Dystonic Reactions to Phenothiazine Derivatives

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Phenothiazine derivatives are widely used and their toxic effects in adults are well recognized. They include dizziness, mild skin reactions, jaundice, motor restlessness, and occasionally neuromuscular reactions. Dystonia and symptoms resembling parkinsonism usually occur only at high dosages. These are well-recognized complications in mental hospitals when drugs are being used to treat psychotic conditions, but have only been infrequently described in children.

Recently we have encountered 5 cases in which alarming side-reactions have occurred, where the diagnosis of tetanus, encephalitis, or cerebral metastases was considered.

Case Reports

Case 1. A 14-year-old girl, in whom Hodgkin's disease had been diagnosed some 2 years previously, initially presented with respiratory difficulty due to a large mediastinal mass, associated with cervical lymphadenopathy. The diagnosis was confirmed by lymph node biopsy. Treatment with mustine and radiotherapy was successful in producing a remission which persisted for 2 years. She then complained of tiredness and abdominal pain. Hb was 11 g./100 ml., and peripheral blood was normal. There was no lymphadenopathy, hepatomegaly, or splenomegaly, the bone-marrow was normal, but a lymphangiogram showed considerable enlargement of para-aortic nodes, and further treatment with mustine was started. This provoked considerable nausea and she was given prochlorperazine (Stemetil) 12.5 mg. intramuscularly. After three doses (0.62 mg./kg. day) she complained of stiffness of her neck, inability to open her mouth, and stiffness of her arms. She became increasingly frightened and a diagnosis of tetanus, possibly following the incision for her lymphangiogram, was considered. She was given promethazine and the neuromuscular symptoms rapidly disappeared. She continues to be well some 3 years after this episode.

Case 2. A 5½-year-old boy was sent from the Sudan by air as an emergency with the diagnosis of encephalitis. Some 4 days previously he had had an upper respiratory infection with a low-grade fever which had been treated with aspirin and chlorpromazine syrup, 10 mg., 8-hourly.

Next day there was no further vomiting but his mother took him to her doctor with the story that he had put his tongue out and had been unable to retract it, after which his speech had been somewhat slurred. He had four further episodes that night and was admitted to a military hospital and seen by other physicians who noted that this mouth appeared dry, that he had some difficulty in swallowing saliva, and that this was followed by him protruding his tongue and being unable to put it in for episodes which lasted for 3-10 minutes. During these attacks he was unconcerned and free from pain, with no alteration of consciousness. On arrival in this country he appeared to be a normal, fit, healthy boy. There were no abnormal physical signs. All investigations were negative and his electroencephalogram showed no signs of active cerebral illness. It was thought likely that this had been a reaction to chlorpromazine, though he was reputed to have taken only 40 mg. over a period of 48 hours (approximately 1 mg./kg. day). He was challenged with doses of up to 50 mg. while in hospital, but untoward side-effects did not recur. He has been entirely well since this episode.

Case 3. This boy, aged 3½ years, had previously been normal but was bitten by a dog 5 days before admission. He had sustained only superficial skin damage and this had healed well. Earlier in the day he had appeared unwell, and it was noticed that he was dribbling from his mouth. He then developed shaking, tremulous movements of all four limbs and was unable to stand. He was found to have increased muscle tone and was admitted with a possible diagnosis of tetanus. He was noticed to stare vacantly, and then began having attacks in which his face twisted towards the left, he dribbled and had constant clonic movements of both arms. The attacks lasted 2-3 minutes during which he was unable to speak, but he did not appear confused, and consciousness was not lost. After each attack he was irritable and then fell asleep only for the attack to be repeated a few minutes later. His mother was a secretary working for a drug firm and he was looked after by his grandmother during the day. Again all investigations, including an EEG, serum calcium, electrolytes, and erythrocyte sedimentation rate were all normal. It seemed possible that he might have been exposed to drug intoxication, and, on closer questioning his mother searched in her bag for a bottle of 25 fluphenazine tablets which she had been given as a free sample recently, and found that 15 tablets were missing (15 mg.). Her son later admitted to taking

these tablets, and examination of the blood and urine showed high levels of phenothiazine. He was treated with promethazine 25 mg. b.d., and over the next 3 days the tremor and cog-wheel rigidity disappeared. He has remained well.

Case 4. This 7-year-old girl was being treated with radiotherapy for lung metastases from Wilm's tumour. In addition she was given actinomycin D and because this provoked nausea and vomiting, she was also given prochlorperazine. She tolerated doses up to 20 mg. (0.9 mg./kg.) per day, but on one day received up to 42.5 mg. (1.9 mg./kg.). That night she developed an odd staring appearance, her neck became stiff, and she went into opisthotonos. Again there was no loss of consciousness, though she was considerably frightened. It was feared that she might be having convulsions due to cerebral secondaries, but it was later realised that these were toxic effects due to prochlorperazine. The neuromuscular dystonia ceased when the drug was discontinued.

Case 5. This girl, aged 10, received prochlorperazine in a dose of 10 mg. t.d.s. (0.8 mg./kg. day) to control vomiting, during a course of irradiation for a cerebral tumour in the region of the pituitary. Vomiting was controlled, but she became very sleepy. It was thought that this might be an effect either of the irradiation or of the drug, which was nevertheless continued for 15 days. The dose was then increased in error to 10 mg. q.d.s. (1.2 mg./kg. day). After a further 3½ days, she developed a violent tremor affecting mainly the arms, with cog-wheel rigidity, a mask-like facies, drooling, and a shuffling gait. Consciousness was fully maintained. Intravenous injection of 10 mg. promethazine caused a dramatic relief of symptoms, which persisted though much diminished for a further week after stopping prochlorperazine.

