1955

Use of chlorpromazine in nausea and vomiting, malignancy, and intractable signultus

Howard Dean Wesely
University of Nebraska Medical Center

THE USE OF CHLORPROMAZINE IN NAUSEA AND VOMITING, MALIGNANCY AND INTRACTABLE SINGULTUS

Howard Dean Wesely

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1955

Omaha, Nebraska

TABLE OF CONTENTS

INTRODUCTION

This paper will review the anti-emetic effects of chlorpromazine and its effect on intractable pain and intractable singultus. Also, this paper will contain reviews of five patients from University of Nebraska Hospital and two from private practice who were observed by the author.

CHEMISTRY

Chlorpromazine is an alkylamine derivative of phenothiazine hydrochloride originally synthesized by H. P. Charpentier, working at the research laboratories of Rhone-Poulenc-Specia, Vitry-Sur-Seine in December of 1950. Its synthesis resulted from a systematic search for a phenothiazine derivative which would have an increased central depressant effect over promethiazine (1).

Chlorpromazine is known by several names in different corners of the globe: (2 and 3)

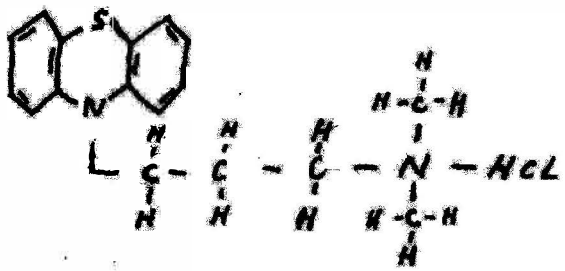
Largactil	Canada
Megaphen	Germany
Amphactil	Argentina
Hibernal	Sweden United
Thorazine	States

The molecular weight is 335.320 and its melting point is 179 to 180 degrees C.

It is soluble in water, chloroform, and ethyl and methyl alcohols. It is stable in 5% aqueous solution for 24 hours at a pH of 4.9. The gray-white powder is photosensitive and will change color when exposed to light.

It is chemically related to promethiazine (Phenergan®) and diethazine hydrochloride (Diparcol®) which are antihistaminic agents. It has also carried various code designations as 4560 R. P., and S.K.F. 2601-a. Its full name is 10-(3-dimethylaminopropyl)-2-chlorophenothiazine hydrochloride.

Its formula is as represented:



Chlorpromazine hydrochloride is available on the market under the trade name of Thorazine® (Smith, Kline, and French). It is available in 10 and 25 mg. tablets, in 50 mg. (2 cc) ampoules for injection, and in syrup containing 10 mg. per 5 cc.

PHARMACOLOGY IN ANIMALS

Lehman et al. (4), using the information published by Rhone-Poulenc-Specia and S.K.F. laboratories, further cite the pharmacologic properties of this substance.

A group of dogs, given 20 mg. per kilogram daily for a month, showed little or no mortality. Chlorpromazine produced a type of depression in the animals which increased with the dose; no hypnosis was observed.

The drug has a pronounced antiemetic action de-creasing the vomiting frequency in dogs following administration of apomorphine hydrochloride by 40 to 100%. It reverses the vasopressor activity of small doses of epinephrine in cats. It possesses a mild adrenergic blocking activity. Chlorpromazine does not modify the hyperglycemia produced by epinephrine. It inhibits the secretion of gastric juice and reduces the incidence of gastric ulcers in rats which have had ligature of the pylorus performed.

A hypothermic effect is observed in rats which show a body temperature drop of 1 to 6 degrees C. after receiving chlorpromazine.

A moderate antihistaminic activity is shown. A marked potentiating effect is observed when chlorpromazine is given in combination with ethyl alcohol, general anesthetics, analgesics, and barbiturates.

Blood levels and elimination of the drug were studied in experimentation with rabbits and reported by the Poulenc laboratories.

After an oral dose of 250 mg. per kilogram, the blood concentration rose to its peak level of 8 mg. per liter in three hours. The total quantity of chlorpromazine excreted by the kidneys in 3 days represented only 7 to 8% of the intake, which suggests that the major proportion of the drug is metabolized in the organism prior to reaching the kidneys.

D. Anton-Stephens-December 13, 1953-(5), writing on the use of chlorpromazine in mental patients, quotes Courvoisier's experimental work which was done mostly with animals. He divides its pharmacologic properties into two categories--namely, hormone antagonism and central nervous system inhibition.

As a hormone antagonist it was found that chlorpromazine neutralized the effects of adrenalin and noradrenalin and protected animals from otherwise lethal doses of adrenalin. However, it did not alter the transient hyperglycemia due to adrenalin. Also, it was found that chlorpromazine acted like other adrenergic blocking agents such as Dibenamine and protected animals later subjected to hemorrhagic or traumatic shock. Anti-acetylcholine activity was demonstrated but less marked than anti-adrenergic activity.

Chlorpromazine was found to exert minimal antihistaminic activity compared to its promethiazine hydrochloride cousin.

Central nervous system inhibition, as reviewed by D. Anton-Stephens, manifested itself as a central depressant with metabolic activity reduction in dogs and mice. Also, it exercised an obliterative effect upon conditioned reflex patterns as was demonstrated by--"rats conditioned to climbing a rope on the ringing of a bell losing the response following administration of chlorpromazine in spite of retaining full muscular power and co-ordination" as observed and recorded by D. Anton-Stephens.

Chlorpromazine antagonized the stimulant effects of caffeine and amphetamine, and reduced the convulsive effects of nikethamide and nicotine, but exerted little action on strychnine convulsions. Also, it appeared to exert a soporific effect of its own, and it is claimed that it renders the higher centers of the central nervous system more susceptible to other cerebral depressants.

The antiemetic effect of chlorpromazine is probably the most important feature of its pharmacologic activity.

