ORIGINAL ARTICLE

Prevention of fecal-orally transmitted diseases in travelers through an oral anticholeric vaccine (WC/rBS)

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Key words

Cholera • Fecal-oral diseases • Vaccine

Summary

Introduction. *Estimate the efficacy of oral anticholeric vaccine Dukoral® in subjects travelling to high-risk areas for traveler's diarrhoea and cholera.*
Methods. *The study involved subjects of both genders who planned to travel to high-risk areas for traveler's diarrhoea and cholera. Immunization with oral anticholeric vaccine Dukoral® was offered to each one of them. Upon returning, all the participants in the study were asked to complete a self-administered questionnaire consisting of 40 close-ended questions mainly concerning: personal and health data, characteristics (length, destination, reason) of the travel, onset of gastrointestinal symptoms, data relating to the assumption of anticholeric vaccine and possible adverse reactions.*
Results. *296 questionnaires have been collected. Mean age was 38.2 years (55.4% males and 44.6% females). Mean travel length was 22.2 days. Reasons for the travel: 66.8% tourism and 33.2% work-cooperation. Most frequent destination was Africa (48.1%), followed by Asia (32.1%) and Central South-America (17.8%). 199 subjects (67.2%) properly executed vaccination with Dukoral®. The diarrhoea affected 14.1% of vaccinated subjects and 20.6% of non vaccinated ones. The following cohorts showed statistically significant differences in incidence of diarrhoea: < 35 years old age (13.7% vs. 27.1%), travel for work-cooperation (14.1% vs. 35%) and travel length > 28 days (12.1% vs. 40%). No serious adverse events were reported following vaccination.*
Discussion. *Oral Anticholeric vaccine proved to be effective and safe in preventing fecal-oral diseases in travelers exposed to high risk conditions.*

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Introduction

Over the last few decades, globalisation has led to an increase in international travels to countries with poor hygiene standards, made for tourism, work or cooperation and humanitarian projects. Fecal-orally transmitted diseases are an important health problem among people involved in these travels: their diffusion is strictly related to environmental fecalisation, limited availability of drinking water and, more generally, poor hygiene and sanitation level. Among the fecal-orally transmitted diseases, the so-called traveler's diarrhoea has a particularly significant epidemiological impact and is identified as one of the most important diseases that occur during stay in developing countries [1-3]: according to different studies [4-6], it causes up to 50% of the demands of health-care services. Traveler's diarrhoea can be caused by different pathogens (bacteria, protozoa and viruses) and is characterised by diarrhoea of variable intensity and various enteric symptoms. In travelers up to 80% of diarrhoeal episodes are caused by bacteria, with Enterotoxigenic *Escherichia coli* (ETEC) that is responsible for 30%-60% of all traveler's diarrhoea cases, but also mild cholera infection can, even if rarely, cause it [7]. In microbiological terms, 140 serogroups of *Vibrio cholerae* are recognised on the basis of O somatic antigens, which are divided into 'O1' and 'non-O1' depending on their capacity to be agglutinated by group O1 antigen antisera [8]. The O1 serogroup is divided into two biotypes (called Classic and El Tor) on the basis of characteristics such as phagic sensitivity and production of haemolysin, and each biotype is further divided into two serotypes: Ogawa and Inaba. Nowadays, only the O1 and O139 Bengala serotypes are considered to be responsible for cholera epidemics [9], whereas the vibrios of the other groups not producing cholera toxin only cause mild intestinal infections. Man is the only known host of *V. cholerae*. Although under-reported, cholera is still a major public health problem and one of the key indicators of social development. Clinically, it ranges from mild or

