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NEUROLOGIC COMPLICATIONS OF PHENOTHIAZINE THERAPY

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In 1953, chlorpromazine (Thorazine) was introduced in the United States as the first phenothiazine drug to be used as a tranquilizer. This was the beginning of a major break-through in the treatment of mental illness, and since that time literally scores of other phenothiazine drugs have been introduced into the medical field, not only for the management of anxiety and agitation, but also in the treatment of other symptoms e.g. nausea, vomiting and skin conditions associated with pruritus. The influence that phenothiazine drugs and other tranquilizing agents have had on the management of mental illness in the United States is evidenced by the fact that in 1956 the inpatient population in State and Federal Mental Institutions decreased for the first time in history. At the end of 1955, the nation's public mental hospitals had 558,922 resident patients. By the end of 1961, the figure had declined to 527,945. Although other factors contributed to this decline, the phenothiazines are widely acclaimed as the biggest single factor. In that same period prescription sales (not including sales to hospitals) for all tranquilizers doubled from 100 to 200 million dollars. The phenothiazines made up about 50 percent of those sales.[13]

There are many side effects which potentially may occur in the use of phenothiazine therapy. Some of these are well known e.g. jaundice, granulocytopenia, cutaneous eruptions, thrombocytopenia, gastroenteritis (which is an early warning of liver involvement,[3] and hypotension. Although hypotension may occur in any patient, those most likely to react this way will be the alcoholics, or those patients having arteriosclerosis or heart disease[9]. Also parenteral chlorpromazine seems to be indicated more than the other phenothiazines. The less well known side effects of this group of drugs may cause considerable bewilderment to the physician who sees them for the first time e.g. galactorrhea, photosensitivity, muscle or joint pains, edema of the extremities, hyperpyrexia, depersonalization, toxic psychosis,[2] hairy tongue and neurologic signs. The hairy tongue has been reported to occur on large doses of chlorpromazine and disappeared within 2 weeks after discontinuation of therapy[4]. The neurological signs are the most bewildering and may be grouped into five clinical pictures: dystonia, grand mal convulsions, Parkinsonism, akathisia, and catatonia. These will be discussed in more detail below.

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When phenothiazine drugs were first administered to children it was felt that the pediatric dose would merely be in proportion to that for adults. However, evidence suggests that much greater sensitivity prevails in childhood which is in contradistinction to other drugs where children have a relative tolerance much greater than that for adults e.g. atropine or digitalis. In infants, the extreme sensitivity of phenothiazine drugs appears to be due to the immaturity of the microsome enzyme system in the liver which functions at only a fraction of its adult efficiency. Consequently, the drug cannot be detoxified rapidly for the kidney to excrete.[14] This same enzyme system is responsible for infants having very little tolerance to many other drugs e.g. ephedrine, aspirin, codeine, chloramphenicol and the sulfa drugs. The phenothiazine dosage in children cannot be extrapolated from that which is appropriate for adults or experimental animals. Although chlorpromazine is secreted in the milk of lactating women, it is barely detectable and well below even the pediatric dose for infants.[15] The pediatric dose of chlorpromazine is 0.1 mgm. per pound every four to six hours.

Much has been written about the safe use of chlorpromazine during labor to enhance the effect of analgesics and sedatives thus making a smaller dose required and minimizing the respiratory depression effect of these drugs on the newborn infant. In the material reviewed Chlorpromazine was given in doses of 25 to 150 mgm. during the 24 hours preceding delivery. However, in mothers receiving 500 mg. or more of chlorpromazine per day in the latter part of pregnancy, there was a significant respiratory depression found in the newborn infants.[17]

The above mentioned neurological signs occur in both children and adults. These reactions are usually alarming and surprising to the doctor who sees them for the first time. A number of factors contribute to the uncertainties of the situation:[10] 1. When these drugs were first introduced a wide and generous dosage range was implied. 2. Many children and some adults appear to be extremely sensitive to these agents and some developed complications well within the propitious dosage range. 3. There may be a several hour or even day latency period between the administration of the drug and the appearance of the side effects. 4. Patients with acute central nervous system infections or with severe dehydration appear to be extremely sensitive to phenothiazine drugs. 5. In some cases even after the drug has been discontinued and anti-Parkinson drug therapy has been instituted, there may be a continuation of side effects for a long time. 6. The neurological signs are not limited to any particular phenothiazine and can occur with any phenothiazine preparation.

