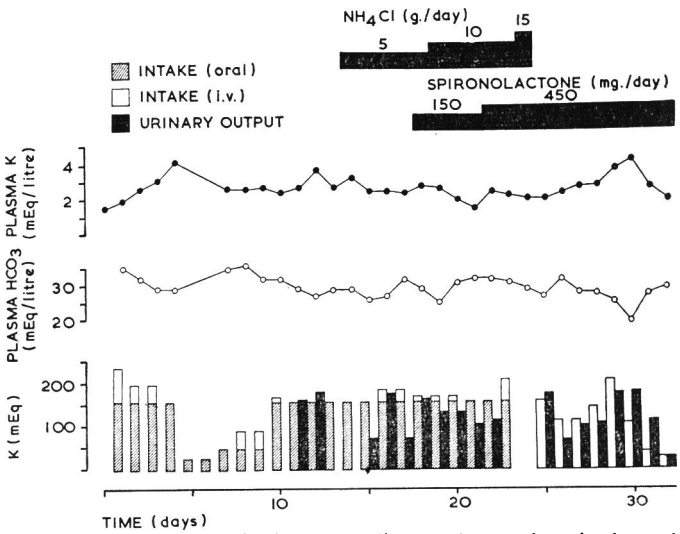
A woman of 23 was diagnosed as suffering from Hodgkin's disease in November 1962. Lymphadenopathy was confined to the abdomen ; at laparotomy biopsy specimens were taken from a large mass in the mesentery and around the coeliac axis. Her general condition improved after irradiation to the abdomen, but she continued to have mild systemic symptoms, and several months later developed enlarged glands in the neck and mediastinum, treated by cobalt beam ; a large new abdominal mass was also irradiated in September 1963. Cytotoxic therapy was not given.

In November 1963 she was admitted to hospital, complaining of weakness, paraesthesiae, and intermittent vomiting of about a month's duration. Muscle power, tone, and reflexes were normal ; there were no signs of Cushing's syndrome. Her blood-pressure was 130/80 mm. Hg, plasma potassium 1.5 mEq/l., and bicarbonate 35 mEq/l. E.C.G. showed the changes of hypokalaemia.

Initially she was given 150 to 240 mEq of potassium daily, of which 160 mEq was administered intravenously in the first three days. By the fourth day her plasma potassium had risen to 4.1 mEq/l. and the bicarbonate had fallen to 29 mEq/l. (see Chart). The urinary *p*H was 6.0 on admission, and subsequently varied between 5.6 and 6.5.

Vomiting and diarrhoea ceased, but hypokalaemic alkalosis recurred immediately when supplemental potassium was reduced to 30 mEq on the fifth day. From the 12th day the daily urinary loss was between 75 and 175 mEq, when her plasma potassium was around 2.5 mEq/l. Administration of ammonium chloride, at first orally and then intravenously, in a dosage of up to 9 g. daily, did not decrease the plasma bicarbonate concentration, while spironolactone did not significantly alter the plasma potassium concentration ; urinary potassium loss continued at around 100 mEq/day. When both drugs had been given for four days the plasma potassium was 1.5 mEq/l. in spite of daily potassium supplements of 160 mEq. Gastro-intestinal loss was still occurring, and it seemed likely that urinary potassium excretion roughly equalled that absorbed from the gut.

The total exchangeable body potassium measured after injection of 30 μc. of ^{42}K on the 24th day was 1,400 mEq, or 28 mEq/kg. of



Plasma potassium and bicarbonate readings and potassium intake and urinary output.

body-weight, a low figure for a thin, non-oedematous female—normal mean for females about 40 mEq/kg. (Moore *et al.*, 1954). The 24-hour aldosterone excretion on the seventh day was 8.6 μg.

From the 25th day between 116 and 216 mEq of potassium was administered intravenously each day. This resulted in some reten-