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moderate disease essentially characterised by diarrhoea with an evolution from benign to severe disease with a high mortality rate [10]. Because of its endemic/epidemic nature, the disease is no longer a threat in countries with even minimal standards of hygiene, but remains a problem where it is not yet possible to guarantee everyone access to potable water and adequate hygiene services. With specific reference to travel medicine, the risk factors associated with the onset of traveler's diarrhoea include: the country of origin (with people from industrialised countries being at greater risk) [11], destination (high-risk areas are the Middle East, South and Southeast Asia, Central and South America, and developing countries in Africa) [12] and particular clinical conditions such as hypochlorhydria [8]. It is important to notice that the ETEC's pathogenic mechanism is similar to the *V. cholerae's* one: both cause a secretory diarrhoea. ETEC produces a thermolabile (LT) and thermostable toxin (ST). LT is structurally closely related to and has the same effect as cholera enterotoxin and exerts its effect through the activation of adenylate cyclase [13]. The main epidemiological risk factor for the development of fecal-oral diseases is the exposure to contaminated water or foodstuffs, or food prepared using contaminated water. Therefore, primary prevention seems to be fundamental for people visiting at-risk areas, and involves respecting the norms of correct personal and dietary hygiene, even if quite often there is no compliance to these rules. Moreover, an oral anti-cholera vaccine has recently become available, and it also protects against traveler's diarrhoea (particularly ETEC-sustained) [14]. The aim of this study was to assess compliance with vaccination and incidence of "traveler's diarrhoea" in subjects vaccinated with oral vaccine Dukoral® and in unvaccinated ones, with regard to different variables such as travel's duration, destination, motivation, subject's age and gender.

Methods

Travel Medicine Centres of Ferrara, Agrigento, Reggio Calabria, Milan, Caserta, Paola, and Lucca participated in the study that involved patients of both genders who have travelled in areas at risk of cholera and traveler's diarrhoea. Before the trip they were offered immunization with the oral anticholeric vaccine (Dukoral®), through an informative phase which took place at the travel medicine centres that participated in the study. Participants were asked to record any side effect appeared after taking the vaccine. At this time, participants received an informative brochure of the study. Upon returning, participants completed a self-administered questionnaire, consisting of 40 close-ended questions mainly related to: personal and health data, characteristics of the travel (visited country, length and motivation), onset of gastrointestinal symptoms during the travel (length, intensity and effects limiting normal activities), data relating to the assumption of anticholeric vaccine and possible adverse reactions. Taken drugs, and present or past illnesses at the time of administration of the vaccine were taken into consideration. All data were collected according to the actual standards related to the protection of privacy and in particular the Law Decree 196/2003, Article 24 (Code for the Protection of Personal Data) [15]. Completed questionnaires were collected by staff of participating Centres. Data were stored through Excel 2003 and processed by the statistical program SAS-JMP 7.0. The chi-squared test or, when required, chi-squared with Yates' correction or the Fisher exact test were applied, and the results were considered statistically significant if $p < 0.05$. Each dose of the offered vaccine contains a total of 10^{11} heat-inactivated cells of *V. cholerae* serotype Inaba and Ogawa classical and El Tor biotypes and the recombinant choleric toxin B subunit, and it induces the formation of secretory IgA directed against these components. So, the vaccine helps the prevention of both the colonization of the gut epithelium by the *Vibrio* and the effect of the toxin.
Given the structural correlation between the cholera toxin and the LT of ETEC, the vaccine also confers protection against the most common pathogenic cause of traveler's diarrhoea through a mechanism of immunological cross-reaction [13]. The protocol of administration involved the use of two oral doses spaced at least a week, with the last one taken at least 7 days before the beginning of the travel.

Results

In the period 2008-2009, a total of 296 questionnaires were collected. For each analyzed variable the non-respondents were excluded from processing. Mean age of the subjects was 38.2 years (SD 13.0), 51.4% of the subjects were younger than 35 years old, males were 55.4% and females 44.6%. Mean journey length was 22.2 days (SD 20.3), the majority of the trips were made for tourism (66.8%, mean 16.8 days, mean age 38.7 years) and the remaining for business or cooperation (mean duration 32.8 days, mean age 37.5 years). Africa, Asia, and Central-South America were the preferred destinations (respectively 48.1%, 32.1% and 17.8% of the travelers). After being informed of the characteristics of the anticholeric vaccine by the personnel of the travel medicine centres, a total of 199 subjects (67.2%, mean age 38.5 yrs, 53% males, 47% females) were properly vaccinated with Dukoral® versus 97 who were not (32.8%, mean age 37.7 yrs, 60.4% males, 39.6% females). At the time of departure, 45 subjects were receiving drugs for concurrent pathologies: 42 of them were vaccinated, none of them was receiving drugs able to interfere with the onset of traveler's diarrhoea or with the vaccine. The presence of traveler's diarrhoea was evaluated with a specific question in the questionnaire. We considered as positive the subjects that reported three or more bursts of diarrhoea in a 24-hours period during their travel. According to this definition, diarrhoea affected 14.1% of vaccinated subjects versus 20.6% of unvaccinated ones. We focused attention on the variables: 'length of

