Chlorpromazine* in the Control of Side Effects of Para-Aminosalicylic Acid Administration

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Courses of antituberculous chemotherapy are more prolonged than ever, and the problem of the unpleasant side effects of the administration of para-aminosalicylic acid (PAS) harasses both patient and physician for longer periods of time. Clinicians who manage tuberculosis are quite familiar with the difficulties entailed in keeping an appreciable number of their patients on an uninterrupted, prolonged course of para-aminosalicylic acid. In my experience, at least 25 per cent of patients receiving this antituberculous drug develop anorexia, epigastric distress, nausea, vomiting, abdominal cramps, or diarrhea. Quite an appreciable number discontinue the medication on their own or have it discontinued by the physician because of these symptoms. Many others who continue the drug despite these unpleasant symptoms, have the extra burden of side effects added to the already heavy burden of tuberculosis, with its physical, social, economic and emotional difficulties.

The physician is faced with the problem of finding either a form of the drug that will be tolerated or an adjuvant that will help control the unpleasant symptoms. Among the variations of the drug used are buffered tablets, granules, coated tablets, and salts of the acid. Recently, potassium para-aminosalicylate has been recommended for use in place of other para-aminosalicylic acid preparations, as carrying a high degree of patient tolerance and acceptance. Many different medicaments have been employed as adjuvants with varied degrees of success in an attempt to control the unpleasant side effects. Among them are the antacids, tincture of belladonna, other antispasmodics, camphorated tincture of opium, and dramamine. The effectiveness of chlorpromazine in the control of drug induced nausea and vomiting is well known. It is the purpose of this paper to present the results of the use of this versatile drug in the control of side-effects of oral administration of para-aminosalicylic acid in the treatment of pulmonary tuberculosis.

Material

A total of 91 patients (87 males and four females) who experienced side effects attributable to para-aminosalicylic acid during courses of chemotherapy, and were treated with chlorpromazine are included in this study. They ranged from 21 to 63 years of age, with an average of 39. Both hospitalized and ambulatory patients are included. Those hospitalized were

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treated by the staff of two private pulmonary disease hospitals. The ambulatory cases were treated by the Veterans Administration Regional Office in San Juan, Puerto Rico and by private physicians. All included in this report were receiving buffered PAS tablets orally in doses of 12 Gm. daily. All complained of symptoms attributable to PAS. These symptoms are listed in Table I in descending order of occurrence. Many had more than one of these complaints. Patients who received medications other than antituberculous chemotherapy and chlorpromazine during the period of this study are not included in this report.

### Table I

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric burning</td>
<td>56</td>
</tr>
<tr>
<td>Anorexia</td>
<td>48</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>20</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>2</td>
</tr>
<tr>
<td>Epigastric fullness</td>
<td>2</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2</td>
</tr>
<tr>
<td>Itching, generalized</td>
<td>1</td>
</tr>
</tbody>
</table>

**Method**

When a patient receiving para-aminosalicylic acid developed symptoms of intolerance, the drug was discontinued for three to seven days. If symptoms improved or disappeared, PAS in full dose was resumed. If symptoms recurred upon resuming PAS, chlorpromazine was given orally in tablet form in doses of 25 mg. three times daily. This "PAS withdrawal" was carried out in 58 of the 91 patients. In the remaining 33, chlorpromazine was administered after the patient had had symptoms of PAS intolerance for several days, without going through the "PAS withdrawal period." In the beginning, both drugs were given simultaneously, but later, chlorpromazine was administered about one hour before each dose of para-aminosalicylic acid. The dose of chlorpromazine was adjusted according to the patient's clinical picture. A placebo tablet, identical in appearance to the commercially available "Thorazine" tablets, was used in carrying out multiple substitutions without the patients' knowledge. These substitutions were carried out in 67 of the 91 patients. Administration of the drug was continued for periods ranging from two weeks to four months. The placebo was used to determine whether discontinuation of chlorpromazine would be accompanied by a return of symptoms of PAS intolerance.
Results

The effective dose was found to be 25 mg. three times daily in 87 cases, 50 mg. three times daily in one, and 10 mg. three times daily in the remaining three. There was complete disappearance of symptoms of PAS intolerance in 64 (70.3 per cent), partial relief of symptoms in three (3.3 per cent) and no relief in the remaining 24 (26.4 per cent). In this latter group, para-aminosalicylic acid had to be discontinued either by the physician or by the patient himself. The one who complained of generalized itching experienced complete relief. Chlorpromazine gave either partial or complete relief of symptoms of PAS intolerance in one to six days. The majority of cases reported complete relief within three days.