Discussion

Three of our cases were girls receiving treatment for malignant disease, and either the therapy or the initial illness may have rendered them more sensitive to prochlorperazine. Individual susceptibility is thought to be higher in females (Ayd, 1961). Again Hunter, Earl, and Thorncroft (1964) showed that cerebral damage might predispose to a permanent hyperkinetic dystonic syndrome when phenothiazine derivatives were given, but so far this has only been described in elderly women patients. None of our cases suffered any permanent sequelae.

There are now many case reports concerning neurological side-effects from the use of prochlorperazine and other phenothiazines. We have reviewed a number of reports involving children and have calculated the daily dosage on the basis of expected body-weight for age when the weight itself was not quoted, and have assessed a rectally

administered dose as half an oral or intramuscular dose. On this basis the daily dose/kg. body weight has varied between 0.33 and 2.6 mg. with an average dose of 0.95 mg. (prochlorperazine), in 20 cases. There were two exceptional cases, one with infective hepatitis who developed symptoms after 0.06 mg./kg. a few hours later, and another who accidentally took 3.63 mg./kg. Symptoms included attacks of dystonia (affecting in order of frequency, the neck and back muscles, jaws and face, eyes, or limbs); lethargy; tremor; dysphagia. The children's ages ranged from 15 months to 16 years. 10 were boys, 7 were girls, and sex was not stated in the remainder. In 18 the drug was prochlorperazine and in one each chlorpromazine (Shaw, Dermott, Lee, and Burbridge, 1959) and fluphenazine (Chamberlin and Tremblay, 1965). In all, the symptoms came on within 48 hours of starting the drug. Persistent intoxication was reported by Malkin (1965) in a psychotic child who suffered recurrent spasms of the jaw muscles while under treatment with phenothiazines, mainly chlorpromazine. The symptoms recurred repeatedly for a year before the diagnosis was eventually made. Dystonic attacks are generally associated with demonstrable anxiety, which is hardly surprising.

The paediatric use of phenothiazine derivatives in Germany was reviewed by Dietel and Köditz (1963). In that country they are used for premedication for painful or anxiety-producing procedures, for functional disorders, such as cyclical vomiting, for vomiting in infancy after the exclusion of serious causes, and for the medical treatment of congenital hypertrophic pyloric stenosis; they are also recommended in children with acute bronchiolitis, hyperpyrexia, burns, meningoencephalitis, and tetanus. American papers give the impression that these drugs are also used widely, not only in the treatment of behaviour disorders and psychosis in childhood (e.g. Bender and Faretra, 1961) but also for the symptomatic control of vomiting, where their use has been assessed by Daeschner, Matthes, and Daeschner (1958), and side-effects have been discussed by Shaw *et al.* (1959) and by Cohlan (1960). Non-psychiatric use of these drugs appears to be less widespread in this country, which may result in failure to recognize the alarming effects that may occur.

In the paediatric age-group phenothiazine toxicity is low at a dosage (chlorpromazine) of 2-8 mg./kg. orally or intramuscularly per day, and rectally at twice this dose (Dietel and Köditz, 1963). The potency and toxicity of prochlorperazine may be taken to be 3-5 times that of chlorpromazine (Ayd, 1961). Daeschner *et al.* (1958), Bender and Faretra

(1961), and Cares and Buckman (1963) found drowsiness but no serious side-effects at dosages of (prochlorperazine) up to approximately 2 mg./kg. day. Extrapyramidal signs which developed with larger doses or in particularly sensitive children were usually readily controlled. Ayd (1961) however, found that in a large series, with ages ranging from 4 to 88 years, children under the age of 16 had the severest and most bizarre neuromuscular symptoms. The dosage of the phenothiazines used was unfortunately not stated, but was probably high as the patients suffered from psychiatric disorders.

Side-effects may occur early and after a single small dose, and have been considered to be independent of the dose or duration of medication (Cares and Buckman, 1961). In our experience, all reactions began within 48 hours of starting the drug, but in Case 5 within 48 hours of increasing the dosage. Individual susceptibility may vary, but dosage is nevertheless important. Most patients will tolerate these drugs without serious reaction when the dosage is kept to the minimum effective level. We have found only two children who developed serious side-effects on a lower dosage than the 0.5 mg./kg. day recommended by the manufacturers. Liver disease or diffuse cerebral disorder makes additional caution necessary.

In children the reactions have so far all been fully reversible. They are sufficiently alarming and distressing to require immediate treatment and, curiously, cerebral depressant and stimulant drugs can both act as antidotes. The following drugs have been used: barbiturates (sodium phenobarbitone, pentobarbitone, and amylobarbitone); antihistaminics (promethazine, diphenhydramine); caffeine; antiparkinsonian drugs (benztropine methane sulphonate 'Cogentin', biperiden 'Akineton'). The speed of response was most gratifying following intravenous promethazine in Case 5.

Summary

Five cases of alarming dystonic reactions to phenothiazine drugs are reported. Although this clinical picture is well recognized in adults receiving

high dosage, it may occur in children on comparatively modest doses. The symptomatology may mimic tetanus, encephalitis, or chorea. Twenty cases are reviewed from the published material.

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