PHENOTHIAZINE TOXICITY, EXTRAPYRAMIDAL SEIZURES, AND OCULOGYRIC CRISES

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Introduction

Prochlorperazine (Compazine, Stemetil) and chlorpromazine (Thorazine, Largactil) frequently produce tremor and rigidity. Less well known are the severe tonic spasms of the muscles of the head and neck which can result from these phenothiazine derivatives. This paper directs attention to these spasms and their similarity with "extrapyramidal seizures" and oculogyric crises.

Tonic Seizures from Phenothiazine Derivatives

Kulenkrampff and Tarnow (15) were among the first to report patients with paroxysmal tonic phenomena from phenothiazine derivatives. The patients had an intermittent sensation that the tongue was about to protrude and noted tight muscles in the neck and throat. It was necessary to discontinue chlorpromazine because of this "oral syndrome".

Freyhan (8, 9) and others (Christian, 2; Delay, 3) have described patients who developed hypertonic muscles in the neck from prochlorperazine. Some of the patients had waves of generalized rigidity, bizarre postures of the head and neck, and anxiety. Two patients who had received perphenazine (Trilafon) were almost catatonic with a type of generalized "waxy flexibility", and had their necks flexed backward as though in spasm (Berry, 1). Muscle pain, hallucinations and headache have occurred in some patients.

Vertical deviation of gaze has been seen in several of these patients who had spasmodic hypertonus in the muscles of the shoulders and neck. Chlorpromazine has been previously reported to produce deviations of gaze indistinguishable from oculogyric crises.

The incidence of severe tonic reactions due to phenothiazines is unknown. Freyhan (9) records severe dyskinesia in eleven out of sixty-seven patients with extrapyramidal symptoms from prochlorperazine. The severe paroxysmal hypertonus probably is caused more often by prochlorperazine than chlorpromazine. This may be related to the high incidence, as great as 50 per cent. (Freyhan, 9; Holman, 12), of extrapyramidal side-effects with prochlorperazine therapy.

Younger patients seem more susceptible to the extreme tonic seizures caused by the phenothiazine derivatives.

The duration of the severe tonic effect from phenothiazine derivatives has been variable, but most patients are markedly improved one or two days after the drug is stopped (Durn, 5).

Extrapyramidal Seizures

There have been occasional reports of seizures which seemed to arise from subcortical structures. Some of the terms suggested for these seizures have included "subcortical epilepsy" (Spiller, 21), "extrapyramidal epilepsy" (Sterling, 22), or "striatal epilepsy" (Wimmer, 26). These seizures usually consisted of spasmodic hypertonia of the muscles of the limbs or of the head and neck. Autonomic symptoms or unconsciousness have occurred. Several of the patients with extrapyramidal seizures had encephalitis lethargica. Wimmer states that "during the rather monotonous progression of the generalized Parkinsonian rigidity and akinesia paroxysmal tonic syndromes may now and again occur".

Recently Matthews (18) discussed four patients with tonic seizures and disseminated sclerosis. During the tonic seizures the posture of the limbs closely resembled tetany, and there was severe pain in the affected limbs. The seizures were of rapid onset, brief duration and great frequency. There is little exact pathologic evidence in these or other cases of tonic seizures, although in some reports mentioned by Matthews, lesions were present in the subthalamic area.

Oculogyric Crises

Seizures from extrapyramidal structures are admittedly atypical, and their actual existence has been questioned. Oculogyric crises on the other hand have been well described and are familiar to most clinicians. The term oculogyric crises describes a group of spasmodic eye deviations which are most often directed vertically, and which last for minutes or hours.

The extensive review by Jelliffe (13) records many patients with oculogyric crises who also had paroxysmal anxiety or a sense of impending doom, tachycardia, crying spells, headaches, and compulsive thoughts with or without hallucinations. Lemos (16) described associated masticatory and glossopalatolaryngeal spasms and spasms of the arms. F. B. Walsh (24) states that in oculogyric crises "the head is usually thrown back and not infrequently the mouth is held open and the tongue may protrude". McCowan and Cook (19) say that "the crises are in the nature of tonic seizures and need not be confined to the eye muscles, a more or less co-ordinated spread to the muscles of the head and neck being not uncommon". Many patients with oculogyric crises have had increased tone in the muscles of the head and neck, generalized hypertonus or axial torsion.

There have been infrequent reports of oculogyric crises associated with brain tumours, manganese poisoning and other diseases, but oculogyric crises have been considered almost pathognomonic of encephalitis lethargica (Duke-Elder, 4). The crises are more likely to occur in youthful patients with encephalitis than in the older ones.

The pathologic changes in patients with oculogyric crises are similar to those in other patients with encephalitis lethargica. Various authors have emphasized the lesions in the basal ganglia, including those in the corpus striatum and subthalamus. McCowan and Cook (19) stated that the lesion "lies in associational mechanisms situated above the four supranuclear centres subserving conjugate movements", but no more specific localization was possible.

The physiologic aetiologies which have been proposed have included paroxysmal vasomotor changes, relaxation of cortical inhibition, or irritation of the oculomotor centres. No one physiologic or pathologic basis for oculogyric crises has been generally accepted.

