

CLINICAL RESEARCH

Controlled trial of chlorpromazine as antisecretory agent in patients with cholera hydrated intravenously

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Abstract

A randomised controlled trial was conducted to investigate the ability of chlorpromazine to reduce intestinal secretion in cholera. Chlorpromazine had reduced loss of intestinal fluid in animals with diarrhoea induced by cholera toxin, and in a preliminary study the drug had reduced purging in patients with cholera.

Forty-six adults with cholera were included in the randomised trial. Of these, 34 were treated with chlorpromazine (1 mg/kg or 4 mg/kg either by mouth or intramuscularly) and 12 served as controls. After treatment with the drug there was a significantly greater reduction in the rate of fluid loss in the treated patients than in the controls during the first ($p < 0.005$), second ($p < 0.05$), and fourth ($p < 0.01$) eight-hour periods but not during the third eight-hour period; the dose of 4 mg/kg was only marginally more effective than 1 mg/kg. The effect of chlorpromazine was strikingly biphasic, with one peak during the first eight hours and another 24-32 hours after administration. Chlorpromazine also significantly reduced the duration of diarrhoea, frequency of vomiting, and amount of intravenous fluid required. The drug induced mild sedation and no hypotension in these well-hydrated patients.

These findings confirm the effectiveness of chlorpromazine in reducing fluid loss in cholera. A sedative effect, however, especially in children, may limit its usefulness and requires further study.

Introduction

Of all enteric pathogens that produce acute diarrhoea in man, *Vibrio cholerae* induces the most dramatic illness. The mortality rate in untreated cases may be 50-70%.^{1,2} The primary cause of death in cholera is dehydration, which in mild and moderate cases may be effectively treated with oral glucose-electrolyte solution; severely dehydrated patients with intense purging, however, require intravenous fluid.^{3,4} Drugs that would reduce the rate of fluid loss in cholera have been sought with a view to decreasing the need for intravenous fluid. Several drugs have been tested in animals and found to have antisecretory properties.⁵

The mechanism of fluid loss in cholera includes the production of a toxin by *V. cholerae* which stimulates the activity of cellular adenylate cyclase in the intestine and increases the intraepithelial concentration of cyclic adenosine monophosphate.⁶⁻¹¹ Chlorpromazine effectively inhibits adenylate cyclase activity in various tissues.¹²⁻¹⁴ In mice chlorpromazine reversed intestinal secretion induced by cholera toxin, heat labile *Escherichia coli* enterotoxin, or prostaglandin E₁, and in piglets the drug inhibited diarrhoea caused by toxicogenic *E. coli*.¹⁵⁻¹⁷ Furthermore, a preliminary study in patients with severe cholera also indicated that chlorpromazine reduced fluid loss by inhibiting intestinal secretion. We therefore decided to see whether the antisecretory effect of chlorpromazine in patients with cholera would be manifested in a larger, randomised controlled clinical trial and also if the drug would have an influence on other aspects of the disease such as vomiting and the duration of diarrhoea.

Subjects and methods

Adult male patients referred to the International Centre for Diarrhoeal Disease Research, Dacca, during August 1978 to December 1979 and who met the following criteria were considered for the study: (a) a history of watery diarrhoea for less than 48 hours, (b) *V. cholerae* in the stool as judged from dark-field microscopy,¹⁸ (c) severe dehydra-

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tion, and (d) no history of current antibiotic use. Patients who gave voluntary informed consent were admitted to the study. After admission patients were rehydrated and fluid balance maintained using intravenous solution containing (per litre) 134 mmol (mEq) sodium, 13 mmol (mEq) potassium, 99 mmol (mEq) chloride, and 48 mmol (mEq) acetate until diarrhoea stopped. Antibiotics and oral rehydration solutions were not given.

The volumes of stool output, urine, and vomit and intake of intravenous fluid and drinking water were recorded every 12 hours. Blood tests for specific gravity, packed cell volume, and serum electrolyte concentrations were done on admission, at 24 hours, and on discharge. Hourly records of blood pressure (lying and standing), clinical vital signs, and state of consciousness were made in the chlorpromazine-treated and control patients. Rectal swabs were taken each morning for isolating *V. cholerae* by standard methods.¹⁹⁻²¹

Patients who continued to have diarrhoea (over 200 ml/hour) 16 hours after admission were allocated at random to one of four chlorpromazine-treatment groups or to a control group; a table of randomised numbers was used. The four treatment groups received either 1 or 4 mg of the drug/kg body weight given as a single dose either by mouth or intramuscularly. For the injections and oral administration chlorpromazine was supplied in glass ampoules and syrup bottles, respectively (Hibernal, AB Leo, Helsingborg, Sweden). After administration the patients were observed for 32 hours. Control patients were similarly observed but not given chlorpromazine; nor were they given a placebo. Nevertheless, chlorpromazine was administered to patients in the treatment groups by the attending physicians without the knowledge of staff responsible for collecting, measuring, and recording the volumes of stool, urine, and vomit. During working hours the staffs were randomly rotated in eight-hour shifts between different wards.

