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Single Dose Treatments in Tropical Infectious Diarrhoea

The Place of Secnidazole

Jean Dupouy-Camet

Laboratoire de Parasitologie, Hôpital Cochin, Paris, France

Summary

Single dose treatments have the important advantages of simple administration, excellent compliance, short-lived side effects (if any) and short period of drug pressure. However, drugs used for single dose treatments must possess important characteristics, namely, long half-life, effective concentration in tissues over a long period, and low toxicity. In tropical medicine, such drugs are an important advance in the treatment of malaria (mefloquine and halofantrine), schistosomiasis (praziquantel and metrifonate), filariasis (ivermectin), and genitourinary tract and intestinal infections.

Intestinal infections are one of the most frequent problems in tropical medicine. While a large number of cases of diarrhoea are of viral (rotavirus) or bacterial (*Salmonella*, *Escherichia coli*) origin, necessitating only oral rehydration, some are of parasitological origin (*Giardia*, *Entamoeba histolytica*, *Strongyloides*, *Trichuris*, *Schistosoma*) and can be cured by a single dose treatment (tinidazole, secnidazole, ivermectin, albendazole, praziquantel). Secnidazole is the nitroimidazole with the longest half-life and is, therefore, used in single dose treatments for *Giardia*, acute intestinal amoebiasis and *E. histolytica* cyst carriers. Single dose treatments of most intestinal parasites will be a major advance in the management of tropical infectious diarrhoea. In the next decade, opportunistic intestinal infections (*Cryptosporidium*, *Isospora*, *Enterocytozoon*) in AIDS patients that are refractory to treatment could be the major problem.

In the past, the treatment of tropical diseases has been hampered by lengthy therapy involving repeated drug administration, low compliance and a high risk of possible side effects. A well known example is the treatment of bilharziasis by niridazole, which necessitated hospitalisation of patients for a week because of possible psychosis. Currently, only a single dose of praziquantel or metrifonate is required to treat bilharziasis in outpatients.[1,2] Important advances in tropical medicine have been achieved with the development of single dose treatments. This was the case for malaria, with the use of new drugs with long half-lives such as sulfadoxine-pyrimethamine, mefloquine or halofantrine.[3-5] A real opportunity to lower the incidence of filariasis and onchocerciasis throughout the world was provided by the development of ivermectin, with treatment requiring 2 tablets every 6 to 12 months.[6,7] Ivermectin has also proven its efficiency for scabies[8] and cutaneous larva migrans.[9] Single dose treatments are also widely used for the treatment of genitourinary infections,

e.g. pefloxacin in gonorrhoea and bladder infections, and tinidazole or secnidazole in genital trichomoniasis and vaginal bacteriosis.[10-13]

One of the major threats to health in tropical countries is diarrhoea. Recently, the WHO estimated that there are 3 to 5 billion individuals with diarrhoea each year and 5 to 10 million die.[14] In tropical countries, children under the age of 5 are particularly susceptible, and diarrhoea accounts for 7% of deaths in this age group. In addition, the development of AIDS led to the frequent occurrence of devastating and treatment-resistant diarrhoeas. Lastly, intestinal infections occur in thousands of travellers each year.[15]

Some of these intestinal infections will be of bacterial or parasitic origin and potentially curable by single dose treatments. This paper will review the main causes of infectious diarrhoea in tropical areas and highlight the cases where single dose therapy is possible. Bacterial food poisoning will not be discussed because diarrhoea is due to ingested toxins and not to the development of microorganisms in the intestine.