The site of its antiemetic effect was explored and possibly best demonstrated in a study comparing the antiemetic effect in dogs and cats made by Brand, Harris, Borison, and Goodman (6). They performed experiments comparing chlorpromazine to Phenergan® in prevention of emesis induced by apomorphine and other substances.

Thes e investigators used 6 mongrel 12 kilogr(Cats) and 25 normal cats in which for control pur- poses threshold emetic doses were determined and
administered to the animals soon after feeding. Chlorpromazine was always given 30 to 60 minutes before the emetic agent in their experiments.

In preliminary observations they found that subcutaneous doses of chlorpromazine of 1.5 mg. per kg. caused no discernible toxicity; the same dose intravenously gave rise to moderate depression and ataxia for 6 to 12 hours. A dose of 3 mg. per kg. caused depression and ataxia lasting for 24 to 48 hours. These toxicity levels caused the authors to use 1.5 mg. subcutaneously a s their standard protective dose.

Using the experience of Wang and Borison who showed that apomorphine produced emesis in the dog by stimulation of the medullary chemo-receptor trigger zone, Brand et al. determined the threshold dose of apomorphine for ea ch dog.

(Two successive, positive responses with no negative response at a given dosage level were considered the emetic threshold dose.) The threshold dose varied for dogs in their study from 10 to 30 micrograms per kilogram with latent period for emesis from 0.5 to 2.5 minutes (1.3 average). They considered chlorpromazine to be protective when two or more consecutive, positive responses were prevented. Chlorpromazine raised the threshold emetic dose of apomorphine 2.5 to 4 times as shown in Table 1:

Table 1 Efficacy of Chlorpromazine Against Apomorphine Induced Vomiting in Dogs (after Brand et al. (6))

Dog No.	Threshold Emetic Dose Apomorphine mgm./kg. "IV"	Dose of apomorphine required to cause nausea and vomiting after standard protective dose of chlorpromazine		Approximate % increase after chlorpromazine
1	20	>60	<100	400
2	30	>60	< 90	250
3	20	>40	< 60	250
4	20	>40	< 60	250
5	10	>30	< 50	400
6	20	>40	< 60	250

The same dosage of chorpromazine intravenously as in dog #1 protected him against five times the emetic dose of apomorphine.

Three mg. per kg. intravenously protected dogs #2 and #3 against three times their emetic dose, and dog #5 against ten times its emetic dose. Dog #4 was not protected against ten times its emetic dose. The latent period of dog #4 for vomiting was prolonged from 1.1 to 3.3 minutes.

Phenergan® in toxic and non-toxic doses showed no antiemetic protective effect against apomorphine emesis in the dogs.

In cats pre-treatment with 2 to 5 milligrams per kg. subcutaneously failed to prevent emetic response to 25 micrograms per kg. of apomorphine.

Brand et al. (5) in similar studies found that chlorpromazine protected dogs from the emetic effect of morphine in uniform emetic dose of 1.0 milligram per kg.

Ergot induced vomiting in dogs using Hydergine® was prevented by standard protective dose of chlorpromazine. The ergot preparation was given intravenously 12 micrograms per kilogram. Hydergine® given to cats caused no emesis; so protective trial could not be run.

Copper sulfate intravenously was found to be uniformly effective in induction of emesis at a dose of 4.8 micrograms per kilogram. Anhydrous salt at a dose of 4 micrograms per kilogram was found to elicit vomiting in 4 of 5 pre-treated dogs; cats on the other hand were induced to vomit when given 10 micrograms per kg. of copper sulfate with a latent period of 1.5 minutes but all died within 18 hours. Cats pre-treated with 1.5 milligrams per kg. of chlorpromazine were not protected from emesis but survived the dose of copper sulfate.

Veratrum, given as Veriloid®, intravenously was found to have a threshold emetic dose of 40 micrograms per kg. except in one dog which required 60 micrograms. The dogs were not protected from emesis by standard protective dose of chlorpromazine.

On cats used in the experiment the emetic dose of Veriloid® intravenously was found to be 25 micrograms-per kilogram. All three cats tried were pre-treated with 2.5 milligrams per kilogram of chlorpromazine which failed to prevent emesis.

This was in line with what could be expected--considering the work of Borison, and Fairbanks (7) in 1952, in which they determined that veratrum induced emesis in cats by its effect on the nodose ganglion of the vagus nerve, which tends to prove the site of action of chlorpromazine.

Lanatoside-C induced vomiting in dogs was not prevented by chlorpromazine in the protective dose of 1.5 milligrams per kilogram.

A summary of the antiemetic efficacy of chlorpromazine against various agents in dogs and cats as compared by Brand, Harris, Borison and Goodman follows:

Table 11 Summary of Anti-Emetic Efficacy of Chlorpro-mazine Against Various Agents in Dogs & Cats (After Brand et al. (6))

emetic agent	site of emetic[1] agent	chlorpromazine protection dogs	cats
apomorphine	CT Zone[2]	Yes	No
morphine	CT Zone	Yes	N.T.[3]
hydergine	CT Zone	Yes	N.T.
copper sulfate "IV"	CT Zone	No	No
copper sulfate "O"	G.I. Tract	No	N.T.
lanatoside-C	CT Zone	No	N.
veriloid	Nodose Ganglion	No	No
nitrogen mustard	Forebrain	N.T.	No
pilocarpine	Forebrain	N. T.	slight protection

1 - under experimental conditions employed
2 - medullary emetic chemoreceptor trigger zone
3 -- not tested

ANTIEMETIC EFFECT

Moyer et al. (8) reported observations made on the antiemetic effect of chlorpromazine on 75 patients experiencing nausea and vomiting associated with drug administration. They found it to be an effective agent for drug induced nausea and vomiting.