A total of 46 patients were studied: nine were included in each of the treatment groups given 4 mg/kg by mouth, 4 mg/kg intramuscularly, and 1 mg/kg intramuscularly; seven were in the group given 1 mg/kg by mouth; and 12 served as controls.

Reduction in fluid loss after chlorpromazine was expressed as a percentage of the 16-hour basal rate—that is, the rate during the 16 hours before allocation to treatment—and compared with that in the controls for each consecutive eight-hour period from 16 hours after admission. Due to the wide variation in purging rate after chlorpromazine a logarithmic transformation was applied to stabilise the variances and all analyses carried out using transformed values. For each time period the purging rates of the five groups were compared using one-way analysis of variance. Data for the control and the treatment groups were also compared in relation to duration of diarrhoea, intravenous fluid requirements, frequency of vomiting, and clinical findings.

Results

Table I gives the clinical characteristics of patients in the control and four treatment groups. The groups were similar in age, sex, distribution, and other clinical variables. After intravenous rehydration patients were well maintained in fluid balance, as indicated by weight gain, urine output, and follow-up measurements of serum specific gravity.

STOOL REDUCTION

Figure 1 shows the reduction in stool output of the chlorpromazine-treated and control patients. Over the 16 hours before administration of chlorpromazine (not shown in fig 1) the mean basal rates of purging (\pm SEM) were similar in the drug-treated groups— 430 ± 111 ml (1 mg/kg by mouth), 537 ± 57 ml (4 mg/kg by mouth), 579 ± 83 ml (1 mg/kg intramuscularly), 481 ± 27 ml (4 mg/kg intramuscularly)—and 500 ± 67 ml in the control group. During the first, second, and fourth eight-hour periods after chlorpromazine the purging rates in the combined four treatment groups were significantly lower than in the controls ($p < 0.005$, $p < 0.05$, and $p < 0.01$, respectively). In the third eight-hour period, however, the difference between the treatment and control groups was not significant. Though differences between the four treatment groups were not significant, there was a tendency for a better effect with the higher dose (4 mg/kg) of chlorpromazine given by either route.

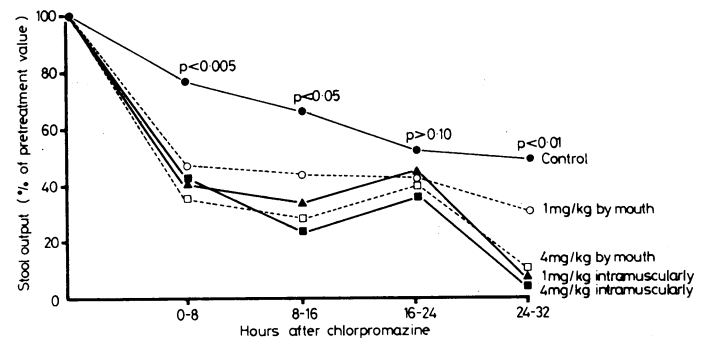


FIG 1—Fluid losses in chlorpromazine-treated and control patients with cholera. Rate of stool output expressed as percentage of output before chlorpromazine during successive eight-hour periods from time of administration. Geometric mean values for different treatment groups (1 or 4 mg chlorpromazine/kg by mouth or intramuscularly) compared with corresponding values for controls studied during same period of illness but not given chlorpromazine.

Figure 2 shows the specific reductions in stool output of each chlorpromazine-treated group. These reductions were calculated by subtracting the percentage reductions in purging rate of the treatment groups from those of the control group during the corresponding periods. In patients given chlorpromazine by either route the drug produced a striking biphasic inhibition with separate peaks during the first and fourth eight-hour periods after administration.