1. Mechanisms and Causes of Tropical Infectious Diarrhoeas

Microbial diarrhoea may result from 2 mechanisms: perturbation of fluid or sodium absorption (toxigenic), or invasion and damage to the mucosa. Several types of diarrhoea exist. These include watery acute diarrhoea from toxins, bloody and exudative dysentery with abdominal pain, caused by gut-invading pathogens, and chronic diarrhoea, often of parasitic origin. Because of the difficulty of surveillance, there have been few community-based studies of the enteropathogens associated with diarrhoea. Among 8139 patients with diarrhoea in Bangladesh, Black et al.[16] reported 26% with enterotoxinogenic *Escherichia coli*, 12% with *Vibrio cholerae*, 5% with *Shigella*, 4% with *Entamoeba histolytica*, 2% with *Giardia* and less than 1% with *Salmonella*. In other studies with children under the age of 5, enterotoxinogenic *E. coli*, *Campylobacter*, *Shigella* and Rotavirus accounted for 9 to 28%, 3 to 25%, 1 to 13% and 8 to 46%, respectively.[15] However, several pathogens are often involved, and it is difficult to establish a correlation between gastrointestinal symptoms and an individual pathogen. For parasitic infections, information can be obtained from residents of industrialised countries who acquired a single infection during travel in tropical countries.[17] Causes and mechanisms of tropical infectious diarrhoea are summarised in table I. In most cases, diarrhoea results from the ingestion of food or water contaminated by human or animal faeces.

1.1 Viral Causes

Rotaviruses are the most common cause of dehydrating diarrhoeal illness in children under the age of 2. Diarrhoea associated with this pathogen is due to disorganised enterocyte renewal and migration. Increased shedding of infected cells in the lumen of the small intestine occurs and the new enterocytes have the characteristics of undifferentiated secretory crypt cells.[18] Production of neurohumoral inflammatory mediators was also reported. Other less commonly involved viruses include Norwalk virus, adenoviruses, astrovirus, and coronavirus. Viruses are transmitted by the faecal-oral route or, less frequently, by the respiratory route.

1.2 Bacterial Causes

E. coli comprise most of the bacterial human intestinal flora. Several types of *E. coli* can cause diarrhoea by different mechanisms: enterotoxigenic, enteroinvasive, enteropathogenic, and enteroadherent. Enterotoxigenic *E. coli* are the most common cause of diarrhoea in young children and in travellers. These organisms may elaborate multiple virulence determinants, including fimbrial adhesins, and heat labile and heat stable enterotoxins. Enteroinvasive *E. coli* cause dysentery by invading epithelial cells of the colon in a similar manner to *Shigella*. Enteropathogenic *E. coli* have no recognisable toxin. They do not invade epithelium but attach themselves to enterocytes, inducing an alteration in cell shape and localised destruction of the brush border.[19]

Other bacteria involved in enteritis are *Shigella*, *Salmonella*, *Campylobacter* and *Yersinia*, which invade host gut epithelium, primarily the ileum and the colon. Mucosal ulcerations with an acute inflammatory response with neutrophil infiltrates and microabscesses in the lamina propria are common features. This local inflammatory response (associated with toxins of bacterial origin) causes secretion, and the damaged epithelium is unable to reabsorb fluids from gut lumen. *Salmonella* and *Campylobacter* are found in the intestine of many vertebrates and are present in water and contaminated food. Humans are the only natural host of *Shigella*, and contamination usually results from person to person transmission. A very small inoculum of *Shigella* (less than 10) can produce a human infection.[20]

Humans are the only known host for cholera, but an inoculum of at least 10^9 *Vibrio* is required to produce acute cholera, especially in individuals with normal gastric acidity. *Vibrio* cause diarrhoea through secretion of a potent toxin, which inhibits adenylate cyclase of enterocytes.[20]

1.3 Parasitic Causes

Intestinal parasites can produce all forms of diarrhoeal illnesses, including acute watery diarrhoea, dysentery or chronic diarrhoea. Most of these infections are common in tropical areas. Giardiasis and cryptosporidiosis are also frequent in industrialised countries, particularly in institutions or daycare centres.[21,22]

1.3.1 Protozoa

Giardia spp. are among the most frequent protozoa in the intestinal tract, and as few as 10 cysts can initiate infection. After excystation, the trophozoite attaches to the epithelium of the small intestine by a ventral disk. Although the majority of infected individuals are symptom free, a villous atrophy resulting from direct physical injury, giardial proteinases and activation of mucosal T cells by giardial antigens may be observed.[23,24]

