

Prevention of traveller's diarrhea: Comparison of different non-antibiotic preparations

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SUMMARY

This investigation was carried out to evaluate the value of four different non-antibiotic preparations for prophylaxis or treatment of traveller's diarrhea. All studies were placebo-controlled double blind field trials with Austrian tourists visiting countries with warm climates. *Lactobacillus acidophilus* and Dodecoral, containing killed micro-organisms for oral immunisation, did not exhibit any prophylactic activity. When treating patients suffering from traveller's diarrhea with Noventerol, a preparation containing various non-specific antidiarrheal agents, no influence on its clinical course could be observed. Only application of *Saccharomyces cerevisiae* (strain Hansen CBS 5926*) decreased the incidence of diarrhea significantly. Attack rates of diarrhea in the placebo treated group, group I (2 x 125mg *Saccharomyces* daily) and group II (2 x 250mg *Saccharomyces* daily) were 42.6 per cent, 33.6 per cent and 31.8 per cent respectively. This reduction was statistically significant ($p < 0.002$). Dose dependency is suggested but not significant in this study. When evaluating the prophylactic efficacy in different geographical areas it could be shown that the reduction of risk amounted to 58, 59 and 40 per cent respectively in northern Africa, western Africa and various tropical islands. This reduction of incidence ($p < 0.0025$ of $p < 0.01$ and $p < 0.05$, respectively) was significant compared with the overall risk reduction rate. As different protection rates according to the destination of travellers were observed, a selective efficacy of *S. cerevisiae* has to be taken into account.

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Traveller's diarrhea is known to be the most common tourist's disease in the tropics (Steffen 1983). Extensive efforts have been undertaken to find an effective and well-tolerated prophylaxis of gastrointestinal disorders during short stays in hot climates. Antibiotics have proved to be effective in preventing diarrhea but at the price of side-effects. At present, general recommendation for the use of antibiotics in order to prevent episodes of traveller's diarrhea is withheld (Sack 1986).

Quite a few non-antibiotic substances have been tested for their prophylactic or therapeutic value but, with the exception of bismuth subsalicylate and antimotility drugs, none could significantly influence the incidence or the clinical course of traveller's diarrhea (Ericsson *et al* 1986; Donowitz *et al* 1986; Steffen *et al* 1986). Failure of various preparations to protect travellers, however, may be due to the heterogeneity of aetiological agents in traveller's diarrhea. Different patients were reported to be infected with distinct pathogenic micro-organisms, but also high frequencies of mixed enteric infections can be found in a single patient, leading to diarrhea (Taylor *et al* 1985).

Nevertheless, enterotoxigenic *E. coli* (ETEC) are thought to be the most common cause of diarrhea (Steffen *et al* 1983; Sack *et al* 1977; Echeverria *et al* 1981). Furthermore, not only the pathogenic mechanisms of traveller's diarrhea are discussed. Even the definition of the clinical picture and description of symptoms are still controversial. Several authors distinguish between two distinct pictures of clinical outcome: loose motions, described as one to two watery stools per day without any other clinical signs and the full picture of traveller's diarrhea covering the entire blurred picture of diarrheal illness among travellers (Taylor *et al* 1985).

In our opinion this rigid definition cannot deal with the problems of clinical practice. It was the aim of this study to compare four different nonantibiotic preparations for their prophylactic and/or therapeutic properties in traveller's diarrhea among Austrian tourists in hot climates.

Patients, material and methods

Patients

A total of 2271 healthy Austrian tourists who contacted the outpatient clinic of the Institute of Specific Prophylaxis and Tropical Medicine, Vienna, participated in these randomised double-blind, placebo-controlled field studies (Table 1). The volunteers consulted the Institute for health advice and prophylactic measures on the occasion of a planned stay in a hot climate. Dependent on their destination they were vaccinated against yellow fever and cholera, all received an oral live vaccine against typhoid fever (Vivotif™, Berna Ltd, Switzerland) and human gammaglobulin, standardised for hepatitis A-antibodies. Malaria prophylaxis was undertaken according to WHO regulations. Whenever necessary, vaccinations against tetanus and/or poliomyelitis were given. Patients with a previous history of chronic gastrointestinal disorder or acute diarrheal illness during the last three weeks and those with lactose intolerance were excluded from participation.

