October 1996

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Annals of Tropical Medicine & Parasitology

ISSN: 0003-4983 (Print) 1364-8594 (Online) Journal homepage: http://tandfonline.com/loi/ypgh19

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To cite this article: Z. Abbas, I. Moid, A. H. Khan, S. M. W. Jafri, S. H. A. Shah, S. Abid & S. Hamid (1996) Efficacy of octreotide in diarrhoea due to *Vibrio cholerae*: a randomized, controlled trial, Annals of Tropical Medicine & Parasitology, 90:5, 507-513, DOI: 10.1080/00034983.1996.11813076

To link to this article: https://doi.org/10.1080/00034983.1996.11813076

Annals of Tropical Medicine and Parasitology, Vol. 90, No. 5, 507–513 (1996)

Efficacy of octreotide in diarrhoea due to *Vibrio cholerae*: a randomized, controlled trial

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Received 19 December 1995, Revised 29 February 1996, Accepted 4 March 1996

Although octreotide, a long-acting analogue of somatostatin, is currently used in the treatment of chronic secretory diarrhoea due to various causes, its role in the management of acute secretory diarrhoea is not well established. In the present study, therefore, the therapeutic value of octreotide in the management of cholera, a classical example of acute secretory diarrhoea, was investigated. During an outbreak of cholera, patients admitted with acute secretory diarrhoea of ≤ 24 h duration and a purging rate >100 ml/h were enrolled on the study and randomly assigned to octreotide ($N=17$) and control ($N=16$) groups. All 33 patients received intravenous fluid replacement and antibiotic treatment (200 mg ofloxacin twice daily for 3 days, by mouth). Each patient in the octreotide group was also given a subcutaneous injection containing 100 μg octreotide every 8 h for a maximum of six doses. The stool output of each patient was recorded every hour until there had been none for an hour, which was taken as the endpoint. Mean (S.D.) total stool output was lower [6·56 (3·7) *v.* 9·7 (6·5) litres] and the mean (S.D.) duration of diarrhoea after admission was shorter [32·9 (15·6) *v.* 47·8 (22·3); $P<0·05$] in the octreotide group than in the control group. However, as both groups generally had similar purging rates, the higher volume of stools from the control group was simply the result of the longer period of diarrhoea in this group. Octreotide therefore only decreased the duration of diarrhoea in the cholera patients.

Vibrio cholerae is an important cause of watery diarrhoea all over the world (Spriggs and Richard, 1993). The organism remains in the intestinal lumen, does not invade the mucosal surface and secretes an enterotoxin which activates adenylate cyclase, resulting in the elevated concentration of cyclic AMP in the intestinal mucosa which is responsible for the increased intestinal secretion (Field *et al.*, 1989). There appears to be a differential action on mucosal cells, there being a direct secretory effect on the crypt cells (increased chloride secretion) and some anti-absorption effect on the villous cells for sodium and chloride (Fine *et al.*, 1989). In addition, there is some evidence that cholera toxin causes release of 5-hydroxytryptamine; this stimulates the formation of prostaglandin E_2 and so activates small-bowel flux and secretion (Beugler *et al.*, 1989). The magnitude of the small-bowel flux overwhelms the absorptive mechanism of the large bowel and large volumes of stools are produced.

Cholera is a classical example of secretory diarrhoea where the balance between absorption and secretion of monovalent ions (Na^+, K^+, Cl^-, HCO_3^-) is disturbed. The results of studies on the efficacy of treatment of various types of secretory diarrhoea with somatostatin and its long-acting analogue, octreotide, have been encouraging. These drugs have been used to treat chronic diarrhoea following ileostomy (Cooper *et al.*, 1986), the diarrhoea of tumours producing vasoactive intestinal polypeptide (Ruskone *et al.*, 1982; Santangelo *et al.*, 1985), carcinoid (Oberg, 1993) and medullary thyroid carcinoma (Smid and Dullaart, 1992),

0003–4983/96/050507+07 $12.00/0

TABLE 1
Clinical characteristics of the patients in the two study groups

	Octreotide	*Control*
NO. OF PATIENTS		
Male	7	7
Female	10	9
All	17	16
Mean (S.D.) age (years)	43·4 (17·5)	43·2 (17·4)
MEAN (S.D.) DURATION OF DIARRHOEA (h)		
Pre-admission	18·5 (7·0)	16·1 (6·9)
Post-admission	32·9 (15·6)	47·8 (22·3)*
Mean (S.D.) total stool volume post-admission (litres)	6·56 (3·7)	9·7 (6·5)

*$P<0·05$.