the journey' (divided into < 15 days, 15-28 days, and > 28 days classes), 'geographical area' (Africa, Asia, Central-South America, Oceania, etc.), 'reason of the journey' (work and cooperation, or tourism). We also took into account the variables: 'age' (< 35, 35-49, > 49 years), 'gender' and 'intensity of diarrhoea'. Regarding the length of the trip (Tab. I), there was a significant difference in incidence of diarrhoea in travel longer than 28 days (incidence of diarrhoea in vaccinated 12.1%; in unvaccinated 40.0%; p = 0.039, efficacy 69.7% and number needed to treat to prevent one case of traveller's diarrhoea is 3.6). In addition, in this kind of travel, the incidence of diarrhoea among vaccinated and unvaccinated subjects was different especially for those who have travelled to Central and South America (0% in vaccinated vs. 80.0% in non-vaccinated; and for those who travelled for purpose of work or cooperation (5% in vaccinated, 43.8% in unvaccinated; p = 0.0121). At the same time, however, the good result obtained by vaccination in these subjects is confirmed considering that, on average, travels in Central-South America last longer than in the rest of the world (27.0 vs. 21.2 days). Another considered variable was the age of the subjects (Tab. II). In this case, there has been a significant difference in the onset of diarrhoea among vaccinated and unvaccinated subjects in the < 35 years age class: the 13.7% of vaccinated presented diarrhoea, compared to the 27.1% of non-vaccinated ones (p = 0.0470), with an efficacy of vaccination equal to 49.3% and a number needed to treat to prevent one case of traveller's diarrhoea of 7.5. In subjects between 35 and 49 years, diarrhoea hit 11.8% of vaccinated and 19.4% of non-vaccinated (p = 0.3457), whereas in the > 50 years age class it involved 19.1% and 5.6% of subjects, respectively (p = 0.2551), but in this late group the number of subjects was really low.

Taking into consideration the length of the trip, it is noteworthy that subjects under the age of 35 years have made longer journeys than those belonging to over 35 age class (24.1 vs. 20.4 days, p = 0.0122). Regarding the reason that led to undertake the journey (Tab. III), and taking in consideration all age classes, it is to be noted that in work or cooperation-related journeys, the 14.1% of vaccinated and the 35.0% of unvaccinated subjects suffered diarrhoea (p = 0.0313). It demonstrated a vaccine efficacy equal to 59.7%. Moreover, considering only the age class < 35 years, there was a difference in the incidence of diarrhoea among vaccinated (16.2%) and unvaccinated (50.0%) subjects in relation to work or cooperation trips (p = 0.0252) compared to trips made for tourism. There was no significant gender-related difference in the incidence of diarrhoea, both in vaccinated (males 13.3%, females 15.5%; p = 0.7288) and in unvaccinated individuals (males 22.4%, females 18.4%, p = 0.6376).

Although the percentage of subjects who experienced diarrhoea have been consistently lower in vaccinated than unvaccinated subjects, there were no significant differences regarding the destination of the trip (Tab. IV) (Central-South America: cases of diarrhoea in vaccinated 14.7%, in unvaccinated 38.9%, p = 0.0819; Africa: cases of diarrhoea in vaccinated 10.6%, in unvaccinated 12.8%, p = 0.7073; Asia: cases of diarrhoea in vaccinated 19.7%, in unvaccinated 21.4%, p = 0.8484). Finally, the onset of diarrhoea with a severe intensity was found more frequently in unvaccinated subjects (15.0% vs. 11.1%), whereas cases of mild intensity occurred more frequently in vaccinated ones (33.3% vs. 25%). Noteworthy, the vaccine was confirmed safe as serious adverse reactions have not been reported.

Discussion

Prevention of fecal-orally transmitted diseases is a priority for subjects who travel to high endemic areas. Among these diseases, traveler's diarrhoea has a considerable epidemiological impact because of the significant reduction of the regular activities during the journey [5]. Prevention of fecal-orally transmitted diseases requires the adoption of specific hygienic and behavioural standards: moreover, nowadays, it is possible to be vaccinated against some of them.

These behavioural rules are well summarized by saying "Cook it, peel it, boil it or forget it!". In fact, the main risk factor for fecal-oral transmission is the ingestion of contaminated water or food: therefore, the main rules

Tab. I. Rate of diarrhoea in subjects not vaccinated and vaccinated, stratified by length of journey.