Cryptosporidium is known to occur in many wild and domestic animals (calves) but is now very frequent in AIDS patients.[25,26] Easier diagnosis through the use of special stains, developed to detect mycobacteria, have shown that *Cryptosporidium* is

Table I. Causes and mechanisms of infectious tropical diarrhoea

Basic mechanism	Microorganism	Localisation	Pathogen in enterocyte	Pathology
Enterotoxin	Rotavirus *Vibrio* ET *Escherichia coli* *Giardia*	Small intestine	No	Shortening and blunting of the villi Intact or vacuolated epithelium Congestive lamina propria Lymphocyte infiltrate
	Isospora belli *Cryptosporidium* sp. *Microsporidia*	Small intestine	Yes	Shortening and blunting of the villi Microvillus alterations Destruction of enterocytes
	Trichinella, Strongyloides *Capillaria philipensis*		No	Helminths inside lamina propria Lamina propria eosinophilic infiltrates
Mucosal invasion[a]	EI *E. coli, Salmonella* *Shigella, Campylobacter,* *Yersinia*	Ileo-colic	Yes	Necrosis of enterocytes Lamina propria neutrophilic infiltrates Microabscesses
	Entamoeba histolytica *Balantidium coli*	Colon	No	Undermined ulcers for *E. histolytica* Microscopic haemorrhages
	Trichuris trichiura *Schistosoma*	Colon	No	Moderate lymphocytic infiltrates Granulomas around eggs Inflammatory polyps

a Enterotoxins have also been described for invasive organisms such as *Shigella*, *Campylobacter* and *E. histolytica*.

Abbreviations: EI = enteroinvasive; ET = enterotoxigenic.

also an important cause of diarrhoea in immunocompetent individuals.[24] Villous atrophy is common and can be accompanied by an inflammatory infiltrate of the lamina propria. The brush border is severely damaged by the intraepithelial development of Cryptosporidia.[27]

Isospora belli is a rare pathogen in immunocompetent individuals. In AIDS patients, the pathogenic changes in the bowel are similar to those observed with *Cryptosporidium.*

Microsporidia spp. are intracellular, spore-forming protozoa, now commonly described in AIDS patients but also found in immunocompetent patients (Datry, personal communication 1994). The mechanism of diarrhoea is unclear as the brush border appears normal, but small infiltrates of mononucleated cells can be observed in the lamina propria.[28,29]

The newly described *Cyclospora* spp. (or CLB for Cyanobacteria-like bodies) belong to the coccidian group and have been observed in diarrhoeal stools from several parts of the world. The mechanism of pathogenicity is unknown but could be similar to *Isospora.*[30]

E. histolytica is predominantly a colonic enteropathogen, but extracolonic disease, particularly liver abscesses, can develop. Although an estimated 500 million people are infected by this parasite, only 1.5 million will develop symptomatic disease, resulting in 50 to 100 000 deaths.[31] This gap between the number of infected and symptomatic people has led some authors to consider the hypothesis that 2 species of *E. histolytica* exist: one pathogenic, the other nonpathogenic.[32] This hypothesis was confirmed by isoenzyme analysis, which showed an association between a specific pattern and pathogenicity.[33] However, this now widely accepted hypothesis was discussed by some authors claiming that a change of pattern was possible after bacterial influence.[34] Experimental studies *in vitro* have shown that the cytolytic potential of *E. histolytica* was dramatically increased when associated with bacteria.[34] The first step in invasion is adhesion to the epithelium, mediated by a galactose binding protein.[35,36] Following contact, cytolysis occurs rapidly and is dependent on phospholipase activity, pore-forming peptides and proteolytic enzymes. *E. histolytica* trophozoites kill and phagocytise cells such as enterocytes and neutrophils, thus allowing deeper penetration in the intestine wall.

Balantidium coli, a large but rare ciliate protozoa living in pig intestine, can provoke a dysenteric syndrome very similar to that produced by *E. histolytica.* It is found in tropical countries where close contact between humans and animals exist (Africa south of Sahara, South America).