TABLE 2
Results of laboratory tests of the patients at the start of the study

	Octreotide group	*Control group*
MEAN (S.D.) RESULTS OF BLOOD TESTS		
Blood urea nitrogen (mM)	3·4 (1·5)	2·9 (0·6)
Serum creatinine (μM)	221·0 (141·4)	185·6 (79·6)
Random blood sugar (mM)	10·1 (3·1)	9·9 (2·1)
Serum sodium (mM)	137·5 (5·7)	136·0 (3·6)
Serum potassium (mM)	4·1 (1·0)	4·1 (0·6)
Serum chloride (mM)	107·6 (5·4)	107·1 (3·3)
Serum bicarbonate (mM)	8·8 (3·8)	8·8 (4·3)
MEAN (S.D.) RESULTS OF STOOL TESTS		
Sodium (mM)	127·5 (18·9)	130·1 (16·6)
Potassium (mM)	21·1 (8·0)	19·8 (8·4)
Chloride (mM)	113·3 (19·2)	115·4 (16·1)
Bicarbonate (mM)	27·5 (8·1)	22·8 (10·5)
Stool osmolality (mOsm/kg)	278·6 (47·5)	278·9 (19·5)

AIDS-related diarrhoea (Manfredi *et al.*, 1993), short-bowel syndrome (Rosen, 1992), dumping syndrome (Lamers *et al.*, 1993) and diabetic diarrhoea (Mourad *et al.*, 1992; Walker and Kaplan, 1993). Octreotide has been used in these studies in doses of 50–100 μg, given subcutaneously every 8–12 h. The role of octreotide in the management of acute secretory diarrhoea has not been extensively studied. The efficacy of this agent in acute secretory diarrhoea due to *Vibrio cholerae* was therefore investigated.

PATIENTS AND METHODS

Patients complaining of acute watery diarrhoea who were admitted during the summer to the Medical Unit of The Aga Khan University Hospital, Karachi, Pakistan, were enrolled on

TABLE 3
Purging rates (ml/h) of the 'on study' patients

Time post-admission (h)	*Octreotide group*		*Control group*	
	N	*Mean rate and (S.E.)*	N	*Mean rate and (S.E.)*
0	17	262·0 (25·2)	16	229·0 (32·0)
DAY 1				
0–4	17	271·1 (28·8)	16	292·5 (37·4)
5–8	17	247·3 (27·6)	16	252·2 (30·8)
9–12	16	228·5 (22·3)	16	235·1 (58·8)
13–16	15	234·6 (35·2)	15	222·2 (30·4)
17–20	15	246·8 (32·1)	15	218·1 (32·8)
21–24	13	204·6 (18·1)	15	201·4 (25·5)
DAY 2				
0–4	13	134·4 (18·9)	14	201·1 (23·6)
5–8	11	120·3 (16·5)	14	177·2 (25·3)
9–12	10	116·1 (21·6)	14	142·7 (25·6)
13–16	6	162·3 (18·4)	11	164·1 (42·4)
17–20	6	124·8 (24·9)	8	203·1 (70·8)
21–24	5	92·4 (22·7)	7	157·0 (28·6)
DAY 3				
0–4	4	79·5 (17·9)	6	170·7 (32·8)
5–8	3	83·3 (33·9)	5	191·0 (37·7)
9–12	1	87	5	170·0 (21·6)
13–16	1	60	5	125·0 (28·6)
17–20	0	—	4	87·2 (13·5)
21–24	0	—	3	87·3 (32·1)
DAY 4				
0–4	0	—	1	206·0
5–8	0	—	1	175·0
9–12	0	—	1	162·0
13–16	0	—	1	150·0
17–20	0	—	1	125·0
20–24	0	—	1	62·0

