A Fatal Reaction to Thioproperazine

Thioproperazine methanesulphonate ("majeptil") is a recently introduced phenothiazine derivative for the treatment of schizophrenia and mania. It has a weaker anti-adrenaline and parasympatholytic activity than chlorpromazine but is a very powerful antiemetic.

Its numerous side-effects have been reported by Denham and Carrick (1961) in a clinical trial of this drug in the treatment of chronic schizophrenia. These resemble many of the symptoms of epidemic encephalitis. There is an akinetic state of extreme lethargy, sometimes with inversion of the sleep rhythm, an akinetohypertonic condition which resembles parkinsonism, and a hyperkinetohypertonic state in which the patient is extremely restless in spite of muscle hypertonia. The neurological disturbances include cogwheel rigidity, myoclonus, choreiform movements, athetosis, catalepsy, and attacks of sudorhoea. Among other complications, they had three cases of hypostatic pneumonia in their series of 60 patients. These three patients were young healthy males and it was thought the pneumonia was secondary to the akinetic state induced by the drug.

Some workers believe there is a positive correlation between these side-effects and clinical improvement (Delay *et al.*, 1959; Denham and Carrick, 1961); others deny this (Perrin *et al.*, 1958). Therefore the former group give the drug in a short high-dosage course. Denham and Carrick recommend an oral dose of up to 50 mg. t.d.s. Coirault *et al.* (1959) give up to 30 mg. intramuscularly daily. The latter group give a smaller continuous-dosage schedule, starting with 5 mg. t.d.s. and working up to 20 mg. t.d.s.

There have been a few fatalities in severely subnormal patients on a high-dosage schedule over several days, but this is the first report of a death resulting from a single injection of thioproperazine in the relatively low dose of 7.5 mg. (one ampoule) intramuscularly.

CASE HISTORY

A single man aged 21 was admitted to St. Ebba's Hospital in November, 1954, suffering from schizophrenia. There was no family history of psychiatric illness and the patient had suffered no serious physical illnesses. He came of a settled home background. He went to a secondary school where he was below average, only reaching standard four. He then worked for seven years in a factory until his admission to hospital. He had been shy and retiring, and had no relations with the opposite sex.

He was a restless, deluded, hallucinated patient who was almost inaccessible and was subject to periods of mutism and retardation. In 1955 he underwent a full endocrine investigation and his 17-ketosteroid urinary excretion averaged 14 mg. per 24 hours. Iodine tracer tests showed normal thyroid function. He had a course of 40 deep insulin comas at the end of 1955 without improvement. There were no complications during this treatment. In 1957 he was given reserpine. He had hypotensive and myotonic symptoms with 5 mg. intramuscularly but tolerated half this dosage for a month without any severe reaction. He developed signs of parkinsonism towards the end of the course. He received thioridazine hydrochloride ("melleril"), 50 mg. t.d.s. in 1960 and perphenazine ("fentazin"), 2 mg. t.d.s. in 1961. In each case he had an epileptic fit but no other major complications.

After a course of seven E.C.T.s failed to control an episode of excitement in July, 1961, it was decided to try

thioproperazine. He was given an intramuscular injection of 7.5 mg. at 8.30 a.m. on July 21. He developed spasms of the neck muscles an hour later and these were controlled with 5 ml. of intramuscular paraldehyde. The spasms recurred at 1.30 p.m., 5.15 p.m., and 8.15 p.m. the same day and at 3 a.m. the next day. On each occasion they were controlled with a further injection of 5 ml. of paraldehyde. He remained restless and overactive, and showed no other side-effects attributable to the drug. However, he suddenly collapsed at 6.45 a.m. on July 22, became very cyanosed, and died five minutes later.

Necropsy Findings.—The deceased was of poor physique, with a moderate degree of generalized muscular wasting, characteristic in cases of active schizophrenia. There was a persistent thymus gland, measuring $1\frac{1}{2}$ by $\frac{1}{4}$ in. (3.8 by 1.9 cm.). There was a little endocardial fibrosis of the interventricular septum.

The most remarkable feature of the necropsy was a complete collapse of the entire posterior wall of both lungs to a depth of $\frac{1}{4}$ in. (6 mm.). Anterior to the collapsed zone the lungs showed an increasing degree of aeration as far as the anterior surface, where, however, some collapse was present. The lungs were reduced to less than a quarter of their normal size. The trachea and main bronchi were free from secretions but the bronchioles in the collapsed areas were filled with mucus. Histology of the lungs merely confirmed the gross morbid anatomical appearances. Microscopy showed several areas of focal fibrosis in the myocardium but no recent activity. Routine examination of the other tissues revealed no pathological changes. Thus the only relevant finding at necropsy was the posterior collapse of the lungs, and its distribution would appear to indicate an almost selective depression of the respiratory centre by thioproperazine.

COMMENT

Fatalities with a single therapeutic dose of a phenothiazine derivative are extraordinarily rare and are usually the result of a hypotensive collapse, mainly in elderly patients. Other fatal complications, such as blood dyscrasias and liver necrosis, generally occur during a course of phenothiazine medication and not after a single administration of the drug.

It appears that thioproperazine can cause a fatal suppression of the respiratory centre in sensitive individuals when given in a moderate dosage. It is possible that the cases of hypostatic pneumonia in Denham and Carrick's trial were also due to sensitivity of the respiratory centre rather than the result of akinesia.

Therefore it is advisable to give a test dose of this drug to a new patient or one known to be unduly susceptible to the side-effects of phenothiazine derivatives.

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