Thirty-eight of the 75 patients were being treated with nitrogen mustard. All but two showed arrest of nausea and vomiting; however, four patients remained nauseated without vomiting, while eight others experienced intermittent nausea without vomiting. All patients receiving nitrogen mustard therapy were not included in this series. If patients receiving the first infusion experienced nausea and vomiting, they received chlorpromazine prophylactically during the second infusion. During the third infusion chlorpromazine was used to relieve nausea and vomiting after it was induced by nitrogen mustard. This was done to show that symptoms followed repeated infusions.

They also found chlorpromazine to be effective in relieving nausea and vomiting due to gastric irrita-tion--as from antibiotics or aminophylline administration. Relief of nausea and vomiting associated with cardiac failure was reported.

Nausea and vomiting associated with peptic ulcer were relieved in 6 of 9 patients. Moyer also reported a nine month old infant unable to retain his feedings since birth due to achalasia of the esophagus. Treatment included 1 mg. chlorpromazine four times daily. This patient was followed for six weeks and was able to retain his feedings for this period without recurrence of difficulty. The subsequent table illustrates results of Moyer et al. in use of chlorpromazine in treatment of cardiovascular and gastro-intestinal ailments.

Table III Diagnosis And Clinical Results In Patients Experiencing Nausea And Vomiting Due To Diseases Of Cardiovascular And Gastro-Intestinal Systems (After Moyer et al. (8))

Etiology of Nausea & Vomiting	No. Patients Treated	Exc.	Therapeutic Response Good	Fair	Failure
Cardiovascular					
Heart Failure	7	6	1	--	--
Cerebral Thrombosis	1	1	--	--	--
Gastrointestinal					
Ulcerative					
Alcoholic Gastritis	6	6	--	--	--
Peptic Ulcer	9	6	--	3	--
Ulcerative Colitis	2	2	--	--	--
Obstructive					
Cardiospasm	2	2	--	--	--
Pyloric Stenosis	1	--	--	--	1
Intestinal Obstruction	7	4	3	--	--
Carcinoma	5	4	--	1	--
Sub-Total	40	31	4	4	1

Moyer cautioned those using chlorpromazine for nausea and vomiting that it may obscure the true diagnosis by masking the symptoms of such severe conditions as intestinal obstruction.

Moyer also pointed out the effect of chlorpromazine on nausea and vomiting induced by anesthesia. Eleven out of the thirteen anesthetic patients reported experi-enced no nausea or vomiting; two were nauseated but did not vomit.

In their series of 78 patients with nausea and vomiting of pregnancy it was found that 55 obtained complete relief. Fourteen were much improved, five were slightly improved, and only four were complete failures. The average period of treatment was two months and the shortest was two weeks. During the first week of therapy occasional hypotensive episodes (syncope) occurred. Sedative effects were combated by 5 to 10 mg. dexedrine given with the chlorpromazine. The minimal effective dose of chlorpromazine was 25 mg. Many responded to 10 mg.

Table IV Diagnosis And Clinical Results In Patients Experiencing Nausea And Vomiting Due To Miscellaneous Cases (After Moyer et al. (8))

Etiology of Nausea & Vomiting	Patients Treated	Exc.	Therapeutic Response Good	Fair	Failure
Post Anesthesia	13	11			
Pneumoencephalogram	1				
Psychogenic Vomiting	4	1			
Meniere's Syndrome	1		1		--
Nausea & Vomiting of Pregnancy	78	55	14	5	4
Sub-Total	97	67	19	5	6

Chlorpromazine has been found to be very effective in controlling the nausea and vomiting of uremia. Many scholars believe that nausea and vomiting of uremia is caused by the retained toxic metabolites, acting on the emetic area of the brain. Others feel that uremia causes gastro-intestinal irritation, causing the nausea and vomiting. It is well known that uremic patients often have gastric or enteric ulcers.

Friend et al. (9) found that 25 to 50 mg. chlorpromazine four times daily suppressed nausea and vomiting in 13 out of 14 cases of uremia. Their patients were selected by trial therapy with sedation and restoration of fluid balance. If these measures did not relieve their patient, he was tried on chlorpromazine.

Twenty-five to fifty mg. chlorpromazine were given four times daily intramuscularly for one day and subsequent oral doses of the same size which were found to relieve nausea and vomiting in 2 to 3 hours. Many were able to eat for the first time in several days. In addition to the antiemetic effect the patients became cheerful, relaxed, and physically stronger. Pruritus-often present in uremia- was relieved in many instances.

In contrast to the previously mentioned data and efficacy of chlorpromazine in prevention of nausea and vomiting due to various causes (6)-including its anti-emetic protection of dogs suffering from swing sickness; it is somewhat surprising to find that it affords little protection from sea sickness. This was shown by Handford et al. (10) in their study of men aboard the U.S.N.S. General William O. Darby in which they compared the anti-motion sickness efficiency of several agents.

Men receiving placebos had a 34% incidence of emesis, while chlorpromazine medicated patients (50 mg. three times daily) had a 26.6% incidence of vomiting. The most effective protective for motion sickness among those substances (Benadryl®, Scopolamine, Postafene®, and chlorpromazine) tried was Benadryl®, 50 mg. three times daily, with an emesis incidence of only 12.9% and a protection of 62.0%.

This probably shows us another bit of the nature of chlorpromazine and its site of activity; as it does not seem to stop vomiting of motion sickness which involves labyrinthine, ocular, cortical, and vomiting center responses.

INTRACTABLE PAIN

In considering the uses of chlorpromazine in the non-psychiatric realm it is necessary for us to consi-der its value in intractable pain and general management of geriatrics. The rationale for the use of chlorpro-mazine in this situation may be seen in the observation of Staehelin and Kieholz (11) in Switzerland, who observed that their patients under chlorpromazine medication were not unlike those who had had leukotomies performed.