Length of journey	Not vaccinated (%)	Vaccinated (%)	p
< 15 gg	21.6	12.3	0.2136
15-28	10.5	16.2	0.5896
> 28	40.0	12.1	0.0390

Tab. II. Rate of diarrhoea in subjects not vaccinated and vaccinated, stratified by age class.

Age class	Not vaccinated (%)	Vaccinated (%)	p
< 35	27.1	13.7	0.0470
35-49	19.4	11.8	0.3457
> 49	5.6	19.1	0.2551

Tab. III. Rate of diarrhoea in subjects not vaccinated and vaccinated, stratified by reason of travel.

Reason of travel	Not vaccinated (%)	Vaccinated (%)	p
Work/Cooperation	35.0	14.1	0.0313
Tourism	16.9	14.2	0.6046

Tab. IV. Rate of diarrhoea in subjects not vaccinated and vaccinated, stratified by destination of journey.

Destination	Not vaccinated (%)	Vaccinated (%)	p
Africa	12.8	10.6	0.7073
Asia	21.4	19.7	0.8484
Central/South America	38.9	14.7	0.0819

imply that a traveler should attend to the exclusive ingestion of bottled water, peeled fruit, and cooked food. Although well known, these rules are frequently disregarded, and especially young people undertake more so-called 'adventurous' trips during which they don't want to, or actually cannot strictly adhere to those rules. These trips, in fact, often provide outdoor activities and a closer contact with nature and the population of the visited areas thus creating situations where it is difficult to avoid contact with contaminated water or food.

These observations could be the basis of the data shown in the present study where we found a significant difference in the onset of diarrhoea among vaccinated and unvaccinated subjects belonging to age group < 35 years, that represented the 51.4 % of the participants to this study. Moreover the younger people will, presumably, find themselves in situations at risk of fecal-oral disease transmission for the style of travel they typically take. Therefore, this age group experiences the greatest number of cases of traveler's diarrhoea and it is consequently possible to verify more accurately the difference in the onset of the disease in subjects vaccinated with Dukoral® vs. unvaccinated ones, and the good efficacy of the vaccine.

The results of the present study are based on a relatively small sample, therefore they should be viewed with caution. The study was not randomized; we therefore cannot exclude that those willing to be vaccinated might be more motivated to avoid diarrhoea risks. The questionnaire was compiled upon returning from the travel and a certain degree of recall bias may have occurred. However, a recent Spanish study [16] is in line with these considerations: it analyzed the occurrence of traveler's diarrhoea in vaccinated and unvaccinated subjects, considering a sample composed exclusively of young travelers (aged 18 to 30 years). It showed that 17.4% of young vaccinated travelers experienced at least one attack of diarrhoea compared to 39.7% of non-vaccinated ($p < 0.01$) and also the length of the episode of diarrhoea in the first group was at least one day shorter compared to the other group. Risk exposure and reason of travel showed a likewise strict relationship in case of journeys aimed at cooperation. We may suppose that international cooperation-related travels expose the subject to hardly controllable environmental and sanitary conditions, and imply an increased length of stay in a foreign country, leading to prolonged exposure to risk factors for fecal-oral diseases. In this context the study showed the best results in terms of decline in the incidence of diarrhoea in vaccinated vs. unvaccinated subjects in long lasting journeys. Therefore, the efficacy of the vaccine emerges more clearly in these situations. Moreover, this study highlights how a vaccine against cholera (Dukoral®) proved effective in preventing traveler's diarrhoea, too (it is anyway important to remember that the EMEA authorized Dukoral® to be sold within European Community as a vaccine against cholera only). The scientific community suggests the advisability of extending the anticholeric vaccination to people living in areas of high endemicity or otherwise exposed to hygiene conditions at high risk of transmission of fecal-oral diseases, as well as in those situations where public health emergencies related to conflicts or natural disasters are existing [17, 18]. In addition, some studies have shown a favourable cost-benefit of vaccination with oral anticholeric vaccine for travelers going to areas at high risk of fecal-orally transmitted diseases, regardless of the length of the journey and the visited country. In fact, due to the very high incidence of traveler's diarrhoea the number needed to treat to prevent one case is really low and in line with the results found by other authors [19].

Conclusions

Oral anticholeric vaccine (WC/rBS, Dukoral®) represents a good opportunity of prevention especially when travelers are confronted with conditions at higher risk of transmission of fecal-oral diseases (in relation to the geographical area they travel to, duration of the travel, ability to control environmental and sanitary conditions).

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