PAPERS AND SHORT REPORTS

Clinical trial of berberine in acute watery diarrhoea

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Abstract

Four hundred adults presenting with acute watery diarrhoea were entered into a randomised, placebo controlled, double blind clinical trial of berberine, tetracycline, and tetracycline and berberine to study the antisecretory and vibriostatic effects of berberine. Of 185 patients with cholera, those given tetracycline or tetracycline and berberine had considerably reduced volume and frequency of diarrhoeal stools, duration of diarrhoea, and volumes of required intravenous and oral rehydration fluid. Berberine did not produce an antisecretory effect. Analysis by factorial design equations, however, showed a reduction in diarrhoeal stools by one litre and a reduction in cyclic adenosine monophosphate concentrations in stools by 77% in the groups given berberine. Considerably fewer patients given tetracycline or tetracycline and berberine excreted vibrios in stools after 24 hours than those given berberine alone. Neither tetracycline nor berberine had any benefit over placebo in 215 patients with non-cholera diarrhoea.

Introduction

To reduce the need for treatment with oral and intravenous fluid in patients with severe diarrhoea due to cholera and similar bacterial enteric infections, agents that reverse the stimulation of secretion of water and electrolytes by cholera toxin and the related toxins of enterotoxigenic *Escherichia coli* are sought.¹ Berberine is an alkaloid derived from the roots and bark of the plant *Berberis aristata*: a spiny, deciduous, evergreen shrub with yellow flowers (berberry bush). Berberine has a broad spectrum antibiotic activity against selective bacteria,² including *Vibrio cholerae*, shigella, pseudomonas,

E coli, proteus, protozoa such as *Entamoeba histolytica*,³ trichomonas,⁴ giardia,⁵ leishmania,⁶ and fungi.⁷ Extracts of this plant have been used in antidiarrhoeal medication in Ayurvedic medicine in India and in the traditional medicine of China for the past 3000 years. More recently berberine has been shown to inhibit the action of *V cholerae* toxin when administered before or with the enterotoxin in animals,⁸⁻¹¹ to have an antisecretory effect in the ligated intestinal loop of the rabbit even when administered after the enterotoxin has been bound to intestinal mucosa,¹² and also to inhibit the secretory response of *E coli* ST (heat stable) toxin in the infant mouse.¹²

Few clinical trials of berberine to date have shown it to be effective in treating acute diarrhoea.¹³⁻¹⁹ No clinical trial studying the antisecretory effect of berberine in diarrhoea has been reported. This report concerns a randomised, double blind, placebo controlled clinical trial of berberine *v* tetracycline *v* berberine and tetracycline to study the antisecretory effect and clearance of vibrios from stools in patients with cholera.

Patients and methods

Adults admitted to the Infectious Diseases Hospital with a history of watery diarrhoea less than 48 hours before admission and no history of antibiotic ingestion, coexisting illness such as pneumonia, systemic illness such as diabetes or hypertension, or diarrhoea within the past two weeks were taken into the study. Patients who were pregnant or had a known history of glucose-6-phosphate dehydrogenase deficiency were not included. All patients had to give informed consent after learning about the nature of the study and the related risk.

After informed consent was obtained patients were placed under observation. Only those who passed at least one liquid motion during the first three hours were accepted into the trial and allocated randomly to one of the following treatment groups: placebo groups 1 and 2—one placebo tablet and one placebo capsule given four times a day; berberine group—one berberine hydrochloride tablet (100 mg) and one placebo capsule given four times a day; tetracycline group—one placebo tablet and one tetracycline capsule (500 mg) given four times a day; and berberine and tetracycline group—one berberine hydrochloride tablet (100 mg) and one tetracycline capsule (500 mg) given four times a day.