Other intestinal protozoa can be found in the stools: flagellates such as *Chilomastix mesnili* or *Trichomonas intestinalis*, amoebas such as *E. coli*, *E. hartmanni*, *Endolimax nana*, *Pseudolimax butschlii*, *Dientamoeba fragilis.* Although this point is discussed, for most authors these parasites are nonpathogenic (except *D. fragilis*) and do not require any treatment.

1.3.2 Helminths

Despite the high prevalence of intestinal helminthic infections, only a few intestinal helminths that invade the gut mucosa cause symptomatic diarrhoea.[17] Adults or larvae of *Trichinella* sp., *Strongyloides stercoralis, Trichuris trichiura, Capillaria philipensis* and, to a lesser extent, *Hymenolepis nana* and hookworms are present in the wall of the intestine. Eggs of *Schistosoma* spp. can be found in the submucosa and lamina propria of the bowel.

Trichinella is found worldwide and is transmitted to humans by the ingestion of inadequately cooked meat (especially pork and horse) containing infective larvae. *Trichinella spiralis* usually induces diarrhoea during the few days preceding the occurrence of the systemic symptoms, i.e. fever, facial oedema and myalgias.[37] Chronic diarrhoea has been described in Inuit populations, who are frequently re-infected by the parasite.[38] A useful mouse model has resulted in a number of studies devoted to the intestinal pathophysiology of *Trichinella.* The presence of adult worms in the mucosa leads to an inflammatory infiltrate and release of vasoactive substances that promote

intestinal motility and secretion.[39] *Trichinella* is the only intestinal pathogen producing diarrhoea that is not caused by faecal contamination of the environment.

T. trichiuria is very common worldwide, infecting at least 800 million people. This worm has a very thin anterior head, which penetrates the mucosa of the caecum. Inflammation is usually mild or absent, but an increased number of mucosal macrophages and mast cells can lead to local anaphylaxis and diarrhoea.[40] Diarrhoea occurs only in heavy infections and correlates with the number of eggs recovered per gram of faeces.[17]

C. philipensis, which is particularly prevalent in the Philippines and Thailand among raw-fish eaters, shares with *S. stercoralis* the ability to replicate within its host.[41] All stages of the parasite are found within the mucosa, where they cause inflammation and a flattening of villi. The parasite is responsible for chronic diarrhoea leading to significant loss of weight, and cachexia, which may be fatal.

Infection with *S. stercoralis* follows skin contact with water or mud contaminated with faeces containing infective larvae.[42] Females of *Strongyloides* invade the proximal small intestinal mucosa and cause partial villous atrophy and inflammatory infiltrates. The colonic mucosa can also be severely damaged during disseminated strongyloidiasis, particularly in immunosuppressed patients where the continuous internal replication of the parasite increases the size of the adult population. In this syndrome, millions of filariform larvae can penetrate the wall of the small intestine, causing mucosal ulcerations and bacterial invasion leading to septicaemia and peritonitis.[43]

More than 300 million people are infected with the 5 species of schistosomes, and intestinal injury occurs most frequently with *Schistosoma mansoni, S. japonicum, S. mekonji* and *S. intercalatum* infection.[44] Contamination follows skin contact with water containing the infective cercariae. The parasite requires an intermediate host (fresh water snails such as *Biomphalaria* sp. or *Onchomelania* sp.) in which the miracidia liberated from eggs can multiply and form cercariae. Eggs are transported through the mesenteric veins into the colonic wall, where they elicit granuloma formation; morbidity results from granulomatous hypersensitivity to egg antigens. The extent and severity of colonic lesions depend largely on the magnitude of infection. In heavily infected patients, colorectal involvement with ulcerations and polyp formation is one of the major clinical problems. The resulting symptomatology is similar to that produced by *E. histolytica* infection.[45]

