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REVIEW ARTICLE

Racecadotril Versus Loperamide

Antidiarrheal Research Revisited

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Racecadotril is an enkephalinase inhibitor, presented as a purely antisecretory agent with advantages over the opiate-receptor agonist loperamide in the treatment of diarrhea. A critical review of the literature and the models used was performed. Although pretreatment with high doses of racecadotril reduced cholera toxin-induced secretion and although clinical efficacy was demonstrated in young infants—a population characterized by 10-fold higher plasma enkephalin concentrations compared with adults, the analysis calls into question the peripheral antisecretory selectivity and relative clinical efficacy. Conversely, loperamide can be proposed as an antisecretory agent at therapeutic concentrations. Its efficacy is well established in acute and chronic diarrhea. Current experimental and clinical comparative studies of both drugs have problems with regard to the selection of the doses, the validity of models, and/or the trial design. The conclusion is that more research is needed before reliable conclusions can be drawn on the place of racecadotril in diarrhea treatment.

KEY WORDS: diarrhea; antidiarrheal; racecadotril; loperamide; antisecretory.

Racecadotril, also called acetorphan, is an enkephalinase inhibitor, presented as a purely antisecretory therapy with advantages over loperamide (Table 1) (1–14), in particular because it does not slow gut transit (15). Loperamide is a peripheral opiate-receptor agonist, with antisecretory and motility-inhibiting properties (16). This review examines the literature on the mode of action and the clinical efficacy of racecadotril in comparison to loperamide. Medline, reviews, and manufacturer's information were used as sources for racecadotril and complemented with relevant literature of loperamide. Because enkephalinase inhibition results in enhanced enkephalin levels, information relevant to the physiology of enkephalins and their actions on the gut is briefly summarized. The objective is to contribute to antidiarrheal research and therapy.

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PHYSIOLOGY OF ENKEPHALINS

Natural enkephalins are pentapeptides of L-amino acids. These opioid peptides and their synthetic (mainly D) analogs, have a wide range of pharmacological actions. They play a role in analgesia, gastrointestinal motility, fluid absorption, olfaction, respiration, cognitive function, and mood (17, 18).

Although enkephalins are often proposed to act selectively on δ-opiate receptors in the gut, thereby reducing the mucosal cyclic AMP levels and decreasing the hypersecretion of water and electrolytes (1, 2, 7, 10), it is recognized that they also bind μ-opiate receptors and influence the motor function and transit of the gut (13, 18, 19). Their complex array of motility-inhibiting, proabsorptive, and antisecretory actions can be effectuated at different levels, from mucosa to brain (13, 20, 21). For instance, in intestinal preparations, enkephalins inhibit the peristaltic reflex and cholinergic-mediated peristaltic contractions (22–25). They modulate motor activity (stimulatory or inhibitory) in a similar way as opiate-receptor agonists, depending on the gut segment studied, and they delay duodenal and cecal transit (25, 26). Centrally acting selective δ-opioid receptor agonists result in potent colonic

TABLE 1. BENEFITS PROPOSED IN COMPARATIVE STUDIES BETWEEN RACECADOTRIL (RAC) AND LOPERAMIDE (LOP) AND SUMMARY OF MAIN COMMENTS RESULTING FROM LITERATURE ANALYSIS

Benefit	*Comments*
Experimental studies	
No inhibition of gastrointestinal transit with RAC, but with LOP(45)	Use of a normal antidiarrheal dose of RAC, but more than 13 times the antidiarrheal dose of LOP. Proabsorptive/antisecretory effects of LOP can confound the charcoal test; there is no dose-dependent inhibition of the charcoal transit by LOP at the dose level studied.
LOP, but not RAC increases bacterial proliferation with *E coli*(2)	Use of a germ-free neonate piglet model (altered in metabolism and bacterial colonisation compared to conventional animals). The higher *E. coli* content may reflect the response of the watery bowel contents of germ-free animals to the pro-absorptive/antisecretory stimulus of LOP. Activation of RACE is not validated in germ-free piglet model. Use of a normal experimental antidiarrheal dose of RACE, but of an established toxic dose of LOP irrelevant to humans.
Clinical studies	
RAC is as effective as LOP in acute diarrhea(5, 6, 101, 102)	Pretreatment duration of diarrhea allowed beyond 48 hr (interference of spontaneous recovery possible). Definition recovery as the time until the first normal stool (should be "until the last unformed stool"). Therapeutic RAC dosing, but constant LOP dosing rather than depending on diarrhea frequency and severity (too high and therefore potentially constipating or too low, compromising efficacy). No placebo control.
Tolerability	
Less constipation with RAC than LOP(5, 6, 101, 102)	Not based on clinical adverse event reporting, unless in two studies using an incorrect constant LOP dose. Calculation of the number of stool-free intervals (of varying duration between studies: 24 or 48 hr); efficacy can interfere as bowel transit normally last $\geq$48 hr and replenishing of the bowel can last longer after effective inhibition of secretions. The mean duration of such intervals did not differ between both products.
Less abdominal distension with RAC than LOP(101)	Nontherapeutic LOP doses were used: abdominal pain/distension was possibly induced by use of constant unneeded doses.

antipropulsive effects and inhibition of gastrointestinal transit (27).