Clinical features on admission to the study, and every eight hours after admission, were recorded by doctors on duty. For every patient hourly intravenous and oral fluids administered and the outputs of stools, urine, and vomit, if present, were recorded. Body weights were measured on admission and eight hourly. Blood samples were taken on admission and daily to measure packed cell volume, serum specific gravity, and serum sodium, potassium, chloride, and bicarbonate concentrations. Urine samples were tested daily to measure urobilinogen concentrations with Ehrlich's

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aldehyde reagent. Swabs of stools were taken in alkaline peptone water on admission and daily until discharge for culture of *V. cholerae*. *V. cholerae* cultures were carried out in thiosulphate citrate bile salts and confirmed by biochemical tests. In a random subsample of 20 patients with cholera, stools passed during the first eight hours and the fourth eight hour period were pooled and aliquots stored at -20°C . A radioimmunoassay of these stools to measure cyclic adenosine monophosphate concentration was carried out by one of us (AK) with a cyclic adenosine monophosphate assay kit (Radio-Amersham).

A factorial design was used to determine: (a) if berberine had a vibriostatic effect comparable with tetracycline so that excretion of *V. cholerae* in stools of patients receiving berberine was reduced to half of that in the placebo groups, tested at a significance level of $p < 0.05$ and a power of 80%; and (b) if berberine had a clinically evident antisecretory effect over and above the vibriostatic or antibiotic effect, by testing whether the output of stools in the group receiving berberine and tetracycline was about half as low as that in the group receiving only tetracycline, tested at a significance level of $p < 0.05$ and a power of 80%. For cholera about 35 patients per treatment group were thought to be necessary and for non-cholera diarrhoea about 40 patients. Thus 185 patients with cholera and 215 patients with non-cholera diarrhoea were entered into the study.

Results

Table I shows that 185 patients with cholera and 215 with non-cholera diarrhoea were comparable. Intravascular haemolysis was not evident as assessed by clinical jaundice and urine for urobilinogen daily. Table II shows

the clinical response in patients with cholera and non-cholera diarrhoea. Among patients with cholera tetracycline significantly reduced the number of motions ($p < 0.05$), duration of diarrhoea in hospital ($p < 0.001$), and volume of required intravenous ($p < 0.001$) and oral ($p < 0.001$) fluid. Patients given both berberine and tetracycline also showed reduction in these variables but to a less extent than in those given tetracycline alone.

According to the factorial design used in our study (appendix), reduced output of stools obtained from patients with cholera given berberine alone compared with that in patients given placebo was expected to represent the sum of the vibriostatic and antisecretory effects of berberine, which was calculated as 1 l (equation 1). Tetracycline, through its vibriostatic effect, reduced the output of stools by about 1.9 l/patient (equation 2) and together with berberine reduced the output by 2.8 to 3.0 l/patient (equation 3). Subsequently, the antisecretory effect of berberine was represented by any reduction in output that patients receiving tetracycline and berberine showed compared with patients receiving tetracycline alone, which was calculated to be between 0.9 and 1.1 l/patient (equations 4 and 5); this was similar to that observed in patients receiving berberine alone compared with those receiving the placebo (equation 1). Thus in this study the antisecretory effect of berberine was represented as a reduction in output of stools by 1 l/patient, which was not significant. Table III shows the cyclic adenosine monophosphate concentrations in the stools of 20 random patients with cholera (later confirmed bacteriologically). Patients with cholera given tetracycline or berberine alone showed significant reductions in faecal cyclic adenosine monophosphate concentrations: by 40% and 77%, respectively.

After 24 hours significantly fewer patients with cholera treated with tetracycline ($p < 0.01$) or tetracycline and berberine ($p < 0.05$) excreted *V. cholerae* in their stools compared with patients treated with placebo or

TABLE I—Comparison of patients with cholera and non-cholera diarrhoea in clinical trial of tetracycline, berberine, and tetracycline and berberine. Values are means (SE)