1.4 AIDS Patients

In addition to the general immunosuppression caused by loss of T cells in AIDS patients, there are also changes in the gut-associated lymphoid tissue and in nonspecific mechanisms of host resistance.[46] In AIDS patients all of the pathogens described above can be a cause of diarrhoea, but those most commonly found are *Cryptosporidium, Microsporidium,* Cytomegalovirus, *Giardia, Salmonella, Shigella* and *Mycobacterium avium-intracellulare. Cryptosporidium,* which causes self-limited diarrhoea in immunocompetent patients, may result in severe, refractory diarrhoea in AIDS patients.[25,29,47]

2. Diagnostic Procedures

Diagnostic procedures are based on the visualisation of the causative agent in a faecal sample, which may require several days before a definitive diagnosis can be made. Newer techniques including enzyme-linked immunoabsorbent assay (ELISA), monoclonal antibodies, and polymerase chain reaction (PCR) may shorten the time to diagnosis but are frequently expensive. We will highlight some simple approaches to the diagnosis of diarrhoea that can be found in the 'Manual of Basic Techniques for a Health Laboratory'.[48] Details on more sophisticated methods are reported in the recent reviews of Cook[49] and Guerrant and Bobak.[14]

Faecal leucocyte examination is useful and inexpensive. A fresh stool sample, preferably containing mucus, is mixed with 2 drops of saline and

examined microscopically under a coverslip. A high leucocyte or erythrocyte count of 20 to 50 per high power field suggests an invasive colonic disease of bacterial or protozoal origin. The absence of leucocytes suggests a small intestinal toxigenic diarrhoea of viral or bacterial origin.

Subsequent cultures (*Salmonella*, *Shigella* and Drigalski media) and specific biochemical tests are required to diagnose *Salmonella* or *Shigella* infection. A keen microbiologist will be able to recognise the curved Gram-negative bacillus of *Vibrio* on wet mounts.

Viruses can be detected in stools by ELISA or by latex agglutination, but this detection is reserved for specialised laboratories.[49]

For dysenteric syndromes or persisting diarrhoea, parasitological investigations should be carried out. Finding live *E. histolytica* or *Giardia lamblia* (also known as *G. intestinalis* and *G. duodenalis*) or trophozoites requires careful examination of a fresh faecal sample. Lugol's iodine can be useful to stain the characteristic nuclei of *Entamoeba* and to aid differentiation from intestinal macrophages. Concentration techniques using formalin and ether sedimentation, with or without zinc sulfate flotation, are recommended to increase the sensitivity of detection of parasites.[50] However, these techniques, which require chemicals and centrifugation, may be difficult to carry out in some laboratories and may destroy trophozoites. The simple Kato thick smear technique[51] can also be used, but this technique is not very effective in demonstrating protozoan parasites. The sensitivity of the diagnosis of *Strongyloides* can be increased by the use of techniques described by Harada-Mori[48] and Baerman,[52] which are based on the attraction of *S. stercoralis* larvae to warm water. Biopsies of rectal mucosa may be indicated to detect eggs of *Schistosoma* if stool examinations are negative. Faecal smears can be stained by Ziehl-Neelsen or auraminephenol to diagnose *Cryptosporidium, Cyclospora* and *Isospora*, or by special dyes (Uvitex 2B, Masson trichrome) to diagnose *Microsporidia*.

Serological tests are of limited value for diagnosing most intestinal pathogens, except for schistosomiasis and intestinal amoebiasis. However, the antibody titres are frequently low in intestinal amoebic infection.

3. Single Dose Treatment in Tropical Infectious Diarrhoea

3.1 Pros and Cons of Single Dose Treatments

Single dose treatments have a number of important advantages that result in excellent compliance: 1) administration is simple, possible in mass treatments, and the intake of the drug can be checked easily; 2) side effects, if any, will last for a short period and will not interrupt treatment; and 3) the rate of emergence of resistant organisms could be lowered by the short period of drug pressure. Continuous metronidazole exposure of *Giardia* over several months resulted in the occurrence of resistant strains.[53]

However, possible disadvantages include the following: 1) absorption could be impaired in patients with diarrhoea or malnutrition; 2) side effects could be more important, because of higher serum concentrations; 3) patients could be disappointed when symptoms persist while they are not receiving any treatment; and 4) the ease of such treatments can lead to frequent self-medication in countries where prescriptions are not required.