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The grouping of the neurological signs into the categories of dystonia, convulsions, Parkinsonism, akathisia, and catatonia is made for clinical reasons because usually only one of the group of these signs will occur in a given patient. However, any or all of the neurological signs may be found in a patient receiving any member of the phenothiazine group. The etiology, however, is felt to be similar, that is, the drugs cause either a stimulation of the basal ganglia and reticular formation or a diminishment of the inhibitory impulses to these areas which come from the cortex. There appears to be a positive correlation between the incidence of dystonia, akathisia, and Parkinsonism and the milligram potency of the phenothiazine. Thus the piperazine subgroup represented by Permitil (fluphenazine), Stelazine (trifluoperazine), Trilafon (perphenazine),

Dartal (thiopropazate), and Compazine (prochlorperazine) have a much higher incidence of these neurologic signs than do the aliphatic subgroup represented by Vesprin (trifluprom azine), Thorazine (chlorpromazine), Tentone (methoxypromazine), and Sparine (promazine). However, the latter group has a higher incidence of convulsions, sedation, autonomic side effects, dermatitis, jaundice, and agranulocytosis.[18]

Some of the dystonic signs are referred to as "pseudotetanus".[10] This includes trismus, difficulty in swallowing, and spasmodic movements of the face, palate, neck and extremities. Occasionally, there is only involuntary spasms of the neck muscles, often unilateral. This may become violent, severe and involve all of the neck muscles. Other signs are: Spasm of the masseters, involuntary movement of the pharyngeal musculature, salivation which may be excessive, loud involuntary shrieks which may resemble the barking of a dog, and extensor spasm of the upper or all four extremities. At times the above signs are so sudden and dramatic in onset that they can be mistaken for an epileptic seizure. One case was reported in which dystonic signs occurred 20 hours after a single injection of fluphenazine (Prolixin or Permitil).[5] Cyanosis due to respiratory distress, protrusion of the tongue, inability to focus the eyes, fixation of the eyes to one side or upwards (oculogyric crisis), or opisthotonos may also occur as additional dystonic signs.[12] The onset of dystonic signs may vary from two hours to as long as six days after the institution of phenothiazine therapy. In fact, 90 percent of the cases of dystonia resulting from phenothiazines had their onset within the first 4½ days after the drug was started.[18] Signs have persisted up to 48 hours after the drug was discontinued.[7] The length of these attacks may vary from a few seconds to one hour.

As mentioned above a grand mal convulsion may be the only manifestation of a phenothiazine idiosyncrasy. With the dystonic signs there is no loss of consciousness, but when a typical grand mal convulsion occurs there will also be unconsciousness. At these times the EEG will show a typical tracing of a seizure pattern. However, there may be some dystonic signs resembling a convulsion with consciousness retained. The EEG then does not show the high voltage spiking of a seizure pattern. The usual EEG pattern in a person taking therapeutic doses of phenothiazine is variable, but usually in the normal (Alpha) range of frequency. However, there may be slower frequencies (Theta) found in the frontal and temporal areas that are similar to tracings found in focal lesions. When toxic doses are given the EEG pattern is one of very low frequency (Delta). The EEG obtained while the patient is having dystonic signs, however, does not show low frequency. This suggests that the dystonic reaction is more of a drug idiosyncrasy than a drug intoxication.

One might ask if abrupt withdrawal of high phenothiazine doses causes convulsions. In my experience I have never seen this. Two articles report other withdrawal manifestations but no seizures. In one study[19] 17 out of 28 patients suffered a moderate withdrawal reaction similar to that noted after opiate withdrawal (tenseness, myalgia, cold sweats, insomnia, nausea, and vomiting) beginning two to five days after withdrawal. However, the patients were given a placebo substitute which was interpreted by both patients and staff as a very powerful and dangerous drug with serious side effects. In another study[20] in which no placebo was substituted, over

500 patients were abruptly withdrawn. The most severe symptoms reported were malaise, insomnia, and diaphoresis.