Of all the patients treated with chlorpromazine either by mouth or intramuscularly, 20 (11 given 4 mg/kg; nine given 1 mg/kg) had basal purging rates exceeding 100 ml/kg/8 hours, which would have been difficult to balance with oral fluids alone. Within the first eight hours after the drug, however, 16 of these patients (nine given 4 mg/kg; seven given 1 mg/kg) had rates below 75 ml/kg/8 hours, which are almost always managed successfully with oral treatment. Out of nine control

TABLE I—Clinical characteristics and results of laboratory investigation of chlorpromazine-treated and control patients (values are means \pm SD)

Characteristics	Chlorpromazine-treated groups				Controls (n = 12)
	4 mg/kg intramuscularly (n = 9)	4 mg/kg by mouth (n = 9)	1 mg/kg intramuscularly (n = 9)	1 mg/kg by mouth (n = 7)	
Age (years)	29.5 \pm 8.5	28.9 \pm 6.8	27.6 \pm 5.6	30.4 \pm 7.4	31.3 \pm 3.2
Before admission:					
Duration of diarrhoea (hours)	12.4 \pm 3.8	14.8 \pm 4.5	13.2 \pm 4.7	14.7 \pm 5.3	14.5 \pm 3.6
No of times stool passed	8.5 \pm 6.3	10.8 \pm 7.4	12.5 \pm 6.8	10.4 \pm 8.0	8.6 \pm 5.3
No of times vomited	8.4 \pm 3.8	4.8 \pm 2.7	10.8 \pm 6.5	6.0 \pm 4.3	7.6 \pm 4.8
On admission:					
Body weight (kg)	42.1 \pm 3.8	41.1 \pm 4.3	42.0 \pm 4.9	40.3 \pm 3.2	40.6 \pm 2.9
Plasma specific gravity	1.028 \pm 0.003	1.029 \pm 0.002	1.028 \pm 0.002	1.029 \pm 0.002	1.027 \pm 0.003
Blood packed cell volume (%)	42.0 \pm 3.5	40.6 \pm 6.3	38.3 \pm 7.4	43.1 \pm 6.3	40.2 \pm 5.6
Body weight loss (%)	9.0 \pm 1.3	8.2 \pm 1.4	9.2 \pm 1.5	8.3 \pm 1.3	9.2 \pm 1.1
After admission:					
Weight gain (%) at 24 hours	10.3 \pm 1.2	9.8 \pm 1.3	10.4 \pm 1.8	9.3 \pm 1.2	9.2 \pm 1.3
At discharge	9.5 \pm 1.5	9.2 \pm 1.3	9.2 \pm 1.3	9.1 \pm 1.5	9.7 \pm 1.3
Urine output (l) { 0-16 hours	0.41 \pm 0.08	0.48 \pm 0.06	0.52 \pm 0.05	0.54 \pm 0.10	0.53 \pm 0.05
{ 16-32 hours	0.83 \pm 0.15	0.96 \pm 0.15	0.86 \pm 0.16	0.98 \pm 0.18	0.90 \pm 0.12
Plasma specific gravity { 8 hours	1.026 \pm 0.002	1.027 \pm 0.002	1.025 \pm 0.002	1.025 \pm 0.002	1.026 \pm 0.002
{ 24 hours	1.025 \pm 0.001	1.026 \pm 0.001	1.026 \pm 0.002	1.025 \pm 0.002	1.026 \pm 0.001

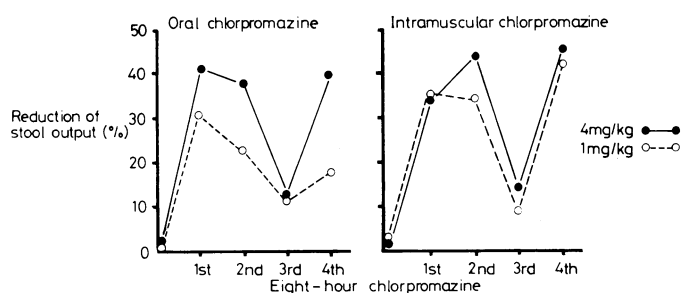


FIG 2—Specific stool reductions in chlorpromazine-treated groups. Chart shows differences in stool output between control and chlorpromazine-treated groups as percentage of initial 16-hour output rate (percentage reduction).

patients with high basal purging rates, only one showed such a reduction. This difference between the control and treatment groups was significant ($p < 0.02$; Fisher's exact test).

DURATION OF DIARRHOEA, FREQUENCY OF VOMITING, AND INTRAVENOUS FLUID REQUIREMENT

Table II shows the duration of diarrhoea, frequency of vomiting, and requirement for intravenous fluid of patients in the treatment and control groups. After chlorpromazine the mean duration of diarrhoea was significantly reduced in each treatment group as compared with the duration in the controls ($p < 0.001$). Also in the treatment groups fewer patients vomited and the mean requirement for intravenous fluid per patient was significantly less than in the controls ($p < 0.01$).