3.2 Single Dose Treatments for Infectious Diarrhoea

The basic treatment for every infectious diarrhoea, particularly in children, includes rehydration by oral solutions such as the standard WHO solution.[54,55] Single dose treatments are mainly used for parasitological and some bacterial infections. Quinolones can be used in single dose for shigellosis or traveller's diarrhoea (e.g. pefloxacin or norfloxacin in a single dose of 800mg), and a single dose regimen with doxycycline has been effective in cholera outbreaks.[56] The single dose treatments that can be prescribed for parasitic diarrhoea are detailed in table II. All parasites de-

Table II. Parasitic diarrhoeas that can be treated with single dose therapy

Parasites	Antimicrobial agent	Dose
Entamoeba histolytica	Secnidazole	2g or 30 mg/kg
Giardia lamblia[a]	Secnidazole	2g or 30 mg/kg
	Tinidazole	2g or 30 mg/kg
Isospora belli	Sulfadoxine-pyrimethamine,	0.5 tablet/10kg
	Mefloquine	25 mg/kg in 3 daily doses
	Halofantrine	25 mg/kg in 3 daily doses
Trichuris trichiura	Albendazole	800mg
Strongyloides stercoralis	Thiabendazole	50 mg/kg
	Ivermectin	200 μg/kg for 2 days
Schistosoma mansoni	Praziquantel	40-60 mg/kg
	Oxamniquine	15 mg/kg
Hymenolepis nana	Praziquantel	15-20 mg/kg

a Also known as *G. intestinalis* and *G. duodenalis*.

scribed above can be treated with single dose treatments except *C. philipensis*, Cryptosporidia and *Microsporidia*. Moreover, in immunosuppressed patients, parasites usually cured by single dose regimens may require several administrations, e.g. isosporosis, strongyloidosis.[57] For intestinal helminths, the most useful drugs in single dose regimens are thiabendazole,[6] oxamniquine,[1,58] albendazole,[59,60] praziquantel[1,61] and ivermectin.[62] Intestinal amoebiasis and giardiasis can be cured by nitroimidazoles with long half-lives, such as secnidazole, tinidazole or ornidazole.

3.3. The Role of Secnidazole

Secnidazole has pharmacological characteristics that make this drug useful for single dose treatments of intestinal amoebiasis and giardiasis.

3.3.1 Long Half-Life and Tissue Concentrations

Secnidazole is the nitroimidazole with the longest half-life *in vivo*.[13] It is rapidly distributed throughout the body and achieves high concentrations in the target biological tissues and organs.[63,64] The distribution half-life of secnidazole is close to 10 minutes. The time of appearance (t_{max}) of the maximum concentration (C_{max}) is one hour and blood levels range from 27 to 68.2 mg/L for an oral dose of 2g (fig. 1). Bioavailability is excellent, and there is no difference between oral and intravenous administration. Secnidazole is probably metabolised in the liver, and 50% of the ingested dose is excreted unchanged in the urine. It has an apparent elimination half-life of 20 hours, in contrast to 8 hours for metronidazole and 12 hours for tinidazole.[65] A longer half-life (as long as 28.8 hours) and high concentrations in gingival tissues (72% and 91% of the serum concentration one hour and 72 hours after intake, respectively) were reported recently by Tenenbaum et al.[66] [fig. 1]. However, data on the concentrations of secnidazole in other tissues and fluids are lacking, but they should be similar to those reported for metronidazole and tinidazole. For these drugs, the maximal concentration (expressed as a percentage of serum concentration) was 70% in the colon, 55% in bile, and 110% in the ileum.[67] Three days after oral administration of secnidazole, mean serum values of 4 mg/L were well above the minimum inhibitory concentrations (MICs) of *Giardia*, *Entamoeba histolytica* and *Trichomonas vaginalis* (see below) [fig. 1]. For tinidazole and ornidazole, serum concentrations 72 hours after intake were 1.3 and 0.8 mg/L, respectively.[63,68]