The Parkinson-like syndrome is the most commonly observed neurological side effect of phenothiazine therapy. In descending frequency the initial Parkinsonian sign is: Cogwheel rigidity of the limbs, loss of associated movements, facial rigidity, skin changes (an oily or waxy texture), gait disturbances, drooling, and poverty of movement. The cogwheel rigidity of the limbs, however, usually is mild, but the loss of associated movements may become very severe if therapy is continued. It is felt that the loss of associated movement is a rather sensitive indicator of the onset of Parkinsonian signs as a result of the phenothiazine therapy and thus is a good subtle clinical sign.[11] Ninety percent of patients who develop Parkinsonism on these drugs will manifest it within the first 72 days of therapy.[18] The duration of signs beyond cessation of therapy would, in a great majority of cases, end within a month. However, some of the signs persist as long as three months after therapy is discontinued. One interesting report[6] claims that of 83 patients who developed Parkinsonian signs on phenothiazine therapy and were concurrently treated with an anti-Parkinson drug, only 17 of these patients had a recurrence of Parkinson signs when the anti-Parkinson drug was discontinued and while the high dose of a phenothiazine was maintained. This would suggest that the Parkinson picture was a transient side effect of phenothiazine therapy.

Another neurological sign which is usually found singularly is akathisia. It is a paradoxical effect of phenothiazine therapy i.e. it seems to make the patient more anxious than he was before therapy began. It is felt to be an unusual manifestation of the Parkinsonian syndrome.[13] Many subjects will complain paradoxically that they cannot sit still or do so only with an effort. They must get up, or move about, or shift the position of their limbs, inactivity having become unbearable. If akathisia is mild, patients complain of a feeling of inner unrest of pulling or drawing sensation in the extremities, but chiefly in the legs. Just as in Parkinsonism, ninety percent of the patients who developed akathisia did so within the first 73 days of therapy.[18] Once akathisia has fully developed, patients pace back and forth and they can neither sit down to read nor play nor sleep. In severe cases, patients appear continuously agitated. In one study[1] when akathisia was found to occur in a patient another potent phenothiazine drug was substituted in which akathisia did not develop.

The fifth neurological side effect that is seen clinically is catatonia. This catatonic-like state may indeed mimic schizophrenia, that is, they may manifest waxy flexibility (catalepsy), decreased motor activity, moderate negativism, tremor, and stereotypy, which means the persistent repetition of senseless acts or words. Although one cannot exclude the possibility that patients with this reaction are basically schizophrenic, the fact that the episodes develop while under phenothiazine medication and disappear following withdrawal of the drug indicated definite participation of the phenothiazine in the symptoms.[8]

The treatment of any of the above neurologic side effects consists of discontinuing the drug immediately if the signs are moderate or severe. If only mild signs occur, an explanation to the patient and the addition of an anti-Parkinson drug usually is

sufficient. The use of caffeine sodium benzoate, 500 mgm. intramuscularly or intravenously, or the use of Benedryl, 10 to 50 mgm. IM or IV, are reported to give dramatic relief from the dystonic reactions. The significance of recognizing these complications of phenothiazine therapy is twofold. One, the psychological effects can be very disrupting to the patient if he is not reassured as to the cause of his distress. The second significance is that the signs may mimic hysteria, epilepsy, bulbar polio, encephalitis (particularly the Von Economo type), catatonic schizophrenia, or tetanus. If the true etiology is not recognized, therapy can be a definite hazard to the patient. In the literature that was reviewed it was noted that there was no positive correlation between neurologic signs and liver dysfunction. Also there was only a weak and equivocal association of neurologic side effects with psychiatric improvement. This then would give less support to the opinions held by some psychiatrists that there is greater psychiatric improvement in those patients developing neurologic side effects while on phenothiazine therapy.

In conclusion, it is hoped that the physician will recognize the relationship between the use of phenothiazine drugs and the unusual and even bizarre side effects that they may produce. By broadening our clinical horizons the doctor-patient relationship is improved and both will benefit from the added knowledge.

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