Sadove et al. (12) observed 30 patients, twenty-nine of whom had cancer. All patients required less narcotics; the eighteen patients who were hospitalized needed only half the former amount. The hospital patients were asked to evaluate the resultant analgesia of 25 mg. chlorpromazine and decreased narcotic dose with that of the previous medications. Blood pressure, pulse rate, body temperature, and blood count were recorded throughout this project.

Sadove reported, "Fourteen of eighteen patients, given chlorpromazine, obtained satisfactory analgesia with dosages of narcotics which had previously proved ineffective in relief of pain; one obtained pain relief, one reported no relief, and two others defaulted in taking the medication. One refused chlorpromazine after the first day, because he believed the drug caused bad dreams and disturbed his sleep; the other, in whom no adverse effects occurred, left the hospital after one week and refused to continue treatment."

Some patients were comfortable on a lesser dose of narcotics; others were comfortable on a dose of a narcotic of lesser potency than previously used. One patient had been receiving 10 mg. Racemorphan every three hours; after chlorpromazine 25 mg. twice daily he was comfortable with 5 mg. Racemorphan every seven hours. When he was put on 25 mg. chlorpromazine four times daily his narcotic need was reduced to 2.5 mg. Racemorphan. Another patient receiving 5 mg. Racemor-phan every 2 to 3 hours to decrease pain of gastric carcinoma became bedridden because of pronounced drowsiness. Fifty mg. chlorpromazine intramuscularly every 4 hours in conjunction with 50 mg. Demerol® hypodermically restored his semi-ambulatory state.

Sadove et al. (12) noted, "Severe nausea, vomiting, and diarrhea were promptly controlled in one patient when he received chlorpromazine to augment narcotic medication." This shows how chlorpromazine's antiemetic effect is useful in management of advanced carcinoma patients.

Of the eight patients favorably influenced by chlorpromazine as far as reductions of required dose of narcotics were concerned, one stopped taking chlorpromazine 25 mg. and one-sixteenth grain codeine because of pyrosis and resumed taking 100 mg. Demerol®.

Very good results were obtained in two out-patients with cancer. Five patients benefited from the antiemetic effect of chlorpromazine; four of these experienced complete relief of nausea and slight reduction in vomiting.

Two patients had complications; one patient illustrated chlorpromazine potentiation of narcotics when she repeated a 25 mg. intramuscular dose in 2 hours in addition to taking one grain of phenobarbital. She became cyanotic, her pulse rose to 164 beats per minute, and her blood pressure fell to 80/40 mm./Hg. Severe dryness of the mouth and drowsiness persisted for 36 hours.

Another patient received 50 mg. chlorpromazine orally and later erroneously received 7.5 mg. of Racemorphan hypodermically. She was semi-comatose for 30 hours. The side effect of this author's patients as well as the other works mentioned will be discussed later.

Howell, Harth, and Dietrich (13) tried chlorpromazine on fifty geriatric patients, taking dosages of 25 mg. orally three times daily; however, after deep drowsiness and staggering gait, the dose was decreased to 25 mg. at ten a.m. and four p.m. twice daily. Patients with neoplasms were given their last dose at bed time. The series consisted of 20 patients with senile psychoses with restlessness, 10 with emotional reactions, 19 in whom pain was a major factor (9 of these had neoplasms), and one patient with vomiting during an infectious jaundice.

Forty-three patients experienced some relief. Eighteen of the 20 demented patients became quieter and more receptive to nursing care. Eighteen of the nineteen patients with pain experienced some relief. "Several expressed the feeling that it put a curtain between them and the pain, so that while they were aware that the pain existed they were not upset by it," as noted by Howell et al. (13).

Six of the 10 patients who were emotional were somewhat improved but less so than those who were restless.

Three patients (one with vomiting due to infectious jaundice and two with emesis due to gastric carcinoma) with nausea and vomiting were much improved. One with carcinoma of the stomach was able to be discharged.

The seven failures in Howell's series were as follows:

senile dementia	4
agitated senile psychoses	2
girdle pain due to tabes dorsalis	1

From the preceding series of Sadove et al. (12) and Howell et al. (13), it is possible for us to realize the value of chlorpromazine in elderly patients with neoplasms, senile mental derangements, and nausea and vomiting. Probably its most important use in patients of this sort will be in cases of advanced malignancy in whom its "medical pre-frontal lobotomy" action will aid in making these persons comfortable, and in lessening their narcotic intake while relieving the nausea and vomiting so often associated with their advancing disease.

INTRACTABLE SINGULTUS

Another use of chlorpromazine is its ability to alleviate persistent singultus. In a recent series reported by Friedgood and Ripstein (14) they found that chlorpromazine stopped singultus in 46 of 50 patients. They used large dosages of chlorpromazine for this purpose--50 mg. intravenously and 25 mg. intramuscularly. In their series of patients, the pre-existing ill-nesses were classified as follows:

thoracic surgery	4
abdominal surgery urology	15
acute coronary	8
thrombosis congestive	11
heart failure uremia	2
idiopathic diseases	7
	3

They exercised many precautions in use of the drug intravenously because of transient syncope, palpitation, and tachycardia, being observed in several of their patients. One case of dermatitis was a complication of chlorpromazine administration in this series.

Moyer et al. (8) treated 10 patients with intractable hiccoughs (all persisting more than two days). Their sigultus was associated with:

heart failure	3
carcinoma	2
genito-urinary surgery	3
idiopathic etiology	2

Six patients were relieved within 20 minutes by 25 mg. chlorpromazine intramuscularly, two after second dose of 25 mg. chlorpromazine intramuscularly, and two experienced no relief. All had been tried on other medications prior to chlorpromazine.