3.3.2 Mechanisms of Antiprotozoal Activity

The antiprotozoal activity of nitroimidazoles is linked to the ferredoxin oxidoreductase-mediated reduction of the nitro group.[69] A short-lived re-

duction product, the protonated one-electron nitro radical anion, oxidises microbial DNA, resulting in strand breaks and cell death (fig. 2). DNAs with high adenine-thymidine contents (e.g. *Trichomonas* and *Entamoeba*) are more susceptible to oxidative damages.[70] In the presence of oxygen, reduction of the nitro group cannot occur; therefore, the nitroimidazoles are toxic only for anaerobic cells or organisms.[71] *Giardia, Trichomonas* and *Entamoeba*, with no mitochondria, are anaerobic protozoa in which ferredoxin oxidoreductase is a key enzyme for anaerobic glycolysis.

3.3.3 Efficacy of Secnidazole

In animal studies, secnidazole was found to be twice as active as metronidazole for amoebiasis, with serum concentrations of 3 to 6 mg/L.[72,73] In *in vitro* assays to test the antigiardial activity of drugs,[74] concentrations inhibiting 50% of the growth of *Giardia* were 0.15 mg/L for secnidazole, 0.38 mg/L for quinacrine, 0.41 mg/L for furazolidone and 1.15 mg/L for metronidazole.[75]

Secnidazole in a single dose of 2g (or 30 mg/kg) is very effective treatment for giardiasis, in common with other long-acting nitroimidazoles[76-78] and for acute intestinal amoebiasis, where other nitroimidazoles require 2 or 3 doses.[79-82] The WHO recommended secnidazole as the only nitroimidazole for use as a single dose treatment for amoebic dysentery.[83] When prescribed for several days, secnidazole is also active against cysts[82,84,85] and hepatic amoebiasis.[79,82]

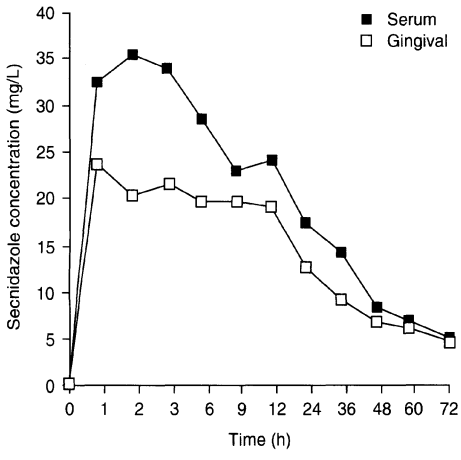

Fig. 1. Secnidazole concentrations in serum and crevicular fluid after a single dose of 2g.[66]

Treatment failures have been reported with nitroimidazoles but these may be linked to malabsorption or reinfection.[74,86] Experimentally, it was possible to induce *in vitro* resistance of *Giardia* to metronidazole and *Entamoeba* to emetine by continuous drug exposure over several months.[53,87] The MICs were 500-fold higher than those before drug exposure. However, the few reports of *in vivo* resistance to nitroimidazoles are not convincing.

3.3.4 Toxicity, Side Effects and Contraindications

Toxicity studies in a mouse model have shown the very low toxicity of secnidazole, with a lethal dose for 50% (LD_{50}) of approximately 2.5 g/kg. In long term studies, secnidazole was well tolerated by dogs at a dosage of 400 mg/kg/day for 1 month; however 200 mg/kg/day for 3 months produced some neurological effects. Tests of mutagenicity using *Salmonella typhi* and *E. coli* were positive.[72] The effect of nitroimidazoles on human DNA is of concern, but this interaction requires a nitroreductase, which is only present in anaerobic microorganisms. In the late seventies, the possible carcinogenicity of metronidazole was evaluated in animal studies. However, the methodology used was questionable, and carcinogenicity in humans is not considered to be a problem.[88]