	Berberine	Placebo 1	Tetracycline	Placebo 2	Tetracycline and berberine
<i>Patients with non-cholera diarrhoea</i>					
No of patients	45	42	45	40	43
Male:female ratio	24:21	21:12	22:23	24:16	17:26
Age (years)	38.8 (2.3)	30.5 (1.86)	37.2 (2.5)	37.6 (1.6)	34.9 (2.6)
Duration of diarrhoea before going to hospital (h)	10.6 (1.2)	10.95 (1.5)	12.8 (1.2)	8.3 (0.94)	13.8 (1.1)
Total No of motions before going to hospital	11.1 (0.7)	10.8 (0.76)	12.4 (0.6)	10.15 (0.81)	12.1 (0.7)
Grade of dehydration:					
I	6 (13.3%)	7 (16.7%)	3 (6.7%)	9 (22.5%)	6 (13.95%)
II	33 (73.3%)	26 (61.9%)	30 (66.7%)	23 (57.5%)	23 (53.5%)
III	6 (13.3%)	9 (21.4%)	12 (26.6%)	8 (20.0%)	14 (32.6%)
Body weight on admission (kg)	44.2 (1.5)	43.9 (1.37)	43.6 (1.4)	44.1 (1.21)	42.0 (1.3)
Body weight on discharge (kg)	46.2 (1.5)	45.5 (1.34)	45.9 (1.5)	45.76 (1.2)	44.9 (1.4)
<i>Patients with cholera</i>					
No of patients	43	36	35	35	36
Male:female ratio	28:15	25:11	18:17	20:15	17:19
Age (years)	37.5 (2.6)	35.3 (3.0)	35.2 (2.8)	35.6 (2.9)	37.9 (2.8)
Duration of diarrhoea before going to hospital (h)	11.5 (1.0)	8.8 (0.8)	13.0 (1.1)	13.7 (1.7)	12.7 (1.5)
Total No of motions before going to hospital	10.7 (0.8)	10.9 (0.8)	13.2 (1.1)	12.1 (0.8)	12.2 (0.7)
Grade of dehydration:					
I	0	1 (2.8%)	2 (5.7%)	2 (5.7%)	0
II	10 (23.2%)	15 (41.7%)	16 (45.7%)	22 (62.8%)	21 (58.3%)
III	33 (76.8%)	20 (55.5%)	17 (48.6%)	11 (31.5%)	15 (41.7%)
Body weight on admission (kg)	42.6 (1.2)	44.2 (1.5)	44.6 (1.9)	42.1 (1.7)	42.6 (1.2)
Body weight on discharge (kg)	45.1 (1.4)	46.6 (1.6)	47.0 (1.9)	44.3 (1.8)	45.1 (1.8)

TABLE II—Clinical response to tetracycline, berberine, and berberine and tetracycline in patients with cholera and non-cholera diarrhoea. Values are means (SE)

	Berberine	Placebo 1	Tetracycline	Placebo 2	Tetracycline and berberine
<i>Patients with non-cholera diarrhoea</i>					
No of patients	45	42	45	40	43
Total No of motions/patient	12.4 (1.8)	13.9 (2.1)	19.4 (2.6)	19.9 (3.7)	14.8 (2.0)
Total volume of stools (l/patient)	2.9 (0.6)	2.6 (0.6)	5.0 (0.8)	3.9 (0.8)	3.3 (0.5)
Duration of diarrhoea in hospital/patient (h)	37.4 (3.0)	37.6 (3.5)	44.9 (3.5)	42.0 (4.9)	38.1 (2.8)
Total volume of intravenous fluids (l/patient)	4.1 (0.6)	3.6 (0.7)	5.7 (0.8)	4.6 (1.0)	4.3 (0.5)
Total volume of oral rehydration solution (l/patient)	4.9 (0.6)	5.5 (0.5)	4.9 (0.3)	5.2 (0.7)	4.7 (0.5)
<i>Patients with cholera</i>					
No of patients	43	36	35	35	36
Total No of motions/patient	29.6 (3.1)	29.5 (3.3)	15.1 (1.8)	30.3 (3.7)	23.3 (2.5)
Total volume of stools (l/patient)	8.2 (1.0)	9.0 (1.2)	7.1 (2.7)	9.2 (1.3)	6.2 (0.7)
Duration of diarrhoea in hospital/patient (h)	60.7 (3.6)	65.0 (4.1)	35.0 (2.7)	65.0 (4.3)	41.3 (2.7)
Total volume of intravenous fluids (l/patient)	11.3 (1.1)	9.8 (1.2)	5.4 (0.6)	10.0 (1.2)	12.3 (5.1)
Total volume of oral rehydration solution (l/patient)	9.0 (0.8)	7.8 (0.7)	4.5 (0.4)	11.6 (2.6)	6.3 (0.7)