The antisecretory action of enkephalins also has been documented, both peripherally and centrally (13, 20, 21). Exposed to human colonic mucosa, they inhibit the PEG_2-induced increase in cyclic AMP, an effect similar to that of morphine and blocked by the μ-opiate receptor antagonist naloxone (20). Administered intracerebrally, they enhance fluid absorption in cholera toxin-induced diarrhea (21). The effect of enkephalins on gut transit thus is likely to be the result of both motor-inhibiting and antisecretory properties.

Enkephalin levels and binding vary across tissues and species, rendering extrapolation of experimental data to human difficult (28). In addition, in brain and plasma, their concentrations are much higher in the newborn than in the adult, and they decrease with age (29, 30). In infant plasma, they are more than 10 times higher than in adult plasma (31). Their ability to cross the blood–brain barrier also declines with age (32–34). In adults, there also is a high variability in plasma levels (35). Enkephalin concentrations further vary according to the meal (36), exercise (37), stress (38), or disease states, such as allergy, uremia, diabetes, or hypertension, or constipation (37–41).

Endogenous enkephalins are rapidly degraded (13, 42). For instance, the increase in enkephalin levels seen after a meal in the dog only lasts for 10 min (36). Their breakdown occurs via endopeptidases, called enkephalinases. They are present in the central nervous system (CNS) and various peripheral organs, such as the gastrointestinal tract (42). Their activity in plasma is lower in elderly than in adult controls (43, 44). Thiorphan inhibits one of these peptidases, called enkephalinase A (13). Racecadotril is its diesterified prodrug, converted to thiorphan by esterases. Both drugs have an antidiarrheal effect in the castor oil test, albeit thiorphan only after parenteral administration (42, 45). This effect is antagonized by naloxone. To date, there is no documentation on the concentrations of natural enkephalins in the gut or plasma during diarrhea and after oral administration of racecadotril.

EFFECT ON GASTROINTESTINAL MOTILITY AND TRANSIT

Experimentally, it has been shown that racecadotril or thiorphan affects the postprandial colonic motor response after central, but not after intravenous administration (46), increases the motor activity of colonic long spike bursts during feeding and fasting (47), and reduces the duration of feeding motor activity, while delaying the return of an MMC after a meal (48). In rats, it did not slow

the colonic transit, in contrast to loperamide (42). The rats, however, received 40 mg/kg of racecadotril, which is the optimal antidiarrheal ED_{50} of the drug in this model, providing "partial" antidiarrheal control for 90 min, or 2 mg/kg of loperamide, which is 13 times its minimally effective oral dose providing "full" antidiarrheal protection for at least 1 hr (49, 50). This high loperamide dose resulted in only a 27% slowing of transit, a magnitude well within the variability of this test, and which may result from the proabsorptive/antisecretory actions of loperamide (see also the discussion of effects of loperamide on gut motility).

In humans, racecadotril 100 mg three times a day had no significant effect on orocecal transit (sulfazalazine test) and excretion of colonic markers (15). There seem to be no studies of the gut transit at higher dosages, in pediatrics or with the lactulose test (classically used with loperamide).

Considering the fact that enkephalins inhibit gut motility and transit (see physiology of enkephalins), it is surprising that such effects have not been demonstrated so far with racecadotril, especially if one assumes that the drug acts peripherally in the gut (see selectivity of peripheral action). Circumstances that can explain the lack of observations in isolated experimental models of diarrhea include:

1. Absent or very slow conversion of the prodrug racecadotril to active thiorphan. The *in vitro* inhibitory potency of racecadotril is 1000 times lower than that of thiorphan, but becomes comparable after prior incubation with "cerebral" membranes (45). Activation has been described in the cerebrum and kidney homogenates, but to the authors' knowledge, not with intestinal contents or mucosa (42). Drug activation is relevant: loperamide oxide, an inactive prodrug, only inhibits propulsion in isolated gut segments after preincubation with gut microflora or gut wall, which *N*-deoxygenates the oxide to active loperamide (51).
2. *In vitro* test conditions, inhibiting the expression of enkephalinase A. *Ex vivo* gut segments are accompanied by massive breakdown of tissue, producing enkephalins and leading to the phenomenon of "fatigue" (progressive loss of contractility of the segment). In the isolated guinea-pig ileum, enkephalinase A is present, but not functional (52).