In our study all reported types of acute diarrheal disease during a stay in a hot climate country were considered to be traveller's diarrhea. All studies were randomised and double blind and placebos were indistinguishable with respect to shape, size, taste and colour.

Study 1

Capsules with viable *Lactobacillus acidophilus* (Antibiophilus-Kapsein™, Germania Pharmazeutika, Vienna, Austria), containing 2×10^8 - 2×10^9 lyophilised *Lactobacilli* per capsule were used for prophylaxis of traveller's diarrhea. Intake of two capsules daily before breakfast had to be started on the day of departure and continued during the whole stay. In case of diarrhea the daily dose had to be doubled until cessation of the diarrhea. After recovery, intake of the prophylaxis had to be continued.

Study 2

In this investigation we tried to evaluate the prophylactic value of an oral vaccine consisting of heat-inactivated Enterobacteriaceae (Dodecoral™, Serotherapeutisches Institut, Vienna, Austria). Each capsule contained 10¹¹ heat inactivated and lyophilised bacteria. The amount of different species of bacteria in one capsule was equal with the following composition:

<i>Salmonella Typhimurium</i>	(B)1,4,5,12;i;1,2
<i>Salmonella Thompson</i>	(C1)6,7,k;1,5
<i>Salmonella Manchester</i>	(C2)6,8,1,v;1,7
<i>Salmonella Panama</i>	(D1)1,9,12;1,v;1,5
<i>Salmonella Enteritidis</i>	(D1)1,9,12;g,m
<i>Salmonella Anatum</i>	(E1)3,10;e,h;1,6
<i>Shigella Flexneri</i>	1 b
<i>Shigella Flexneri</i>	2 a
<i>Escherichia Coli</i>	0 111 K58 H12
<i>Escherichia Coli</i>	0 124 K72 H32
<i>Escherichia Coli</i>	0 125 K70 H19
<i>Escherichia Coli</i>	0 127 K63

Ten daily doses of one capsule had to be taken before departure and volunteers were advised to take their daily dose one hour before breakfast.

Study 3

Ibis investigation evaluated the therapeutic value of a non-antibiotic preparation containing various non-specific anti-diarrheal agents (Noventerol™, Laves Ltd, Wil/St Gallen, Switzerland). Each capsule contained:

Carbo Medicinalis	162.5mg
Bolus Alba	195mg
Pectin	13.0mg
Lactose	84.5mg
Whey Powder	195.0mg

Intake had to be started on the day of onset of diarrhea (4 x 2 capsules per day) and continued on days two and three with a reduced amount (3 x 2 capsules per day). During this short time patients were advised to avoid any other medication except rehydration. In cases of severe diarrhea for more than three days, intake had to be stopped and further treatment was recommended under medical advice. These patients were withdrawn from the study because of influences of other medication (eight cases).

Study 4

In this trial the prophylactic efficacy of viable, lyophilised *Saccharomyces cerevisiae* Hansen CBS 5926 (SMC) was evaluated. As it was a further aim of the study to find an optimal dosage of SMC (Perenterol™, Thiemann Arzneimittel Ltd, West Germany) two different regimens were compared with placebo.

The volunteers were advised to take according to randomisation, either placebo or 2 x 125mg *Saccharomyces cerevisiae* (2.5×10^9 viable cells per capsule) or 2 x 250mg (5×10^9 viable cells per capsule) per day, before breakfast with water or non-alcoholic beverages. Intake was started five days before departure and continued during the whole stay in a tropical or sub-tropical country. Prophylaxis was continued in the same manner even in cases of diarrhea.

It was verified that none of our test preparations lost their activity when kept at 37° for more than four weeks.