Side Effects of Chlorpromazine

The only side effects attributable to chlorpromazine were drowsiness (18 cases), dizziness on standing (two cases, one of them hypertensive), vague feeling of dizziness or “light-headedness” (three cases), and terrifying nightmares (two cases). If a patient complained of drowsiness, the dose of the drug was either reduced or continued at the same level and it was explained that within a few days he would be able to tolerate the drug. In four to five days, drowsiness disappeared. In those cases in which the dosage had been reduced and it was felt that the higher dose was needed, the latter was resumed without recurrence of drowsiness. In only one (female) did the drug have to be discontinued because of sleepiness that occurred even on 10 mg. once daily. The two who complained of dizziness on standing were controlled by reducing the dose of chlorpromazine to 25 mg. twice daily. The “light-headedness” of which three complained disappeared spontaneously without change in drug dosage. In the two who had nightmares chlorpromazine was discontinued entirely. One of them had nightmares even after the drug had been discontinued for one week and the placebo administered instead. He refused further medication.

Discussion

It is well known that many patients who develop symptoms which may be described as side effects of para-aminosalicylic acid are able to tolerate the drug after having been reassured by their physicians. This applies particularly to gastrointestinal symptoms. The reassurance may aid in relieving the tensions and anxieties which are so common in the tuberculous. Moyer and others\(^5\) reported good results with the use of chlorpromazine in ambulatory psychiatric cases who had tension and anxiety states. Winkelman\(^6\) also reported good response to chlorpromazine in these cases. Without doubt, the mood ameliorating properties of chlorpromazine account in great measure for the relief experienced by many patients in this study. In quite a few instances they reported a sense of well-being. This particular property of chlorpromazine may well have accounted for the relief of itching in those who had this complaint.

Anorexia was a particularly troublesome complaint in this group. Patients’
concern over the fact that they were not eating made matters worse. There was rapid increase in appetite once chlorpromazine was begun. Moyer and others have reported striking stimulation of appetite by chlorpromazine to such an extent that this was utilized as a method of increasing weight. Diarrhea due to PAS was a common complaint among our patients, but subsided rapidly with chlorpromazine. Constipation is the most frequent gastrointestinal disturbance produced by this latter drug, and has been listed as a sign of the effect of the drug on the autonomic nervous system. In patients with diarrhea, this effect is of definite benefit. Paradoxically, of four patients who complained of constipation apparently due to PAS, three were relieved upon administration of chlorpromazine. This may have its explanation in relief of tension and anxiety. Nausea and vomiting were relieved promptly, as were the other gastrointestinal manifestations of PAS intolerance listed. Regardless of the mechanisms involved, the impressive fact is the prompt relief of unpleasant symptoms.

Chlorpromazine was not administered parenterally. Many were receiving streptomycin intramuscularly two or more times a week, and it was not considered either wise or necessary to add more injections to their treatment. The oral route of administration proved effective.

Placebo tablets were used for multiple substitutions to eliminate as completely as possible the psychogenic effect of this extra added medication as an important factor in the results obtained. In many instances we were able to reproduce or relieve at will the manifestations of intolerance to para-aminosalicylic acid. The placebo was used also to determine whether the patient would continue to tolerate PAS without adjuvants thereafter.

In the majority of cases, it was necessary to continue chlorpromazine for two to six weeks. Others had to continue up to four months. In the doses used, there were practically no side effects of chlorpromazine that were not easily controlled by reducing dosage temporarily. In most cases, once tolerance to the drug was developed, we were able to resume its administration at a higher dosage. Judging from this study it would seem advisable to start on 25 mg. of chlorpromazine orally when symptoms of PAS intolerance develop. This amount is high enough to bring about rapid relief of symptoms and low enough to cause little difficulty. The patient should be informed of the possibility of drowsiness and assured that this will disappear once he develops tolerance. Once an aversion to PAS develops, it may be difficult to convince him to take it regularly over long periods of time. This is why the slightly high initial dose of chlorpromazine is recommended. Thereafter the dose has to be adjusted according to the clinical picture.