In animals and humans, the effects of loperamide on gut motility and gut transit are dependent on its dose, the gut segment studied, the postprandial or fasting state and the species studied (53–61). For instance, in cats, loperamide does not change motility in the small intestine (the delayed transit therefore being attributed to increased fluid absorption), but it induces rhythmic activity in the colon (53). In humans, a single 12-mg dose of loperamide inhibits jenunal, but not ileal and colonic transit (54). In rats, loperamide fails to affect propulsion of charcoal in a dose-dependent manner, at any dose up to 1000 times its minimally effective antidiarrheal dose in the castor oil test (50). In healthy humans, 4 mg loperamide (the start dose to treat acute diarrhea) does not affect or increases the fasting propagating motor activity in the small intestine (59), and it does not slow orocecal transit (61). Slowing of the orocecal transit occurs in "normal" subjects taking a high single dose ($>$4 mg) or repetitive doses (taken in the absence of loose stools) (60, 62). A plausible explanation is an increased occupation of the intestinal μ-receptors during normal transit (compared to the diarrheal state), due to enhanced loperamide absorption, enrichment in the intestine via enterohepatic cycling and slower fecal elimination (the drug and its metabolites are excreted via the feces) (57, 62). The therapeutic dosing of loperamide is 4 mg to start, and 2 mg after each liquid bowel movement. In patients with diarrhea, such flexible dosing normalizes gut transit (63–65). It increases the feeding motor activity, while shortening its duration and prolonging the phase III of the MMC (66). Some of these motor effects correspond to those described experimentally with thiorphan (47, 48).

ANTISECRETORY ACTION

Antisecretory effects of racecadotril have been documented *in vivo* against cholera and *Escherichia coli* toxins (2, 67, 68). They were antagonized by naloxone (2, 67). Reduction of mucosal cyclic AMP, proposed to result from its indirect selective δ-opioid receptor interaction (7, 9, 69), was not documented. The studies used high oral doses, administered prior to the induction of secretion, or systemic administration.

For instance, in dogs with a Thiry-Vella loop (a closed gastrointestinal segment with orifices only on the dog's flank, but with preserved blood perfusion and innervations), 10 mg/kg of racecadotril was given orally 1 hr before induction of secretion, but not topically in the loop exposed to the toxin (2). The drug was thus absorbed from the remaining anastomosed oroanal canal to exert its effects in the loop. In rats, *Escherichia coli* toxin-induced secretion could only be antagonized after intraperitoneal but not topical racecadotril; in the case of cholera toxin, however, topical administration was effective (67). It is not known whether this is due to differences between the toxins in their onset of secretions (instantaneous excessive with *E. coli* toxins, delayed with cholera toxins), affecting the drug's absorption, and/or in the mechanism and reflex pathways causing the secretion.

In the human jejunum, a single dose of 300 mg racecadotril, administered 2.5 hr before induction of secretion by cholera toxin, prevented jejunal water and electrolyte secretion (68). The effect of a therapeutic 100-mg dose or of a dose given after induction of the secretion, was not documented.

Loperamide was developed as a μ-receptor antagonist and an inhibitor of gut transit in the early 1970s. This drug, however, also binds to other receptors (57, 70). In the villi of the human ileum, it binds to δ-receptors at concentrations as low as 10 nM (= 5 ng/ml, easily reached during therapeutic dosing in the human gut) (70). Its antisecretory actions, discovered since the 1980s, have been documented in gut membranes, isolated gut segments, and *in vivo* in various species and humans, before and after induction of secretion, for various secretagogues and also at therapeutic dose levels (57, 71–74). They occur via opiate and nonopiate receptor mediated interactions, including Ca^{2+} antagonism, inhibition of calmodulin, and stimulation of the colonic sodium chloride cotransport in the human brush border (57, 71, 74).

SELECTIVITY OF PERIPHERAL ACTION

So far, there appears to be no documentation of selective peripheral antisecretory or motility-inhibiting antidiarrheal properties of racecadotril (or its active compound thiorphan) in isolated gut segments. The selectivity of its action in the gut has been proposed based on the observation of intensive radiolabeling of the gut after administration of ^{14}C-labeled racecadotril in the rat and based on its failure to inhibit enkephalinase in human cerebrospinal fluid (10–12). The sensitivity of these tests to exclude CNS activity has not been published. In the autoradiographic study, 10 mg/kg of ^{14}C-labeled racecadotril was orally administered: this dose corresponds to the lowest orally effective ED_{50} in this model and needs to be administered intraperitoneally in order to result in an antidiarrheal effect comparable to oral loperamide in that species (10, 42). The test did not identify peripheral or central formation of enkephalins, which is highly tissue-dependent, with velocity rates 100 times higher in the brain than in the plasma (28, 75).