Management of data

All volunteers received a detailed, serially numbered questionnaire, which had proved useful in other studies (Kollaritsch *et al* 1987) and were fully informed about its use. In particular, statements concerning sex, age, body weight, previous travel history, actual destination, duration of stay, accommodation (four possible items), environmental conditions (five possible items) and dietary hygiene (adherence to dietary recommendations during stay) were demanded. Furthermore, patients were requested to comment on diarrheal episodes in detail: Day of onset, duration in days, mean frequency of stools per day during the acute illness, quality of stools (watery, mucous, blood-stained), clinical symptoms such as abdominal cramps, nausea, vomiting, fever and prostration, maximum temperature and duration of fever, as well as duration of the other accompanying symptoms.

In addition, patients were asked in Studies 1 and 4 whether or not prophylaxis was continued during illness. Side-effects due to prophylaxis had to be listed and commented. Data registration followed on a personal computer (NCR DM V) using d-Base (Ashton Tate). Only questionnaires completed with respect to epidemiological and clinical data were accepted. These participants reported complete and regular intake of prophylactic medication/treatment and did not take any other medication for prophylaxis and/or treatment of traveller's diarrhea during their stay.

Results

Characteristics of patients

Demographic data (Table 1) show comparable characteristics of our volunteers. Mean duration of stay was nearly three weeks, as most subjects stayed in the tropics as tourists. Around 60 per cent had a previous travel history (Table 1). The number of travellers within the groups in all trials was nearly identical and no statistically significant differences of demographic data within the groups could be found.

Prophylactic efficacy of *Lactobacillus acidophilus* and Dodecoral

Lactobacilli and Dodecoral were not able to reduce the attack rates and the incidence of traveller's diarrhea ranged between 47.3 per cent and 53.2 per cent.

Table 1
Demographic data and characteristics of patients in four studies

PARAMETER	LACTOBACILLUS		DODECORAL		NOVENTEROL		SACHAROMYCES		
	Plac.	Verum	Plac.	Verum	Plac.	Verum	Plac.	Verum 1	Verum 2
Subjects	165	154	141	169	205	224	406	426	399
Male	85	84	73	83	103	113	196	208	211
Female	80	70	76	86	102	111	210	218	188
Age (years)	35.8	34.8	35.4	36.3	36.1	37.2	43.2	42.4	41.5
X±SD	±16.8	±16.3	±13.4	±14.9	±14.4	±14.7	±14.8	±14.6	±13.2
Weight (kg)	68.6	69.3	n.e.*	n.e.*	70.4	69.2	70.2	69.8	70.0
X±SD	±16.4	±17.2			±19.6	±19.8	±13.7	±14.2	±14.3
Duration of stay(days, X±SD)	19.2 ±11.6	20.8 ±11.1	23.8 ±17.8	22.6 ±17.4	20.6 ±12.8	20.5 ±13.6	19.2 ±10.1	18.1 ±8.6	18.6 ±9.4
First stay (Overseas)	n.e.*	n.e.*	n.e.*	n.e.*	96	104	159	164	153
Repeated stays					109	220	247	262	246

* n.e. = not evaluated

Therapeutic capacity of Noventerol

The clinical aspects of traveller's diarrhea when treated with Noventerol are shown in Table 3. Our three-day regimen could not influence the clinical course in any parameter mentioned and no significant differences *versus* the placebo-group could be detected.

Prophylactic efficacy of *Saccharomyces cerevisiae*

173 of 406 subjects of the placebo group developed traveller's diarrhea (42.6 per cent). In group 1 (2 x 125mg SMC) 33.6 per cent (143/424) and in group 2, 31.8 per cent (127/399) patients reported an episode of traveller's diarrhea (Table 2). Attack rates in SMC receiving groups were significantly lower ($p < 0.007$ and $p < 0.002$ respectively, Chi-square -test). Reduction of incidence was 21.2 per cent in group 1 and more than 25 per cent in group 2 compared with the placebo group. The difference between group 1 and group 2 may suggest dose dependency but was statistically not significant.