TABLE II—Effect of chlorpromazine on duration of diarrhoea, frequency of vomiting, and intravenous fluid requirement

Treatment groups	Mean duration of diarrhoea \pm SD (hours)*	No (%) of patients vomiting within 24 hours of chlorpromazine†	Requirement for intravenous fluid (l/patient/32 hours)‡	
			Mean total intake \pm SD	Mean volume saved \pm SD
Intramuscular				
4 mg/kg	94.6 \pm 2.4	2/9 (22)	6.48 \pm 1.32	5.62 \pm 0.71
1 mg/kg	92.1 \pm 2.3	1/9 (11)	8.69 \pm 1.45	3.41 \pm 0.73
Oral				
4 mg/kg	97.1 \pm 2.5	3/9 (33)	6.79 \pm 0.98	5.31 \pm 0.69
1 mg/kg	99.0 \pm 3.0	3/7 (43)	6.79 \pm 1.24	5.31 \pm 0.79
Controls	135.6 \pm 1.9	9/12 (75)	12.10 \pm 1.94	

*Chlorpromazine-treated patients in each group showed significantly shorter duration of diarrhoea than controls ($p < 0.001$ range of t -test values for four comparison groups 5.32 to 8.26).

†Frequency of vomiting significantly less in chlorpromazine-treated groups than in controls ($p < 0.001$ χ^2 test 8.77).

‡Significantly less intravenous fluid required in chlorpromazine-treated groups than in controls ($p < 0.01$ range of t -test values 4.42 to 7.47).

CLINICAL EFFECTS

The hypotensive effect of chlorpromazine was evaluated in nine well-hydrated patients given 4 mg/kg by mouth or intramuscularly. Before treatment the mean systolic and diastolic blood pressures were 130 and 85 mm Hg respectively. During the first eight hours after chlorpromazine the lowest recorded readings were 125 and 80 mm Hg respectively. The mean of the differences between horizontal and erect blood pressures also did not differ before and after administration of the drug (4 v 6 mm Hg). There was no appreciable change in radial pulse, respiratory rate, and oral temperature after any of the given doses of chlorpromazine.

Discussion

This study supports the preliminary observations on the antisecretory effect of chlorpromazine in patients with cholera.²² The drug, which effectively reduces fluid loss in mice and piglets,¹⁵⁻¹⁷ was also effective in man at comparable doses. The

antisecretory effect of the drug began within two hours of administration and continued through the first two eight-hour periods. A second peak of inhibition was observed during the fourth eight-hour period (24-32 hours). This pattern of bimodal inhibitory response was seen in each of the four treatment groups. Though we cannot explain this biphasic response, the first peak probably reflects a toxin-antagonising effect of chlorpromazine, whereas the second may be due to the generation of some metabolite of the drug which also has antisecretory activity.²³ Alternatively, the second peak might reflect the weak antibacterial action of chlorpromazine. Further studies will be needed to examine these hypotheses.

Though there was no significant difference in response between groups given 4 mg/kg and 1 mg/kg, there was a tendency for a lower purging rate in the higher-dose group. This finding is consistent with the dose-response studies in animals: in mice 4 mg/kg gave complete and 1.5 mg/kg gave half-maximal inhibition of the secretory response to a high dose of cholera toxin.¹⁵

The mechanism by which chlorpromazine reduces fluid loss in cholera has not been established but may include inhibition of adenylate cyclase activity in the intestinal mucosa.^{3 15} There may, however, be other effects as well.¹⁵ Chlorpromazine reportedly modifies several cell membrane functions, such as expansion of the lipid bilayer and release of calcium ions.²⁴ It also inhibits intestinal membrane protein kinase activities.¹⁵ All these effects, alone or in combination, may interfere with the membrane transport process. A unifying hypothesis linking the observed inhibition of adenylate cyclase activity to a postulated action of chlorpromazine on the calcium-binding protein calmodulin in intestine^{25 26} has been advanced to explain the antisecretory effect.²⁷

Our results indicate that chlorpromazine is also effective in reducing the duration of diarrhoea, frequency of vomiting, and requirements for intravenous fluid, which are important determinants of the disease. Use of the drug in cholera might therefore obviate the need for much intravenous fluid and simplify rehydration procedures, particularly in a rural outbreak. Children with intense vomiting are especially difficult to manage with oral rehydration fluids, and use of chlorpromazine in these cases may be more beneficial. The standard treatment of cholera, however, is still rehydration fluid and tetracycline, and whether chlorpromazine can further simplify these treatment procedures in a more practical way needs to be determined. Sedation from the drug could be one limitation of its usefulness. The sedative effect of chlorpromazine was manifested by mild drowsiness, which gradually improved over four to six hours. In children, however, an optimal antisecretory dose of the drug might produce stronger sedation and interfere with the intake of oral rehydration fluid. Hence the ability of chlorpromazine to reduce the failure rate in patients with cholera rehydrated by mouth, especially children, needs to be examined. Also, further studies to determine whether the antisecretory effect of the drug extends to non-cholera diarrhoea—for example, toxicogenic *E coli* diarrhoea—would be particularly important, since *E coli* is a major diarrhoeal agent in many parts of the world.