berberine alone (table IV); none of these patients continued to excrete *V cholerae* in their stools at 48 hours. In this instance also berberine did not show vibriostatic activity noticeably different from placebo.

FIG 1—Effect of tetracycline 500 mg four times daily (---) v berberine 100 mg four times daily (...) v tetracycline and berberine (— · — · —) on purging volumes measured every eight hours in patients with cholera. Placebo groups 1 (○—○) and 2 (●—●) also shown.

Among patients with non-cholera diarrhoea berberine, tetracycline, and berberine and tetracycline were not significantly more beneficial than placebo (table II).

Among patients with cholera purging volumes every eight hours and changes in percentage of purging volumes (figs 1 and 2, respectively) were not significantly different between patients given berberine alone and those given placebo, whereas patients treated with tetracycline alone or tetracycline and berberine had significantly lower purging volumes from the second eight hour period ($p < 0.05$) up to the end of 48 hours ($p < 0.001$). No difference was noticed in the purging volumes and changes in percentage of purging volumes among patients with non-cholera diarrhoea (figs 3 and 4, respectively) given placebo, berberine, tetracycline, or berberine and tetracycline.

FIG 2—Effect of tetracycline 500 mg four times daily (---) v berberine 100 mg four times daily (...) v tetracycline and berberine (— · — · —) on purging volumes measured every eight hours in patients with non-cholera diarrhoea. Placebo groups 1 (○—○) and 2 (●—●) also shown.

TABLE III—Mean (SE) faecal cyclic adenosine monophosphate concentrations in patients with cholera before and after administration of drugs

Group	Cyclic adenosine monophosphate (nmol/l)		
	Before drugs	24 h after drugs	% Of reduction
Placebo (n=3)	28.1 (3.6)	28.2 (6.2)*	
Tetracycline (n=7)	68.3 (4.4)	41.0 (8.1)**	40
Tetracycline and berberine (n=7)	18.9 (2.3)	13.9 (4.7)*	27
Berberine (n=3)	9.1 (1.3)	2.1 (0.3)***	77

*Not significant at 5% probability level compared with initial value.

** $p < 0.02$, *** $p < 0.01$ compared with initial value.

Conversion: SI to traditional units—Cyclic adenosine monophosphate: 1 nmol/l $\approx$ 0.33 ng/ml.

TABLE IV—Effect of berberine and tetracycline on excretion of *V cholerae* in stools

	Placebo 1 (n=36)	Berberine (n=43)	Placebo 2 (n=35)	Tetracycline (n=35)	Berberine and tetracycline (n=36)
Before administration of drugs	36	43	35	35	36
Day 1	19 (52.8%)	18 (41.9%)	21 (60.0%)	8 (22.8%)	13 (36.1%)
Day 3	2 (5.6%)	1 (2.3%)	4 (11.4%)		

Discussion

Berberine is effective against *V cholerae* and inhibits the action of *V cholerae* enterotoxin in animals^{8,12} and in human cholera.^{13,19} These studies, however, did not compare purging volumes, duration of diarrhoea, or excretion of vibrios in stools and did not study the antisecretory effect of berberine.