Clinical course of traveller's diarrhea in the studies (Table 3)

To evaluate the clinical outcome of diarrheal episodes, symptom sheets were distributed and patients were advised to comment on detailed clinical symptoms during acute illness. Most episodes start at the end of the first week of stay. Duration was mostly between three and four days and frequency of stools was in more than half the cases of diarrhea less than four times a day (Table 3). Most of the stools were watery and only about 10 per cent of patients reported mucous quality (Table 3).

Table 2
Prophylactic efficacy of *Lactobacilli*, *Dodecoral* and *Saccharo*

<i>PREPARATION</i>	<i>No. of subjects</i>	<i>TRAVELLER'S DIARRHEA</i>		<i>IN</i>
		<i>Developed</i>	<i>Not developed</i>	
<i>Lactobacilli</i>				
Placebo	165(51.7%)	78	87	47
Verum	154(48.3%)	82	72	53
<i>Dodecoral</i>				
Placebo	141(45.5%)	70	71	49
Verum	169(54.5%)	85	84	50
<i>Saccharomyces</i>				
Placebo	406(33%)	173	233	42
Verum 1	426(34.5%)	143	283	33
Verum 2	399(32.5%)	127	272	31

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Table 3
Comparison of clinical course of traveller's diarrhea in four different trials

PARAMETER Plac.	LACTOBACILLI		DODECORAL		NOVENTEROL		SACCHAROMYCES
	Verum	Plac.	Verum	Plac.	Verum	Plac. only	
Day of onset X±SD	n.e.	n.e.	n.e.	n.e.	7.8 ±5.2	8.1 ±6.0	8.5 ±6.1
Duration (days) X±SD	3.6 ±2.5	3.3 ±2.9	5.8 ±4.9	6.3 ±6.1	2.6 ±2.4	2.5 ±2.2	3.4 ±3.2
Frequency of stools							
1-3x/day	39(50%)	41(50%)	27(41%)	37(44%)	36(39%)	38(41%)	99(58%)
4-6x/day	25(33%)	26(32%)	22(32%)	32(38%)	50(54%)	43(47%)	60(35%)
>6x/day	13(17%)	15(18%)	18(27%)	16(18%)	7(7%)	11(12%)	14(7%)
Quality of stools							
Watery	75(96%)	78(95%)	66(94%)	76(89%)	88(95%)	92(100%)	149(86%)
Mucous	3(4%)	4(5%)	3(4%)	8(9%)	5(5%)	—	24(14%)
Sanguinary	—	—	1(2%)	1(1%)	—	—	—
Concomitant symptoms (multiple choice)							
Abd. cramps	44(56%)	46(56%)	30(43%)	41(48%)	66(71%)	62(67%)	101(58%)
Nausea	28(36%)	24(29%)	22(31%)	14(18%)	23(28%)	23(25%)	28(16%)
Vomiting	9(11%)	7(9%)	9(13%)	11(13%)	11(12%)	7(8%)	17(10%)
Fever(>37.5°C)	9(11%)	11(13%)	13(20%)	13(15%)	15(16%)	15(16%)	14(8%)
Duration of concomitant symptoms (days: mean)	2.9	3.1	3.2	2.6	2.4	2.5	3.4
Mean height of fever (maximum temp. in °C)	38.4	38.2	38.2	38.5	38.1	38.0	38.5

* As *Saccharomyces* exhibited prophylactic efficacy, verum-groups were excluded
n.e. - not evaluated

In only two cases (Dodecoral-study) were bloodstained stools observed (Table 3). Abdominal cramps occurred in more than 50 per cent of cases of diarrhea. Around 25 per cent complained of nausea and 10 per cent suffered from vomiting. Fever occurred in nearly 10 per cent and lasted less than two days. The average maximum temperature of patients with diarrhea exceeded 38°C. Concomitant clinical symptoms lasted mainly for three days and showed a direct connection with the duration of diarrhea. The clinical course of traveller's diarrhea was obviously not influenced by prophylactic intake of lactobacilli or Dodecoral. In addition, Noventerol lacks any therapeutic value as neither duration of illness, frequency nor quality of stools and concomitant clinical symptoms were influenced significantly. Some minor differences of the clinical course in the four different studies (Table 3) may be due to seasonal influences, but these differences are apparently of no clinical relevance.