This lower dosage administered intramuscularly by Moyer et al. (8) is much safer than the intramuscular and intravenous dosage of Friedgood and Ripstein (14), probably even a lower dosage may be effective--as will be shown in a patient observed in the course of this study. However, conclusions cannot be drawn from a series of one case.

One case of intractable hiccoughs treated with chlorpromazine was observed: (15)

Case 1

> Mr. H., a 74 year old man, suffered from hiccoughs of 7 days duration. He contacted his physician on the seventh day, and was given a prescription for 20 tablets of 10 mg. chlorpromazine with instructions to repeat 10 mg. dosage every 2 hours for 3 doses; then to take 1 tablet four times daily.

His hiccoughs ceased after the second tablet, and he completed the course of therapy (20 tablets) with no recurrent episodes or evidence of side effects.

SIDE REACTIONS

In Moyer's (8) study fifteen, entirely normal adults were given a 50 mg. test dose of chlorpromazine. Side effects were observed as follows:

sedation	14
vertigo	3
tachycardia	3
dry mouth	2
slight hypotension	2

The five patients, receiving 25 mg. chlorpromazine orally experienced sedation but none of the other side effects. With these results in mind Moyer et al. (8) concluded that in view of vertigo and hypotension, frequently associated with initial doses of chlorpromazine, it would be desirable to keep patients non-ambulant for first few doses.

Burnstein and Sampson (16) reported a severe case of hypotension in a 71 year old, white male who was being treated for carcinoma of the esophagus. Chlorpromazine was given him mainly because of mental irritability.

Four hours after the initial dose of chlorpromazine orally his blood pressure fell from 104/60 to 70/40. He required neosynephrine, oxygen, and nor-ephedrine intravenous drip therapy to restore a systolic blood pressure range of 110 to 92. However, after being given 25 mg. chlorpromazine by accident, his blood pressure fell to 70/50--necessitating the use of four more hours of nor-ephedrine in intravenous drip and hydrocortone for 16 hours to stabilize his blood pressure at 120/70. This case demonstrates the severity of hypotension which may occur even in oral chlorpromazine therapy; greater hypotensive effects can be expected from intra muscular route of administration.

Of the total 306 patients cited by Moyer et al., 47% experienced varied degrees of sedation, 24% experienced vertigo, 19% experienced dryness of mouth, 14% experienced tachycardia, and 12% had reduced blood pressures. Most of their patients who experienced sedation were not depressed to the point of interference with normal activity. Two patients were sedated to the point that they could not be aroused after 50 mg. dose of chlorpromazine intramuscularly. Patients, receiving oral medication of 100 mg. every 4 hours, experienced the lightest sedation.

The patients with vertigo and light sedation were able to continue normal activity. However, a few experienced syncope on arising which was corrected by bed rest.

The dryness of mouth was reported as mild and not serious.

Tachycardia, when it occurred, showed an increased pulse rate of 10 to 20 beats per minute.

Seven patients experienced blood pressure drops of 30 to 40 mm./Hg.; two of these three patients were given "accidental overdosage" of 100 mg. chlorpromazine intramuscularly with the result of nasal congestion in one and headache in the other.

Moyer et al. (8) observed one case of maculo-papular skin eruption. They also observed a case of jaundice in a patient being treated for psychiatric illness. The patient with jaundice suffered pruritus, elevated serum bilirubin and alkaline phosphotase; all of which receded markedly within two weeks.

These men showed a greater incidence of side effects, especially sedation, with parenteral use of the drug.

Fifty-five of Moyer's patients received chlorpromazine for an average of 12 days or more; forty-four received 25 mg. or more daily.

Side effects in these patients were diminished after several days of medication; however, the antiemetic and opiate potentiating effects were unchanged.

Friend and Cummings (9) found that one-fourth of their patients experienced drowsiness on doses as small as 25 mg. four times daily. It is of interest that these men felt that chlorpromazine relieved pruritus present in their patients, thus giving the idea that chlorpromazine may have some antihistamine-like activity.

Sadove et al. (12) noted side effects in thirty cases as follows:

drowsiness	11
dryness of mouth	9
hypotension	2
palpitation	2
pyrosis	2
dyspnea	2
oliguria	1
ataxia	1
disturbed sensorium	1

These workers also noted that in patients receiving chlorpromazine and codeine there were complaints of gastric irritation.

It is interesting to note the claims of the various authors about the minimal side effects in patients, as I had the opportunity to interview a physician who received chlorpromazine for nausea and vomiting during hospitalization for gastric ulcer.

He experienced quite pronounced drowsiness, nasal congestion, dryness of mouth, and disturbed sensorium with 25 mg. intramuscular dose.

He described his feelings as--"Feeling somewhat detached and very talkative, drowsy but not sleepy." In response to inquiry of gastro-intestinal, subjective symptoms he stated, "I felt as though I had a total physiologic obstruction of the gastro-intestinal tract." Also, he stated he did not sleep any more with the medication than without it.

The following is a case of hyperemesis gravidarum treated with chlorpromazine orally (15).

Case 11

> Mrs. M., a 36 year old, white female, Gravida 11, Para 11, was in the ninth week of her pregnancy. She was hospitalized one day a week prior to present admission because of vomiting. At that time emesis subsided under intravenous fluid and sedation therapy but recurred four days later. On the third day of vomiting she was hospitalized and the same therapy was repeated with relief of emesis but not of the nausea after several hours.

As parenteral form was unavailable, chlorpromazine was started orally at 25 mg. every 4 hours. Six hours after the initial dose vomiting recurred; therefore, chlorpromazine was discontinued with cessation of emesis within 3 hours. A 15 mm./Hg. drop in blood pressure was recorded during four day hos-pitalization period. This may have resulted from other medication and bed rest; no poten-tiation of barbiturate sedation was noted.