the study, which was approved by the Ethics Committee of the hospital. Eligibility criteria were acute secretory diarrhoea of $\leqslant 24$ h duration and a persistent purging rate >100 ml/h during the first 8 h post-admission. Children, pregnant women, patients suffering from other concurrent illness and patients who had received antimicrobial or antidiarrhoeal agents before presentation were excluded. Informed consent was obtained before the patients were randomly assigned to the treatment group or the control group. All patients received standard supportive care, including intravenous fluid replacement, until there had been no stool output for an hour, and antibiotic treatment by mouth (200 mg ofloxacin twice daily for 3 days). Each patient in the treatment group was also given octreotide by subcutaneous injection for 40 h or until there had been no stool output for an hour, if this occurred sooner: 100 μg (0·5 ml) every 8 h.

On presentation, the hydration state of each patient was assessed from the changes in pulse and blood pressure that occurred as the patient

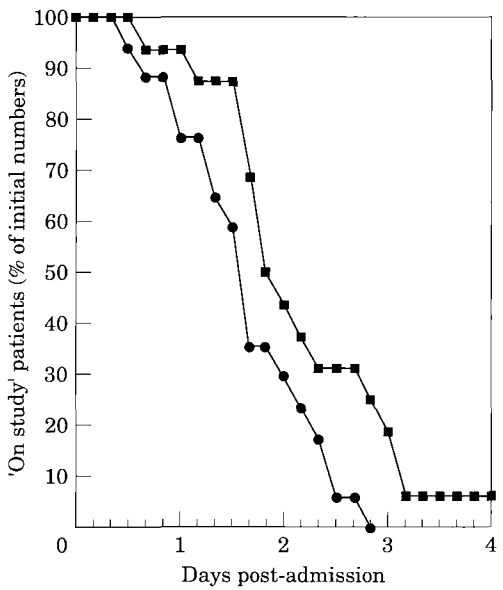

Fig. 1. The decrease in the numbers of patients 'on study' (i.e. producing stools every hour) in the treatment (●) and control (■) groups.

changed posture. Routine tests comprised complete blood counts, blood urea nitrogen, creatinine and electrolytes. Stools were examined, and sampled for culture to check whether *Vibrio cholerae* was present and to determine electrolyte concentrations and osmolarity. The secretory nature of the diarrhoea in each patient was defined by the osmotic gap (i.e. the difference between stool osmolality measured directly and that estimated as twice the combined concentrations of Na^+ and K^+); this was always $\leqslant 40$ mOsm. Hourly stool outputs were subsequently measured using rectal catheters (22F Foley's) connected to urine bags; an empty bag at the end of a 1-h sampling period was taken as the endpoint of the study for each patient.

Statistical Analysis

All statistical analyses were made using commercial software (Epi-Info). One-way analysis of variance was used for normally distributed data. Homogeneity of variance was checked with Bartlett's test, Mann-Whitney tests were used for samples with unequal standard deviations and Fisher's exact tests were used for comparison of discrete variables.