Regarding duration of diarrhea in our Dodecoral study, however, a statistically significant ($p < 0.05$, Chi-square-test) prolongation of diarrhea was found in comparison with the mean duration of illness in the other trials.

Evaluation of prophylactic efficacy of *Saccharomyces cerevisiae*

SMC was able to reduce the overall incidence of traveller's diarrhea in a significant manner (Table 2). In Tables 4a-4c the protective capacity of SMC versus placebo is listed, exhibiting different protection in different geographic regions. The reduction of incidence of diarrhea in groups 1 and 2 versus the placebo group ranged between 0 and around 59 per cent. Protection rates in north and west Africa, and in the islands of Ceylon, Mauritius, Seychelles and the Maldives amounted to 58, 59 and 40 per cent respectively in group 2, and were significantly higher ($p < 0.0025$, $p < 0.01$ and $p < 0.05$ respectively) than the overall risk reduction rate (Table 2). For other regions significance could not be evaluated, mainly due to small numbers of travellers.

Comparing data of different regions exhibiting different risk reduction, with respect to hotel accommodation, personal behaviour and clinical symptoms, no correlation between protection rates and other parameters could be detected. It should be emphasised that demographic data of our volunteers with respect to different regions did not differ significantly ($p > 0.05$) at any parameter mentioned (e.g. age, sex, duration of stay, first or repeated stays).

Discussion

As it was the aim of our study to evaluate the prophylactic or therapeutic value of four different preparations often used in middle-European countries for prophylaxis or treatment of traveller's diarrhea, we have to concede that neither *lactobacilli*, Dodecoral nor Noventerol exhibited any efficacy regarding the incidence of traveller's diarrhea or the clinical course of gastrointestinal disorders during short-term stays in warm climates.

Preparations of *Lactobacillus acidophilus* have been widely used for therapeutic purposes in cases of antibiotic-induced colitis or in the therapy of functional gastrointestinal disorders as well as in cases of non-specific diarrhea in adults. Two double blind studies dealing with the prophylactic efficacy of *lactobacilli* performed in distinct geographic regions with selected groups (students) showed no protective capacity of such preparations (Pozo-Olano *et al* 1978; Clements *et al* 1981). Nevertheless, such preparations are often recommended for prophylaxis of diarrheal diseases and are widely used on the assumption that *lactobacilli* modify the intestinal flora favourably without causing adverse side-effects. In our study *lactobacilli* were not able to influence the attack rates of traveller's diarrhea or the clinical course of diarrheal disease, even when the prophylactic regimen was double during the onset of illness.

Dodecoral, containing a series of heat-killed micro-organisms often responsible for severe diarrheal disease, showed good results when tested in a mouse-protection model (Raettig 1980). This was the first study for evaluating its prophylactic efficacy when used under field conditions. The failure of Dodecoral is disappointing in as much as enteral vaccines are hopefully expected to play a major role in future immunisation programmes (Consensus Development Conference Statement 1986). However, this failure may have complex reasons: possibly the used enterobacteriaceae play only a minor role as causative agents in traveller's diarrhea. Furthermore, an enteral immunisation may fail in particular cases caused by enterotoxin producing micro-organisms.

Noventerol, a combination of antidiarrheal components, activated charcoal, kaolin and pectin, was used for treatment of diarrheal episodes. All components of this preparation are known to be of value in non-specific and uncomplicated cases of diarrhea. As this preparation lacks any side-effects we tried to influence the clinical course of traveller's diarrhea in a three day treatment. The results indicate clearly that this combination could not influence frequency of stools, mean duration of diarrheal illness, quality of stools, abdominal cramps, nausea or fever in a significant manner.