Although no evidence of any teratogenic effect has been observed in experimental studies of secnidazole,[72] the drug should not be administered during the first trimester of pregnancy or during lactation because secnidazole can be detected in the placenta and breast milk. This could be a potential limitation for mass treatment. However, a review of more than 2000 pregnant women treated with metronidazole did not identify an increased incidence of malformations.[88,89] The only real but rare contraindication to secnidazole is a known hypersensitivity to nitroimidazoles (urticaria). Ingestion with alcohol can provoke an an-

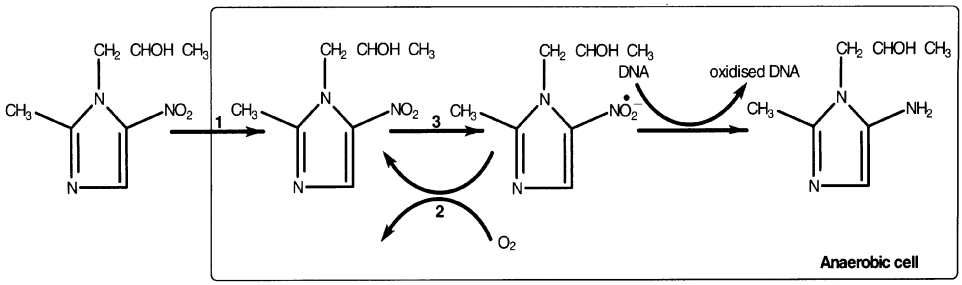

Fig. 2. Probable mechanism of action of secnidazole. **1** = passive diffusion in the cell; **2** = detoxification in the presence of oxygen; **3** = ferredoxin reductase.

tabuse-like effect, and close monitoring is recommended if the patient is taking warfarin.[6]

Side effects common to all nitroimidazoles include gastrointestinal disturbances (abdominal pain, diarrhoea, a metallic taste, nausea), headache, and dizziness. These side effects are significantly lowered by evening administration[11] Urticaria, leucopenia, and neurological complications (such as paraesthesias) have not been reported for secnidazole.

3.3.5 Possible Limitations to Single Dose Secnidazole Therapy

Patients with intestinal amoebiasis may be reluctant to receive single dose regimens for a disease with such a bad reputation, but intestinal symptoms of amoebiasis can disappear in a few hours following treatment with secnidazole.[79]

Diarrhoea causing poor drug absorption could be responsible for treatment failures reported by some authors treating giardiasis in children. However, data concerning the absorption of nitroimidazoles in the presence of diarrhoea are lacking. In contrast, some studies have shown that malnourished children have increased serum concentrations of metronidazole.[90] Despite higher serum concentrations, side effects are less frequent than those observed with long term metronidazole therapy.[76]

4. Conclusion

In most cases, the treatment of tropical infectious diarrhoea will require oral rehydratation. In some instances (e.g. shigellosis, intestinal amoebiasis, giardiasis, bilharzia, strongyloidosis), a single dose treatment will be effective, producing a significant advance in the management of these infections. Unfortunately, some parasites are naturally resistant to existing drugs (cryptosporidiosis) or require long courses of treatment (microsporidiosis, *C. philipensis*). Moreover, some pathogens that are usually easily cured prove to be relatively refractory to treatment in immunosuppressed patients.

Prevention of tropical infectious diarrhoea should be a high priority for international health authorities. Faecal contamination of water and the environment is of crucial importance in transmission and is linked to poor socioeconomic conditions and inadequate sanitation.[91] The development of vaccines against enteric pathogens is an area of active research,[15] but prevention of diarrhoea could be achieved by education (hand-washing), sanitation (disposal of excreta), and improved availability and quality of water.

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Correspondence and reprints: Dr *J. Dupouy-Camet*, Laboratoire de Parasitologie, Hôpital Cochin, 27 rue du Faubourg St Jacques, 75014, Paris, France.