In our study the reported vibriostatic effect of berberine was not evident.^{2, 19} Berberine did not reduce excretion of vibrios in stools significantly (table III). Clinically also our patients with cholera given tetracycline and berberine were more ill, suffered from diarrhoea for longer in hospital, purged stools more often, and required larger volumes of intravenous fluid than did those given tetracycline alone. This suggests that the vibriostatic action of tetracycline may have been antagonised by berberine. Whether this antagonism results from two antibiotics acting on the same site in bacterial protein synthesis and showing a subadditive effect is not known.

A significant antisecretory effect of berberine was not evident in our study. Volumes of stools, however, were reduced by 1 l in the group given berberine compared with that in those given placebo; similarly, volumes of stools were reduced by a further 1 l if berberine was added to tetracycline compared with when tetracycline was given alone. These two results might show that berberine has a small, though not significant, antisecretory effect. That berberine reduced the cyclic adenosine monophosphate

FIG 3—Effect of tetracycline 500 mg four times daily (---) v berberine 100 mg four times daily (....) v tetracycline and berberine (-.-.-) on relative changes in purging volume measured every eight hours (as % of first measurement) in patients with cholera. Placebo groups 1 (○—○) and 2 (●—●) also shown.

FIG 4—Effect of tetracycline 500 mg four times daily (---) v berberine 100 mg four times daily (....) v tetracycline and berberine (-.-.-) on relative changes in purging volume measured every eight hours (as % of first measurement) in patients with non-cholera diarrhoea. Placebo groups 1 (○—○) and 2 (●—●) also shown.

concentration in stools significantly (by 77%) also appears to suggest that in these patients with cholera berberine had a small antisecretory effect, although this effect was not clinically significant.

Berberine does not benefit the duration of diarrhoea, frequency of stools, and fluid requirements for rehydration, but these are less critical measurements of antisecretory action than is the volume of stools as they may be caused by factors other than the secretion of fluid. Tetracycline, as expected,²⁰ reduced not only the volume of diarrhoea in patients with cholera but also the frequency of diarrhoeal motions, duration of diarrhoea, and required rehydration fluids through its vibriostatic action compared with the placebo.

Possibly at the dosage we used (100 mg four times daily) berberine did not produce a noticeable antisecretory effect. To show clinically apparent vibriostatic and antisecretory effects in these patients with cholera who are rapidly purging large volumes of gastrointestinal contents a higher dosage of berberine may need to be given. A clinical trial using a higher dosage of berberine is in progress and will be reported later. The mechanism of the vibriostatic action of berberine²¹ and its interaction with tetracycline and other antibiotics may also have to be studied before more clinical trials can be planned.

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Appendix

The factorial design used in our study led to the following equations.

Equation 1: Mean diarrhoeal stools from patients in placebo group 1 (9.2 l)—mean diarrhoeal stools from patients in berberine alone group (8.2 l)=presumed antisecretory and vibriostatic effects of berberine (1 l).

Equation 2: Mean diarrhoeal stools from patients in placebo group 2 (9 l)—mean diarrhoeal stools from patients in tetracycline group (7.1 l)=vibriostatic effect of tetracycline (1.9 l).

Equation 3: Mean diarrhoeal stools from patients in placebo group 1 or 2 (9.2 l or 9 l)—mean diarrhoeal stools from patients in tetracycline

and berberine group (6.2 l)=vibriostatic effect of tetracycline and antisecretory effect of berberine (3 l or 2.8 l).

Equation 4: Mean diarrhoeal stools from patients in tetracycline group (7.1 l)—mean diarrhoeal stools from patients in tetracycline and berberine group (6.2 l)=antisecretory effect of berberine (0.9 l).

Equation 5: Vibriostatic effect of tetracycline and antisecretory effect of berberine from equation 3 (3 l or 2.8 l)—vibriostatic effect of tetracycline from equation 2 (1.9 l)=antisecretory effect of berberine (1.1 l or 0.9 l).

Thus the antisecretory effects of berberine calculated by equations 1, 4, and 5 are similar, which suggests that the effect of berberine observed in our patients was due to its antisecretory effect and that its vibriostatic effect was not evident here.