So far only two groups of drugs brought advances for the non-antibiotic treatment of traveller's diarrhea besides the use of oral rehydration measurements with electrolyte cocktails (Donowitz *et al* 1986; Consensus Development Conference Statement 1986). First, the use of antimotility agents such as diphenoxylate or loperamide is one approach but these provide prompt symptomatic but only temporary relief of symptoms. However, the use of antimotility agents is restricted to cases of diarrhea without fever or bloody stools. Furthermore, the use of these drugs should be discontinued if the symptoms persist beyond 48 hours (Consensus Development Conference Statement 1986). Recently, bismuth subsalicylate (BSS) was tested for its therapeutic value in cases of traveller's diarrhea *versus* loperamide, showing both medications to be effective for relieving diarrhea (Johnson *et al* 1984). In addition, a double-blind placebo controlled trial with BSS in liquid form exhibited a significantly beneficial effect on the clinical course of traveller's diarrhea (Du Pont *et al* 1977). Thus, the use of such preparations can be recommended for treatment by tourists but they have to be instructed about possible adverse side-effects and contraindications (Consensus Development Conference Statement 1986).

According to data (Table 2) only *Saccharomyces cerevisiae* (SMC) was able to reduce overall incidence of diarrhea by around 25 per cent and in some areas even up to 59 per cent (Tables 4a-4c). A further aim of this study was to find an optimal dosage of SMC as no recommendations for prophylactic use are available at present. Both dose regimens proved to be effective, but 2 x 250mg SMC daily may be assumed to be more effective. An increase of the daily amount of SMC will be possible, as tolerance is excellent and toxicity negligible (N.N. 1976). No participant complained of side-effects whilst nine patients reported improvement of acneiform skin lesions.

By now, SMC has been shown to be effective in the treatment of various kinds of diarrheal illness including non-specific diarrhea in elderly patients, diarrhea in connection with ulcerative colitis, and antibiotic-induced diarrhea (Donat 1970). A broad spectrum of different modes of action is discussed and will possibly influence intestinal microecology and the host-invader interplay; production of vitamins, amino acids, lipases, proteases, sterins and a self-limiting colonisation of SMC in the bowel (Cotte 1967; Donat 1970). The interfering effects in mixed cultures with enteropathogenic bacteria were described by Brugier (1975); in addition, SMC inhibits the adherence of pathogenic microbial agents to enterocytes (Stickl 1986). Furthermore, interactions with the defence mechanisms of the host were investigated, as complement activation via the alternative pathway (Petzold and Müller 1986; Elmer 1987), stimulation of phagocytic activity and respiratory burst of phagocytic cells (Riggi 1961) and increase of lysozyme-levels (Kokoshis 1978). Nevertheless, the exact mode of action of SMC in preventing diarrhea remains to be clarified.

SMC did not effect any clinical improvement in non-preventable cases of diarrhea. In particular, time of onset and mean duration of disease, frequency and quality of stools and even concomitant symptoms did not show any differences of clinical or statistical relevance within the groups. Mean duration of diarrheal episode and concomitant symptoms were almost equal.

Surprisingly, the protection rate with respect to destination of our travellers could be extraordinarily different. Protection rates ranged from more than 50 per cent (north and west Africa) to 0 per cent in India, Nepal, Mexico, and Antilles. Compared with a study evaluating the prophylactic effect of BSS (bismuth subsalicylate) (Du Pont *et al* 1980), our results may indicate a selective efficacy of SMC as BSS did not show regional differences in efficacy. Oral BSS showed protection rates of around 40 per cent.

Table 4a
Incidence of traveller's diarrhea in regions with excellent efficacy of SMC

REGION	GROUP Group 1 = 250mg Group 2 = 500mg	Yes	No	TRAVELLER'S DIARRHEA		
				Incidence	Reduction vs. Placebo	Significance vs. overall reduction*
NORTHERN AFRICA (n = 208)	Placebo	33	32	50.7%	—	p<0.002
	Group 1	22	51	30.1%	41% (p<0.01)	
	Group 2	15	55	21.4%	58% (p<0.01)	
WESTERN AFRICA (n=51)	Placebo	10	9	52.6%	—	p<0.01
	Group 1	6	12	33.3%	37%	
	Group 2	3	11	21.4%	59%	
MIDDLE EAST (ISLES) (n = 123)	Placebo	18	27	40.0%	—	p<0.05
	Group 1	13	32	28.9%	28% (p<0.1)	
	Group 2	8	25	24.2%	40% (p<0.05)	