This woman illustrates the fact that chlorpromazine may cause gastric irritation in some individuals; the patient received no codeine which is supposed to cause gastric irritation when given with chlorpromazine.

I believe that in view of the several side effects during the initial doses of chlorpromazine it should be routine procedure to employ bed rest for at least 24 hours with dosages above 25 mg. four times daily (oral or parenteral), to record blood pressures four times during first two to three hours after the medication, and again to determine blood pressure on their arising (in presence of attendants) in order to detect possible orthostatic hypotensive tendencies.

In view of the potentiating effects on other sedatives the dose of opiates, barbiturates, and such should be discontinued or reduced substantially for a few hours prior to initial medication with chlorproma-zine.

Patients in whom the drug is to be used for a period of more than one week should have some liver function survey made prior to onset of chlorpromazine therapy
in order to detect evidence of liver malfunction.

Jaundice

In considering the hepatic toxicity associated with chlorpromazine therapy, it should be remembered that chlorpromazine may give a false test for bile in the urine; for this reason urine bile should be determined by the Hammarsten test, Huppert-Nakayama test, or "Ictotest"® (Ames).

There have been three cases of regurgitation type jaundice associated with chlorpromazine reported by Lemire and Mitchell (17) in which the onset of icterus was noted on the 15-32 day of therapy in the dosage range from 50-200 mg. per day. All three patients experienced severe pruritus.

Laparotomies were performed; two had no evidence of extra-hepatic obstruction, and the third had a stricture of the distal common duct but free bile was present in the duodenum with a 2 cm. stone found in the gall bladder. Liver biopsies showed plugging of bile canaliculi with brownish pigment deposits in the surrounding parenchymal cells. No evidence of obstruction of the portal areas or larger bile ducts was found.

Recently, three more cases of obstructive jaundice, similar in nature, were reported by VanOmmen and Brown (18).

In all cases reported there were no severe alterations in tests for hepato-cellular damage as zinc sulfate flocculation, albumin-globulin ratio, or prothrombin time. In Lemire's cases alkaline phosphotase was found to be elevated 17.2 to 35.8 Bodansky units while in the other series it ranged from 2.2 to 16.6 units.

It is recommended that chlorpromazine be discontinued with the first sign of liver involvement and that the usual program of liver therapy be instituted, including dietary measures, vitamins, and bed rest.

The preceding views and papers are surprisingly conservative in view of a recent article by Moyer et al. (19) in February, 1955 discussing psychiatric patients in which dosages as high as 4 grams per day have been found to cause a lesser increase in side effects than would be expected.

Moyer et al. (19) in the paper just mentioned found increased severity of the Parkinsonian syndrome. In view of evidence previously cited it appears desirable to refrain from use of chlorpromazine in patients with systolic blood pressures below 110 mm./Hg., because the blood pressure drop subsequent to chlorpromazine administration cannot be predicted by the amount of dosage.

CASE PRESENTATIONS

Case 111

H. W. is a 70 year old, white female admitted to the University of Nebraska Hospital on 8/16/54 for diagnostic studies to determine the nature of her anemia which had not responded to various means of therapy. She received blood transfusions periodically, but these did not raise her hemoglobin above 8.8 grams/100 cc.

On August 27, a bone marrow biopsy was scheduled but the patient became quite restless and apprehensive, and was given morphine sulfate 0.015 gram which she stated did little to calm her; subsequently, the dose was repeated. Approximately three hours later the patient became nauseated and began vomiting which continued for 20 hours. At that time 25 mg. of oral chlorpromazine was given, followed by 10 mg. orally every five hours for 3 doses. Nausea and vomiting subsided within one hour. No side effects were noted.

This patient demonstrated the use of chlorpromazine in nausea and vomiting induced by morphine.

Case IV

C. B., a 17 year old, white female--Gravida 1, Para 0, was admitted to University of Nebraska Hospital with complaint of vomiting several times during the 4 months of her pregnancy. Physical examination revealed nothing of significance. She was re-admitted on 10/3/54 with the complaint of inability to retain food or water and a 10 pound weight loss in preceeding week. She was placed on parenteral feedings and "Thorazine"® in dosage of 50 mg. intramuscularly twice a day was initiated on 10/3/54 and continued through 10/10/54.

On 10/8/54 wet and dry feedings were instituted. She then received chlorpromazine 25 mg. four times daily for 3 days and 10 mg. twice daily with 25 mg. at bed time for 3 days. No recurrence of nausea and vomiting was noted after the initial dose. This patient, being immature in her behavior, was thought to need psychia-tric care. The patient signed out of the hospital against medical advice on 10/17/54.

Case V

Mr. N. M. is a 34 year old, white male admitted to University of Nebraska Hospital with the diagnosis of chronic glomerulo-nephritis in the uremic phase. The patient had been vomiting almost daily for 9 weeks prior to onset of chlorpromazine therapy. On 10/28/54, he received 10 mg. of chlorpromazine by the intramuscular route followed by 10 mg. three times daily. He remained completely free of nausea and vomiting from 10/8/54 to 11/15/54 with the exception of one episode of vomiting on 11/1/54. No history or evidence of side effects could be elicited from the patient. He was always very cheerful and co-operative when seen. He stated that the "orange pills seem to be the only thing that keep me from vomiting."

November 15, 1954 was the last day of interview with this patient; he was subsequently hospitalized at Veterans' Administration Hospital of Omaha, Nebraska where he expired.

This case demonstrates the desirable effects that can be had from low dosages of chlorpromazine in certain cases of nausea and vomiting due to uremia.

Case V1

J. Y., a 19 year old, white male, was re-admitted to University of Nebraska Hospital on 10/18/54 with abdominal and chest pain due to generalized metastasis from a teratocarcinoma of the testis previously removed.