Precipitating factors for individual crises include fatigue or psychic trauma, and suggestion can either precipitate or abort an attack.

Treatment

Lowering the dose of phenothiazines or the use of anti-Parkinsonian drugs usually has been sufficient treatment for the mild Parkinsonism due to the phenothiazine derivatives. In fact, the extrapyramidal side-effects have been called a guide to adequate dosage (Goldman, 10; Holman, 12), and therapy of the mild tremor and rigidity is often unnecessary. On the other hand, treatment of the acute severe motility disturbances caused by phenothiazines may be difficult, especially if suspicion of hysteria or central nervous system injury obscures the correct diagnosis.

There are few leads to treatment of the tonic seizures due to phenothiazines that can be found in the reports of extrapyramidal seizures or oculogyric crises. Treatment of the scattered cases of extrapyramidal seizures has been indefinite and unsatisfying. Treatment of oculogyric crises has also been disappointing. Hyoscine or other belladonna derivatives, amyl nitrate, and the newer anti-Parkinsonian drugs have been only moderately successful. Klemme's (14) operative removal of the premotor cortex at the junction of the first and second frontal convolutions has been only occasionally done. Chemopallidectomy may prove to offer significant amelioration of the crisis.

The frequency and severity of oculogyric crises may be lessened by rest and a bland environment. Lying down shortens the crises for some patients and oculogyric crises disappear during sleep.

Adrenaline and caffeine are reported to decrease the severe motility disturbances due to phenothiazines, but there is no explanation of their beneficial effect (Durn, 5; Freyhan, 9). The use of amobarbital sodium (amylobarbitone, Amytal) to induce sleep was effective in one patient with tonic seizures from prochlorperazine (Christian, 2). Amytal previously had been reported to mitigate somewhat the autonomic seizures of a patient who had encephalitis lethargica (Ostow, 20).

Comments

The sequelae of encephalitis lethargica include many muscular, psychic and autonomic responses; and most of the neurologic complications from phenothiazines are within the range of post encephalitic Parkinsonism. Although the tonic seizures from phenothiazines are only one more of the extrapyramidal complications of these drugs, their occasional severity and their resemblance to the disputed extrapyramidal seizures and to oculogyric crises makes these tonic phenomena of special interest. Furthermore, observation of the neurological effects of phenothiazines may elucidate features of post-encephalitic Parkinsonism, just as the appearance of encephalitis lethargica directed attention to subcortical neurophysiology.

The pharmacological data on the phenothiazines do not yet explain the production of Parkinsonism by these drugs. Monkeys which are given chlorpromazine can have signs of toxicity which are similar to those in man. Essig and Carter (6), using doses of chlorpromazine as high as 77 mg./kg. reported bizarre searching behaviour suggestive of hallucinations. In two of the monkeys prominent movements of the head and eyes resembling oculogyric crises and retrocollic spasms were observed.

The primary locus of the central nervous system action of phenothiazines is not entirely clear. A recent article by Vogt (23) reviews evidence of an effect of chlorpromazine on the reticular system in particular, but also an effect on the limbic system and posterior hypothalamus. Though studies of the localization of chlorpromazine are being done with radioactive isotopes, the results are not yet available (Durn, 5).

The extrapyramidal symptoms caused by encephalitis lethargica are sometimes attributed to overactivity of cortical areas in the absence of adequate suppressor or modifying effects by the diseased basal ganglia. Decrease in inhibitory influences on fibre tracts, or "release" phenomena, are among the suggested pathophysiologic bases of post-encephalitic Parkinsonism. The fact that phenothiazines can reproduce these extrapyramidal symptoms does not necessarily imply that these tranquillizers actually exert their effect through a reduction of inhibitory influence on cortical fibre tracts. If this were true, then the "arousal" response on EEG, which Wilson and Glotfelty (25) have shown to be blocked by some phenothiazine derivatives, might appear to represent a reflection of inhibitory activity. The local effects of phenothiazines are probably numerous, and the end result of these effects may vary in different parts of the brain.

The permanent effects of the phenothiazine derivatives on the human brain are unknown. The fact that the neurological signs of the phenothiazine toxicity are transient suggests, but does not prove, that these drugs do not cause permanent local lesions. There are other drugs which have been reported to injure specific areas of the brain. For example, Hoffman (11) found marked loss of Purkinje cells in the cerebellum of a patient who received parenteral diphenylhydantoin phenytoin (Dilantin) for severe epileptic convulsions. The anti-metabolite 3 acetyl-pyridine can selectively destroy neurons in a specific hippocampal area (MacLean, 17). For chlorpromazine itself, Fallik and Treves (7) describe a patient who developed a left hemiparesis and disturbances of the left V, VII, X and XII cranial nerves after 2355 mg. of chlorpromazine given over a twelve-day period. The patient was well within two weeks after medication was discontinued.

When used in therapeutic doses, the phenothiazines may never permanently injure the central nervous system. Their innocence may, however, be difficult to prove to a patient who develops idiopathic Parkinsonism years after having had identical symptoms as a side-effect of tranquillization.

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