*Significance versus overall reduction rate in Group 2 = 25.4%

Table 4b
Incidence of traveller's diarrhea in regions with moderate efficacy of SMC

REGION	GROUP Group 1 = 250mg Group 2 = 500mg	Yes	No	TRAVELLER'S DIARRHEA		
				Incidence	Reduction vs. Placebo	Significance vs. overall reduction*
EASTERN AFRICA (n = 251)	Placebo	34	36	48.6%	—	n.s. †
	Group 1	35	63	35.7%	27% (p<0.05)	
	Group 2	30	53	36.1%	26% (p<0.1)	
SOUTH AMERICA (n = 97)	Placebo	19	19	50.0%	—	n.s.
	Group 1	8	16	33.0%	34%	
	Group 2	13	22	37.1%	26%	
WORLD-WIDE TOURS (n = 34)	Placebo	6	6	50.0%	—	n.s.
	Group 1	3	9	25.0%	50%	
	Group 2	4	6	40.0%	20%	

*Significance versus overall reduction rate in Group 2 = 25.4%

† n.s. = not significant

Table 4c
Incidence of traveller's diarrhea in regions with missing efficacy of SMC

REGION	GROUP Group 1 = 250mg Group 2 = 500mg			TRAVELLER'S DIARRHEA		
		Yes	No	Incidence	Reduction vs. Placebo	Significance vs. overall reduction*
MIDDLE EAST (n = 85)	Placebo	14	7	66.6%	—	
	Group 1	22	10	68.6%	0	
	Group 2	21	11	65.6%	0	n.s.
FAR EAST (n = 228)	Placebo	27	59	31.4%	—	
	Group 1	18	54	25.9%	20%	
	Group 2	21	49	30.0%	5%	n.s.
MIDDLE AMERICA (n = 76)	Placebo	10	22	31.3%	—	
	Group 1	7	11	38.9%	0	
	Group 2	8	18	30.7%	0	n.s.

*Significance versus overall reduction rate in Group 2 = 25.4%

As the mode of action of SMC is not fully understood, we are not able to explain this possible selectivity by our knowledge of the activity of SMC. According to studies dealing with the aetiology of traveller's diarrhea and to our work showing different protection rates, country-specific difference of causative agents can be suggested. Recent studies from Thailand (Taylor *et al* 1985; Echeverria *et al* 1985) show that *Salmonella Enteritidis*, *Shigella spp.*, *Campylobacter spp.*, *Aeromonas hydrophila* and *Plesiomonas shigelloides* are characteristic causative agents in this region, while ETEC play a minor role with only some 30 per cent isolates. On the other hand, Sack and colleagues (1977) found mainly ETEC in Kenya and rarely *Salmonella spp.* and other enteric pathogens. In a recent overview concerning the aetiology of travellers's diarrhea (Steffen 1986) it is suggested that the nature of the causative agent is closely related to the geographical region. Furthermore, in many cases of traveller's diarrhea more than one potentially enteropathogenic agent could be isolated (Sack *et al* 1977; Echeverria *et al* 1981; Taylor *et al* 1985; Sack *et al* 1978). On the other hand, even in studies performed with excellent experimental accuracy and under optimal laboratory conditions, 20 to 50 per cent of episodes could not be clarified with respect to aetiology (Taylor *et al* 1985).

We have shown that SMC prophylaxis is capable of reducing the attack rates of traveller's diarrhea significantly. Higher number of organisms and acid-resistant formulations for oral administration may further enhance the protection capacity. Lack of any side-effects and negligible toxicity improve the value of SMC, a micro-organism known to be non-pathogenic, as the only comparable nonantibiotic preparation, bismuth subsalicylate, bears a risk of severe, though rather rare side-effects like encephalopathy when overdosing (Steffen *et al* 1986; Du Pont *et al* 1980). SMC does not interact with any other drugs and long-term prophylaxis in hot climates may be valuable, especially in elderly patients.

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