SUMMARY

1. A group of 91 patients who had developed unpleasant side effects (mostly gastrointestinal) attributable to para-aminosalicylic acid (PAS) during courses of antituberculous chemotherapy, were treated with chlorpromazine orally. This latter drug was administered in doses of 25 mg. three times a day for two to six weeks in most cases.
CHLORPROMAZINE IN CONTROL OF SIDE EFFECTS

2. There was complete relief of symptoms in 70.3 per cent of patients, partial relief in 3.3 per cent, and no relief in 26.4 per cent. Subsidence of symptoms was brought about in one to six days.

3. In the doses used, side effects of chlorpromazine were few and not troublesome. Drowsiness occurred in 19.7 per cent, dizziness on standing in 2.2 per cent, vague feeling of dizziness or "light-headedness" in 3.3 per cent, and terrifying nightmares in 2.2 per cent. In all cases, except two with nightmares, symptoms were controlled by reducing the dosage of chlorpromazine.

4. Oral administration of chlorpromazine is an effective method in the control of most unpleasant side effects of para-aminosalicylic acid.

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RESUMEN

1. Se trataron con cloropromazina (Largactil) los efectos desagradosables de la mayorìa gastrointestinales, atribuibles al PAS en 91 enfermos de tuberculosis, dándose la cloropromazina por vía oral. Esta droga fue usada a la dosis de 25 mg. tres veces al día por seis semanas en la mayoría de los casos.

2. Hubo alivio completo de los síntomas en 70.3 por ciento de los enfermos; alivio parcial en 3.3 por ciento y ningún alivio en 26.4 por ciento. El alivio de los síntomas se obtuvo en uno a seis días aproximadamente.

3. A las dosis usadas los efectos de la cloropromazina fueron pocos y no molestos. Somnolencia 19.7 por ciento, mareo al estar de pie en 2.2 por ciento, vaga sensación de mareo o de ligereza de cabeza en 3.3 por ciento y pesadillas terroríficas en 2.2 por ciento. En todos los casos excepto en dos con pesadillas, los síntomas se dominaron disminuyendo la dosis de cloropromazina.

4. La administración oral de cloropromazina es un método efectivo para el control de los desagradosables efectos colaterales del PAS.

RESUME

1. Un groupe de 91 malades qui furent atteints de manifestations désagréables (pour la plupart gastro-intestinales) imputables à l’acide para-aminosalicylique (PAS) au cours de la chimiothérapie antituberculeuse, furent traités par la "chlorpromazine" par voie buccale. Cette dernière drogue fut administrée dans la plupart des cas aux doses de 25 mg/m. trois fois par jour pendant deux à six semaines.

2. Il y eut un soulagement complet des symptômes chez 70,3% des malades, un soulagement partiel chez 3,3% et aucun soulagement chez 26,4% d’entre eux. La régression des symptômes se fit en un à six jours.

3. Dans les doses utilisées, les effets secondaires de la "chlorpromazine" furent rares et non pénibles. Une somnolence survint chez 19,7%, des vertiges à la station debout chez 2,2%, une vague impression de vertige ou de "tête légère" chez 3,3% et des cauchemars chez 2,2%. Dans
tous les cas, sauf deux qui manifestèrent des cauchemars, les symptômes furent jugulés en réduisant la dose de chlorpromazine.

4. L'administration de chlorpromazine par voie buccale est une méthode efficace pour juguler les effets secondaires les plus désagréables de l'acide para-amino-salicylique.

ZUSAMMENFASSUNG

1. Eine Gruppe von 91 Patienten, bei denen unangenehme Nebenwirkungen (meist gastrointestinal) im Verlauf einer antituberkulösen Chemo-Therapie aufgetreten waren, die der PAS zuzuschreiben waren, wurde oral mit Chlorpromazin behandelt. Dies letztere Mittel wurde verabfolgt in Dosen von 25 mg. 3 täglich, während 2-6 Wochen in den meisten Fällen.

2. Es ergab sich eine vollständige Beseitigung der Symptome in 70,3% der Kranken, eine teilweise Beseitigung in 3,3%, und keine Beseitigung in 26,4%. Zu einem Nachlassen der Symptome kam es innerhalb von 1-6 Tagen.


4. Orale Verwendung von Chlorpromazin ist eine wirksame Methode bei der Bekämpfung von unangenehmen Nebenerscheinungen von PAS.

REFERENCES


