

for tubercle bacilli even when tuberculous meningitis is only remotely suspected. As tuberculosis becomes less common, atypical cases are more likely to be missed unless a high index of suspicion is maintained.

Summary

A case of mixed meningitis in a young infant involving *Strep. pneumoniae* and *M. tuberculosis* is reported that emphasizes the diagnostic difficulties and the importance of searching for tubercle bacilli at the slightest suspicion.

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Diazepam for fenfluramine intoxication

Fenfluramine (Ponderax) is used increasingly as an adjunct to a low calorie diet in the treatment of obesity. There are an increasing number of reports of both children and adults who have suffered fenfluramine poisoning (Riley *et al.*, 1969). At least 5 have been fatal (Fleisher and Campbell, 1969; Gold *et al.*, 1969). Signs and symptoms shown by these patients were agitation and slight tremor, particularly of the lower jaw, with dilated pupils and tachycardia. Those with more severe poisoning

have had abnormal eye movements, marked tremor, convulsions, unconsciousness, facial flushing, and hyperpyrexia, and cardiac and respiratory depression leading to cardiac arrhythmias and death.

We report 2 children who recovered from severe fenfluramine poisoning as judged by their clinical state and blood levels. Their treatment included the use of large doses of parenteral diazepam.

Case reports

Case 1. At about 5 p.m. this normally healthy 3½-year-old girl was found by her mother in the garden acting oddly. She could not walk properly and her eyes 'looked funny'. Shortly after this her mother discovered that her fenfluramine tablets (20 mg each) had disappeared. 56 tablets were missing which, if all had been consumed, would have corresponded to a dose of 70 mg/kg body weight. She was admitted to this hospital at 6.20 p.m. at which time she was restless, flushed, and her pupils were widely dilated but responsive to light. Her heart rate was 150/min and her systolic blood pressure was 140 mmHg.

She was given 5 mg diazepam intramuscularly and vomiting was induced with 20 ml of syrup of ipecac (BPC). The vomitus was copious and contained white matter but no complete tablets were found. Over the next hour she deteriorated, becoming increasingly restless with semivoluntary movements. She was flushed and was sweating profusely. She lay in opisthotonus, her limbs were stiff, and she was semiconscious. Her pupils were widely dilated and no longer responded to light. There was a coarse nystagmus and occasionally her eyes rolled upwards. Tachycardia increased to 190 to 200/min, respirations were shallow, rapid, and irregular, and blood pressure remained raised. Throughout this time her temperature remained normal.

Intravenous fluids were given and repeated slow intravenous injections of diazepam, 5 mg at a time, were administered to control her agitation and muscular spasms.

At 8.30 p.m., after a total of 35 mg diazepam, she was asleep but her limbs were stiff. Respirations continued to be irregular and rapid, but tachycardia subsided.

At 9.15 p.m. she awoke and it was immediately apparent that her condition had improved. Her muscle tone and movements were normal. She remained awake and restless throughout the night and was therefore given two further doses of diazepam. Though her pupils remained dilated for about 24 hours the nystagmus ceased.

Over the following 48 hours she was drowsy but her general condition gradually improved. She had some difficulty in micturition, passing large quantities of urine infrequently. She was discharged on the third day having made a full recovery.

Case 2. A boy, aged 2 years 11 months, had been seen previously in outpatients because of behavioural

difficulties, poor appetite, and thin physique. He was considered to be a healthy but hyperactive child.

He was admitted at about 8 p.m. having reputedly taken about 20 of his mother's fenfluramine tablets 2 hours previously; that is a total of 400 mg, equivalent to about 30 mg/kg body weight. He had had a stomach washout at another hospital about half an hour after the ingestion.

On admission he was conscious, flushed, and restless, lying in opisthotonus with frequent coarse muscular twitching, which became more convulsive on occasions. His respirations were shallow and became irregular with the abnormal movements. He was hypertensive (blood pressure 150/80 mmHg), heart rate 130/min, and temperature 37.4 °C. His pupils were widely dilated, responding only sluggishly to light, and he had a marked nystagmus.

He was given oxygen by face mask and intravenous fluids. 5 mg intravenous diazepam was given over about 5 minutes until there was a reduction of abnormal movements. It was repeated as the twitching recurred; a total of 30 mg diazepam was administered in the 2 hours after admission.