RESULTS

Overall, 35 patients were initially enrolled in the study, 18 of whom were given octreotide. However, two patients, one from each group, were excluded from the final analysis as *Vibrio cholerae* could not be detected in their stool cultures. The two groups were similar in terms of patient age and sex and the durations of diarrhoea before admission (Table 1) and in terms of their basal concentrations of blood urea nitrogen, creatinine, random blood sugar, serum electrolytes and stool electrolytes and osmolarity (Table 2). The mean (S.D.) duration of diarrhoea post-admission (Table 1) was shorter in the octreotide group than in the control group [32·9 (15·6) *v.* 47·8 (22·3 h); $P=0{\cdot}03$]. The one member of the control group who had diarrhoea for >3 days (i.e. 4 days) accounted for much of the difference; if the result for this patient is excluded, the mean duration of diarrhoea for the remaining controls decreases to 44·6 (18·8) h and the significance of the difference from the result for the treatment group also decreases ($P=0{\cdot}06$). Mean (S.D.) total stool output was less for the treatment group [6·56 (3·7) litres] than for the controls [9·7 (6·5) litres]. At any particular time after the first 8 h, the number of 'on study' patients (i.e. those still producing stools every hour) was less in the octreotide group than in the control group, though the difference was never statistically significant (Table 3, Figs 1 and 2). Purging rates (ml/h) for those 'on study' were always the same for the two groups except at 28 h ($P=0{\cdot}04$) (Table 3). However, pooled purging rates (ml/day) were significantly lower in the treatment group on day 3 than in the controls ($P=0{\cdot}04$). No side effects were noticed by any of the patients receiving octreotide.

DISCUSSION

The mechanism of secretory diarrhoea in cholera is complex. The cholera toxin activates

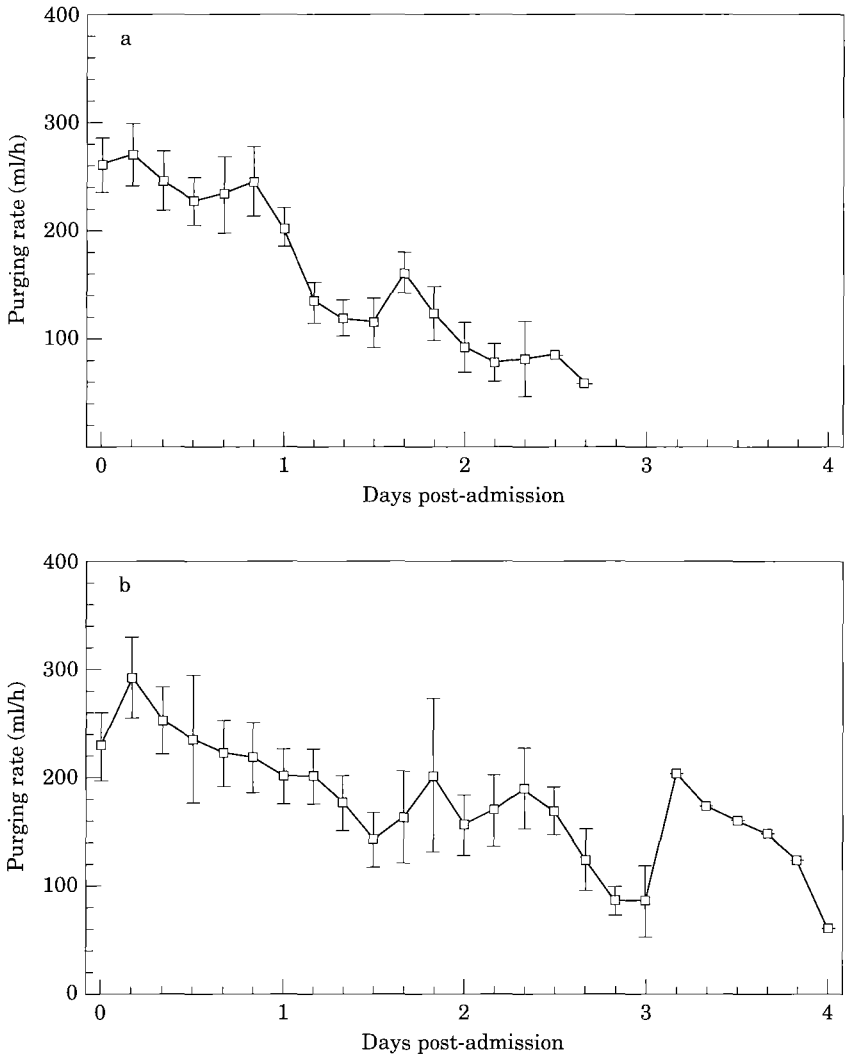

Fig. 2. Changes in purging rates with time in (a) the treatment group and (b) the control group.