This work was jointly supported by the International Centre for Diarrhoeal Disease Research, Bangladesh; SAREC, Sweden; and the Swedish Medical Research Council.

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(Accepted 11 February 1982)

OF FEVERS IN GENERAL.

AS more than one half of mankind is laid to perish by fevers, it is of importance to be acquainted with their causes. The most general causes of fevers are, *infection, errors in diet, unwholesome air, violent emotions of the mind, suppression of usual evacuations, external or internal injuries, and extreme degrees of heat or cold*. As most of these have already been treated of at considerable length, and their effects shewn, we shall not now resume the consideration of them, but shall only recommend it to all, as they would wish to avoid fevers and other fatal diseases, to pay the most punctual attention to these articles.

FEVERS are not only the most frequent of all diseases, but they are likewise the most complex: In the most simple species of fever there is always a combination of several different symptoms. The distinguishing symptoms of fever are, *increased heat, frequency of pulse, loss of appetite, general debility, pain in the head, and a difficulty in performing some of the vital or animal functions*. The other symptoms usually attendant on fevers are, *nausea, thirst, anxiety, weariness, wasting of the flesh, want of sleep, or the sleep disturbed and not refreshing*.

WHEN the fever comes on gradually, the patient generally complains first of languor or listlessness, soreness of the flesh, or the bones, as the country people express it, heaviness of the head, loss of appetite, sickness, with clamminess of the mouth; after some time come on excessive heat, violent thirst, restlessness, &c.

WHEN the fever attacks suddenly, it always begins with an uneasy sensation of excessive cold, accompanied with debility and loss of appetite; frequently the cold is attended with shivering, oppression about the heart, and sickness at stomach, or vomiting.

FEVERS are divided into continual, remitting, intermitting, and such as are attended with cutaneous eruption or topical inflammation, as the small-pox, erysipelas, &c. By a continual fever is meant that which never leaves the patient during the whole course of the disease, or which shews no remarkable increase or abatement in the symptoms. This kind of fever is likewise divided into acute, flow, and malignant. The fever is called *acute* when its progress is quick, and the symptoms violent; but when these are more gentle, it is generally denominated *flow*. When livid or petechial spots shew a putrid state of the humours, the fever is called *malignant, putrid, or petechial*.

A REMITTING fever differs from a continual only in degree. It has frequent increases and decreases, or exacerbations and remissions, but never wholly leaves the patient during the course of the disease. Intermitting fevers, or agues, are those which, during the time that the patient may be laid to be ill, have evident intervals or remissions of the symptoms.

As a fever is only an effort of Nature to free herself from an offending cause, it is the business of those who have the care of the sick, to observe with diligence which way Nature points, and to endeavour to assist her operations. Our bodies are so framed, as to have a constant tendency to expel or throw off whatever is injurious to health. This is generally done by urine, sweat, stool, expectoration, vomit, or some other evacuation.

MANY of those who follow sedentary employments are constantly in a bending posture, as shoemakers, tailors, cutlers, &c. Such a situation is extremely hurtful. A bending posture obstructs all the vital motions, and of course must destroy the health. Accordingly we find such artificers generally complaining of indigestions, flatulencies, head-achs, pains of the breast, &c.

THE aliment in sedentary people, instead of being pushed forwards by an erect posture, and the action of the muscles, is in a manner confined in the bowels. Hence indigestions, costiveness, wind, and other hypochondriacal affections, the constant companions of the sedentary. Indeed none of the excretions can be duly performed where exercise is wanting; and when the matter which ought to be discharged in this way, is retained too long in the body, it must have bad effects, as it is again taken up into the mass of humours.

A BENDING posture is likewise hurtful to the lungs. When this organ is compressed, the air cannot have free access into all its parts, so as to expand them properly. Hence tubercles, adhesions, &c. are formed, which often end in consumptions. Besides, the proper action of the lungs being absolutely necessary for making good blood, when that organ fails, the humours soon become universally depraved, and the whole constitution goes to wreck. (Buchan's *Domestic Medicine*, 1786.)