Physical examination revealed an emaciated white male with liver palpable at 3 finger breadths below the costal margin at the mid-clavicular line and palpable abdominal mass, and a 3 cm. palpable node in the supra-clavicular area on the right.

The patient was nauseated and vomited on 10/19, 22, 24 to 26/54. His blood pressure ranged from 110/90 to 130/90. The patient was treated with radiation and nitrogen mustard. He first received chlorpromazine 25 mg. intramuscularly on 10/26/54 with subsequent relief for about 4 hours. Also, he received 10 mg. orally four times daily and obtained much relief of nausea and vomiting though it did not completely subside.

On 10/28/54, the patient was given 25 mg. chlorpromazine intramuscularly at 4:20 p.m. followed by 6 mg. nitrogen mustard at 5:20 p.m. with no vomiting noted. Nitrogen mustard 8 mg. was given on 10/31/54 at 1:15 p.m. with same precautions as before with one episode of emesis at 5:30 p.m. Nitrogen mustard was repeated on 11/2/54 at 8:00 p.m. and followed by 25 mg. chlorpromazine intramuscularly at 8:30 with no vomiting noted until 11/4/54. The patient continued to fail progressively and expired on 11/6/54.

The patient was of the opinion that the drug made him much more comfortable and less nauseated although vomiting did not completely cease.

The dosage, although very low in this case, was effective and of value to the patient as nausea and vomiting was not continuous as prior to medication. Also, illustrated is the effect of chlorpromazine in decreasing nausea and vomiting induced by radiation and nitrogen mustard.

Case VII

H. W. is a 46 year old white female admitted to University of Nebraska Hospital on 11/5/54 with history of pain in right hip for past 6 months and 63 pound weight loss in same period.

The patient had had a surpra-cervical hysterectomy in 1948. She began having vaginal spotting on 12/9/51. A biopsy done in 1952 showed carcinoma of the cervix, Stage lV. She was treated with radium and x-ray therapy at that time.

The present admission physical examination revealed a poorly nourished female, appearing somewhat older than 46. Bilateral palpable inguinal nodes of 2 to 3 cm. diameter and bilateral supra-clavicular nodes of 1 to 1½ cm. diameter were present. Gynecological speculum examination revealed no visible cancer. The adenexae were thickened and hard. Intravenous urography showed a non-functioning right kidney. The diagnosis of recurrent and metastatic carcinoma of the cervix was made.

Radiation therapy was given 11/8/54 through 11/30/54 with heavy doses of x-ray through right and left, gluteal, inguinal, lateral and supra-clavicular areas. She was in much pain and vomiting daily from onset of therapy; Demerol® and codeine were given with minimal relief obtained.

The patient was started on 25 mg. chlorpromazine intramuscularly followed by 25 mg. orally four times daily; nausea and vomiting subsided within one hour.

"Thorazine Evaluation Questionnaire".
appears on reverse side

On 11/14/54 chlorpromazine was increased to 35 mg. every 6 hours per os until 11/28/54. Demerol® and codeine proved ineffectual in control of pain; therefore morphine 10 mg. with 25 mg. chlorpromazine orally every 3 hours was started with subsequent relief on 11/28/54. At that time an episode of vomiting was charted in nursing notes of patient's chart.

This patient was interviewed daily during the first three days on the medication; she reported only slight dryness of mouth and some vertigo, the latter of which she had experienced prior to medication. She felt that the medication was very beneficial for relief of nausea and vomiting but did not notice any potentiating effect of narcotics administered concurrently.

This patient demonstrated the value of chlorpromazine in relief of nausea and vomiting associated with radiation therapy; also, some potentiation of morphine was present during her last days of hospitalization.

DISCUSSION OF CASES

In the interviews with the patients I followed as closely as possible the Thorazine Evaluation Questionaire (20) used by the University of Nebraska department of surgery. (Questionaire form appears on facing page.)

Side effects in the seven patients were very minimal; two reporting slight vertigo (one patient thought it was present prior to medication), one reporting dryness of mouth, and one reporting exaggerated nausea and vomiting apparently due to chlorpromazine administration.

Though no statistical significance can be attributed to analysis of so few cases; these cases do illustrate some therapeutic uses of chlorpromazine in low dosage. The lightest dosage being 40 mg. per day and the heaviest being 200 mg. per day. The cases and their responses may be tabulated as follows:

Table V Summary of Cases Abstracted.

Case	Diagnosis	Cause of Nausea & Vomiting	Average Daily Dose	Side Effects	Therapeutic Response
I	persistent singultus	none	40mg/day	0	excellent
II	hyperemesis gravidarum	none	150mg/day	emesis	poor
III	chronic refractory anemia	morphine sulfate	55mg/day	0	excellent
IV	hyperemesis gravidarum	none	100mg/day	0	good
V	uremia	none	40mg/day	0	excellent
VI	teratoma of testis	nitrogen mustard & x-ray	40mg/day & prn dose	0	fair to good
VII	metastatic ca, cervix	radiation	100mg/day	vertigo, dryness of mouth	good

Case 1 illustrated the use of chlorpromazine in intractable singultus and contrary to dosages cited by others this patient responded remarkably well under 40 mg. per day.

Cases 11 and 1V demonstrated that chlorpromazine may be used successfully in some cases of nausea and vomiting of pregnancy, especially as an adjunct to other therapy as in case 1V. Case 11, however, illustrated a possible side effect of nausea and vomiting when other therapy had stopped vomiting but not nausea.

Case 111 illustrated effectiveness of chlorproma-zine in relieving vomiting induced by morphine sulfate administration.

Cases 1V and V possibly showed the best response to chlorpromazine's use as an antiemetic agent; relief obtained with as little as 40 mg. daily.

Cases V1 and V11 demonstrated the reduction of nausea and vomiting due to metastasizing malignancy, radiation, and nitrogen mustard therapy. Case V11 showed some narcotic potentiating effect late in hospitalization period.