His clinical state improved over the next few hours, though he was drowsy and, like the previous child, had difficulty in passing urine for a couple of days. He had fully recovered at the time of discharge and investigations did not reveal any organic basis for his poor appetite and thinness.

Results

Fenfluramine and norfenfluramine plasma levels. Fenfluramine is partially de-ethylated to the active metabolite norfenfluramine in the liver. Plasma from the children was analysed for both substances by gas-liquid chromatography and the results are given in the Table and the Fig.

TABLE

Plasma concentrations of fenfluramine and norfenfluramine after ingestion

Approximate interval from ingestion (hr)	Fenfluramine (ng/ml)	Norfenfluramine (ng/ml)
Case 1		
7.5	1140	280
16	660	460
Case 2		
3.3	630	91
5.25	470	96
15	260	120
27	80	47

The approximate plasma level reached in an adult after taking 60 mg (3 tablets) is 60 ng/ml fenfluramine and 10 ng/ml norfenfluramine. Biological half-life for both products is found to be between 16 to 20 hours, but may be slightly shorter in children. The levels obtained in these children

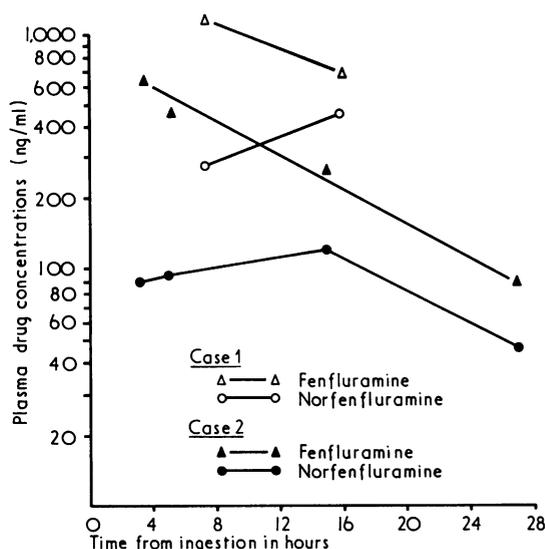


FIG.—Plasma concentrations of fenfluramine and norfenfluramine.

are within the severely toxic range, the first level obtained in Case 1 of 1140 ng/ml being one of the highest recorded in a surviving patient.

Discussion

Kündig (1971) has investigated the effects of the toxicity of fenfluramine in both anaesthetized and unanaesthetized primates. They appeared sedated and in a stupor during the acute intoxication stage and convulsions were readily precipitated by stimulation. Death in the more severely poisoned, i.e. those receiving 50 mg/kg or more, occurred after 90 to 240 minutes during repeated clonic-tonic convulsions with respiratory impairment. He studied a number of drugs as possible antagonists and found that diazepam and its derivatives gave the most promising results.

In the 2 children reported here, the dose of diazepam required to reduce their symptoms was massive. Case 1 required 45 mg over 8 hours and Case 2 had 30 mg in 2 hours. (The recommended dose for status epilepticus for children of this weight is between 2.5 to 5 mg (Wood, 1970).) Both children appeared to tolerate this dose and in neither was there any evidence of respiratory depression or hypotension. It was felt the diazepam significantly modified the toxic effects of fenfluramine, possibly by direct antagonism, and it may well be responsible for their survival.

Forced diuresis with acidification was not used for either child. Theoretically, it may assist excretion

of the drug, and Beckett and Brookes (1967) have shown that excretion in the urine of fenfluramine and its metabolites is increased by reduction of the urinary pH to less than 5. However, the extra quantities excreted appear to be too small to justify the complications of this form of therapy in small children.

Summary

Two preschool children with severe intoxication with fenfluramine are reported. Their symptoms were suggestive of those observed with atropine poisoning but with extra-pyramidal features similar to those found with phenothiazine reactions. Both children were treated with large doses of intravenous diazepam (45 mg and 30 mg) and made a full recovery.

I am grateful to Professor I. C. S. Normand for his advice and permission to report Case 2; to Dr. D. A. J. Williamson for Case 1; and to Mr. D. B. Campbell, Servier Laboratories, for the analysis and the Fig. which has been modified to include both children.

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