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Sustained release choline theophyllinate in nocturnal asthma

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Abstract

Nocturnal wheeze is common in patients with asthma, and slow release theophyllines may reduce symptoms. As theophyllines are stimulants of the central nervous system the effect of 10 days' twice daily treatment with sustained release choline theophyllinate or placebo on symptoms, overnight bronchoconstriction, nocturnal oxygen saturation, and quality of sleep were studied in a double blind crossover study in nine stable patients with nocturnal asthma (five men, four women, age range 23-64 years; forced expiratory volume in one second (FEV₁) 0.85-3.8 l; vital capacity 1.95-6.1 l). When treated with the active drug all patients had plasma theophylline concentrations of at least 28 mmol/l (5 µg/ml) (peak plasma theophylline concentrations 50-144 mmol/l (9-26 µg/ml)). Morning FEV₁ was higher when treated with sustained release choline theophyllinate (2.7 (SEM 0.3) l) than placebo (2.1 (0.3) l) ($p < 0.01$). Both daytime and nocturnal symptoms were reduced when the patients were treated with sustained release choline theophyllinate and subjective quality of sleep was improved ($p < 0.002$). When treated with the active drug, however, quality of sleep determined by electroencephalography deteriorated with an increase in wakefulness and drowsiness ($p < 0.05$) and a reduction in non-rapid eye movement sleep ($p < 0.005$). Treatment with choline theophyllinate had no effect on either the occurrence or the severity of transient nocturnal hypoxaemic episodes or apnoeas or hypopnoeas.

In conclusion, sustained release choline theophyllinate prevents overnight bronchoconstriction but impairs quality of sleep defined by electroencephalography.

Introduction

Nocturnal and morning wheeze are common symptoms of patients with asthma. These patients have overnight decreases in peak expiratory flow rate or forced expiratory volume in one second (FEV₁).¹ Possibly as a result of this bronchoconstriction they sleep less well and become more hypoxaemic during the night than do normal subjects.^{2,3}

Although regular inhaled treatment reduces the overnight fall in peak flow rates in those patients who have taken their treatment "as required," some patients still complain of nocturnal symptoms despite adequate inhaled treatment. As a result of this the therapeutic effect of oral long acting β_2 agonists and theophyllines has been studied,^{4,5} and sustained release theophylline can improve nocturnal symptoms and the morning decrease in peak flow rates ("morning dip") in such patients.⁶ Preparations of sustained release theophyllines are now used widely to treat nocturnal asthma. Theophylline is also, however, a stimulant of the central nervous system and caffeine, a related derivative of xanthine, interferes with the quality of sleep in normal volunteers.⁷ We therefore determined the effect of sustained release choline theophyllinate on both symptoms and peak expiratory flow rate and also on quality of sleep and nocturnal hypoxaemia in patients with nocturnal asthma.

Patients and methods

Nine asthmatic patients were studied (table I) in whom the airways obstruction showed an improvement of greater than 15% in FEV₁ with inhaled β_2 agonists and spontaneous variability of more than 20% in the FEV₁ recorded at outpatient clinics during the previous two years. All patients complained of nocturnal wheeze, all were atopic, and none smoked. All were clinically stable, none having had an exacerbation of their asthma during the previous six weeks. Each patient regularly inhaled β_2 agonists, eight inhaled steroids, two inhaled disodium cromoglycate, and three inhaled ipratropium bromide. No patient was taking oral theophyllines, oral β_2 agonists, ketotifen, oral prednisolone, sedatives, hypnotics, or anti-histamines. All inhaled treatment was withheld for six hours before the start of recording on the study night. Patients were also asked to avoid drinks containing caffeine (coffee, cola, cocoa, or tea) for six hours before recording as caffeine is a bronchodilator.⁸ Each patient gave written informed consent to enter the study, which was approved by the hospital ethical committee.

A randomised placebo controlled double blind crossover study design was used. The patients received 1272 mg of a sustained release choline

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