adenylate cyclase (AC), a bound enzyme that is complexed through stimulatory (Gs) and inhibitory (Gi) G proteins (Gilman, 1984). In enterocytes, AC is located exclusively in the basolateral membrane and is stimulated when the cholera toxin activates Gs; the activated a_s subunit of Gs protein dissociates from the rest of the apical-membrane-bound molecule and attaches to the catalytic subunit of AC in the basolateral membrane, activating the enzyme (Field *et al.*, 1989). Somatostatin inhibits enterocyte AC activity by a cholera-toxin-insensitive, pertussis-toxin-sensitive Gi protein (Reyl-Desmars *et al.*, 1986). Cholera toxin also causes release of 5-hydroxytryptamine, stimulating the formation of prostaglandin E_2 (Beubler *et al.*, 1989). Prostaglandins of the E series in turn increase water and electrolyte secretion via the activation of AC (Kimberg *et al.*, 1971). Somatostatin has also been shown

to inhibit this activation in an animal model (Pawlotsky *et al.*, 1993).

Although Fedorak and Allen (1989) failed to show any alteration in cholera-toxin-stimulated secretion in rats given somatostatin analogue, Yoshioka *et al.* (1987) had earlier reported the effectiveness of somatostatin in the treatment of cholera-induced, secretory diarrhoea in rats. Yoshioka *et al.* (1987) found that the drug had a suppressive effect on the diarrhoea and inhibited the appearance of glyco-enzymes in the intestinal lumen and lymph production induced by the administration of cholera toxin but did not affect the elevated cAMP concentration. They postulated that the drug exerts its inhibitory effect beyond cAMP formation. It is possible that octreotide also fails to alter existing cAMP and that its effectiveness depends on some other mechanism. The results of a study by Sjoqvist (1992) demonstrated the anti-secretory effect of octreotide in anaesthetized rats and were consistent with octreotide inhibiting the nervous secretomotor reflex activated by the cholera toxin. cAMP induced by cholera toxin may serve as a physiological mediator for acetylcholine release from myenteric plexus neurons. Somatostatin inhibits release of acetylcholine evoked by various cAMP agonists in a dose-dependent manner (Wiley and Owyang, 1987). Octreotide has been shown to increase jejunal transit time (Dueno *et al.*, 1987). Somatostatin hyperpolarizes the submucous plexus neurons of guinea-pig by increasing the conductance of a set of inwardly rectifying potassium channels; this hyperpolarization is unaffected by cholera toxin (Mihara *et al.*, 1987).

Molla *et al.* (1984) assessed the ability of somatostatin to reduce the stool output of cholera patients in a double-blind, randomized, controlled trial. In this study, the drug was given for 12 h in a continuous infusion, was followed by a 12-h observation period and had no apparent effect on output when compared with control values from patients given placebo. However, the number of patients studied was small, the drug was given over a relatively short period and the follow-up period was also short, ending while the patients still had diarrhoea. Although the present results indicate that octreotide had little effect on purging rates, the drug did reduce the total duration of diarrhoea significantly. It may be that the persistent activity of this long-acting analogue of somatostatin overcomes the secreting factors and eventually shifts the balance in favour of diarrhoea-inhibiting mechanisms.

What are the therapeutic implications of this study? Should we include octreotide in future regimens of cholera treatment? Diarrhoea was arrested 14·9 h earlier by adding this expensive drug to the usual hydration and antibiotic therapy. Although this improvement may not make much difference in otherwise healthy adults, it could be much more significant in the treatment of the young and the elderly. The study could not be continued further because the outbreak of cholera which produced the influx of patients who were subsequently enrolled ended. A larger randomized trial using higher dosages may further clarify the role of octreotide in the management of secretory diarrhoea due to cholera.

ACKNOWLEDGEMENTS. The authors wish to thank the faculty members of the Department of Medicine for their contributions to the study and S. S. Gilani for his secretarial assistance.

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