SUMMARY

Chlorpromazine is a phenothiazine derivative which s several pharmacologic properties.

a- It acts upon the chemo-receptor trigger zone of the medulla to prevent vomiting induced by substances stimulating the chemo-receptor trigger zone as apomorphine, morphine, Hydergine®, and intravenous copper sulfate. It does not protect the dog against emesis induced by Veriloid® which affects the nodose ganglion. Cats were protected only to a slight degree against pilocarpine nausea and were not protected against emesis induced by most other substances mentioned because of the lack of a well differentiated chemo-receptor trigger zone.

b- It has adrenaline neutralizing properties and protects animals from ordinarily lethal doses of adrenaline.

c- It produces central nervous system effects mainly manifested by sedation and obliteration of conditioned reflexes in animals.

d- It enhances or potentiates the effect of other sedatives.

In Humans:

a- It has an antiemetic effect in cases of vomiting due to uremia, morphine, apomorphine, nitrogen mustard, radiation, nausea and vomiting of pregnancy, and even in bowel obstruction.

b- It has been found ineffective for treatment of nausea and vomiting of sea-sickness.

c- It has been found effective in potentiating analgesia of opiates used to control pain in cases of advanced malignancy. It appears to have the effects of a "medical lobotomy", thus helping lessen severity of pain.

d- It has been found effective in treatment of persistent hiccoughs.

Cases, demonstrating most of these features, were abstracted in this paper. These cases were on dosages of 40 to 200 mg. per day.

Side effects observed were urticaria, vertigo, sedation, orthostatic hypotension, obstructive jaundice, dryness of mouth, nasal congestion, pyrosis, and even nausea and vomiting in rare instances. Hypotension is probably its most serious side effect because its severity cannot be predicted by the size of the dosage. Jaundice is obstructive in character with stasis in the smallest --radicals it has been reversible in all cases. Since only 7 to 8% of chlorpromazine is eliminated through the kidney, it is probable that the liver is the major site of detoxification.

Bibliography

1. Winkleman, N. W. Jr.: Chlorpromazine in Treatment of Neuropsychiatric Disorders. J. A. M. A. 155: 18 (May) 1954.

2. Wortis, J.: Review of Psychiatric Progress 1953, Physiologic Treatment. Am. J. Psychiat. 110:507 (Jan.) 1954.

3. Dundee, J. W.: A Review of Chlorpromazine Hydrochloride. Brit. Journal of Anesth. 26 (5):358 (Sept.) 1954.

4. Lehman, H. E., and Hanrahan, S. E.: Chlorpromazine: New Inhibiting Agent for Psychomotor Excite-ment and Manic States. Arch. Neurol. & Psychiat. 71: 227 (Feb.) 1954.

5. Anton-Stephens, D.: Preliminary Observations on the Psychiatric Uses of Chlorpromazine (Largactil). J. Ment. Sci. 100: 543 (Dec.) 1953.

6. Brand, E. D.; Harris, T. D.; Borison, H. L.; and Goodman, L. S.: The Anti-Emetic Activity of Chlorpromazine in the Dog and Cat. J. Pharm. & Ex. Therap. 110: 86 (Jan.) 1954.

7. Borison, H. L., and Fairbanks, A. I.: J. Pharm. Ex. Therap. 105: 317 1952.

8. Moyer, J. H.; Kent, B.; Knight, R. W.; Morris, G.; Dizon, M.; Rogers, S.; and Spurr, C.: Clinical Studies of an Anti-Emetic Agent, Chlorproma-zine. Am. J. M. Sci. 228: 174 (Aug.) 1954.

9. Friend, D. G., and Cummings, J. F.: Use of Chlorpromazine in Treatment of Nausea and Vomiting of Uremia. New Eng. J. of Med. 250: 997 (June) 1954.

10. Handford, S. W.; Cone, I. E. Jr.; Chinn, H. I.; and Smith, P. K.: Drugs Preventing Motion-Sickness at Sea. J. Pharm. & Ex. Therap. 111: 447 1954.

11. Staehelin, J. E. and Kielholz, P.: Largactil in Mental Disturbances (from translation S.K.F.) Schweiz. Med. Wchnschr 83: 581 (June) 1953.

12. Sadove, M. S.; Levin, M. J.; Rose, R. F.; Schwartc, L.; and Witt, F. W.: Chlorpromazine and Narcotics in Management of Pain of Malignant Lesions. J. A. M. A. 155: 626 (June) 1954.

13. Howell, Trevor H.; Harth, J. A.; and Dietrich, M.: The Use of Chlorpromazine In Geriatrics. Practitioner. 173: 172 (Aug.) 1954.

14. Friedgood, E. E.; and Ripstein, C. B.: Chlorpromazine in Treatment of Intractable Hiccoughs. J. A. M. A. 157 (4): 309.

15. Myers, H. D.: Personal Communication

16. Burnstein, Sandor, and Sampson, J. J.: Severe Hypotensive Reaction to Oral Chlorpromazine Therapy. Calif. Medicine. 82: 1 (Jan.) 1955.

17. Lemire, R. E., and Mitchell, R. A.: Regurgitation Type Jaundice Associated with Chlorpromazine. Proc. Cent. Soc. Clin, Res. 27: 70 (Oct.) 1954.

18. VanOmmen, R. A., and Brown, C. H.: Obstructive Type Jaundice Due to Chlorpromazine (Thorazine). J. A. M. A. 157 (4): 321 (Jan.) 1955.

19. Moyer, J. H.; Kinross-Wright, Vernon; and Finney, M.: Chlorpromazine as a Therapeutic Agent in Clinical Medicine. Arch. of Med. 95(2): 202 (Feb.) 1955.

20. Jourdan, Harold: Personal Communication