In humans, enkephalinase inhibition was lacking in the cerebrospinal fluid after an oral dose of 20 mg/kg (9, 11), but not after intravenous infusion of 26 μg/kg/min for 60 min (76). The maximal velocity of enkephalinase in the human cerebrospinal fluid is, however, 10 times lower than in the plasma and 1000 times lower than in brain homogenates (75). Furthermore, an acute oral dose of the enkephalinase inhibiting the drug captopril does not significantly inhibit the enkephalinase in human cerebrospinal fluid, despite crossing the blood–brain barrier (77).

In contrast to the idea of a selective peripheral action in the gut, racecadotril may owe its antidiarrheal potential to its lipophylic nature, which allows it to easily penetrate in to the brain, where it is converted to active thiorphan (13, 45). Thiorphan barely penetrates the blood–brain barrier and is not effective orally in humans. Other arguments supporting a potential central action include: (1) extensive binding and inhibition of cerebral enkephalinase after parenteral administration of 1–10 mg/kg racecadotril in mice and rats (45, 78); (2) inhibition of the break-down of synthetic enkephalins in the rat brain, after peripherally administered racecadotril (76); (3) exertion of various centrally mediated effects, some of which are naloxone-reversible (45) and opioidlike, such as antinociceptive or analgesic effects (45, 80, 81), and others naloxone-insensitive, such as the inhibition of gastric acid secretion (82, 83). The central opioid effects after racecadotril, however, are not subjected to the typical opioid (morphinelike) withdrawal effects (45, 84, 85).

Analysis from different sources showed that after parenteral administration of racecadotril, published effective doses for central effects ($<$1 mg/kg) (45, 80, 81), are lower than the minimally effective antidiarrheal doses ($\geq$5 mg/kg) reported elsewhere in the same species (42). Clear pharmacological differentiation between its antidiarrheal and central (analgesic) effects, by dose within one species, was not found in the literature reviewed.

Loperamide was developed based on the high dissociation of its ED_{50} for antidiarrheal efficacy in the castor oil test ($\geq$0.15 mg/kg orally, $\geq$0.02 mg/kg parenterally) compared to the ED_{50} for central depressant activity in the tail withdrawal test ($>$160 mg/kg orally, $\geq$3.18 mg/kg parenterally) (49, 50). Its peripheral selectivity is due to its high binding to intestinal tissues and complete hepatic extraction from mesenteric blood (22, 49, 86). It is fully excreted via the feces. Even if there is spillover in the systemic circulation due to insufficient hepatic extraction, loperamide normally does not cross the blood–brain barrier, due to extensive binding to plasma protein (87). Exceptions occur in the case of an immature or deficient liver function and blood–brain barrier and in rare cases of overdosing (88). Oral loperamide is thus normally devoid of morphinelike central analgesic, addictive, or CNS-depressant effects.

BACTERIAL PROLIFERATION

According to a study in piglets challenged with an *E. coli* strain, loperamide, but not racecadotril, entails

"risks" for bacterial proliferation (3). The model merits following comments:

1. The newborn piglets were kept germ-free (rather than gnotobiotic) on various antibiotics in a sterile isolator. Germ-free animals have a prolonged gut transit and enterohepatic circulation (89, 90). Their bowel contents are much more liquid. Exposure to fecal flora rapidly leads to bacterial colonization, normalization of gut transit, and condensation of the watery bowel contents (90). The slightly higher *E. coli* content in the proximal jejunum during high-dose loperamide administration may simply reflect the result of the antisecretory/proabsorptive stimulus. Overall, the model is irrelevant to real life, because during secretory diarrhea, bacteria remain present in the gut (91).
2. The newborn animal is "immature": in the rat, enkephalinase activity in some structures develops only progressively after birth (92). It is not known whether the enkephalinases, and similarly esterases for activation of racecadotril, are sufficiently expressed in the newborn germ-free piglet.
3. The loperamide doses (1 and 5 mg/kg twice daily) were excessive in comparison with its minimally effective oral antidiarrheal dose (0.15 mg/kg) and close to its established lethal LD_{50} dose in "one-day" old "conventional" rats (6 mg/kg) (49). The germ-free status may have further exaggerated the dose effect due to accumulation of loperamide via an enhanced enterohepatic circulation, as has been observed for bile acids in this model (12 instead of 2 days). In contrast, a normal antidiarrheal dose in this model was used for racecadotril (20 mg/kg twice daily) (42).

The theoretical risk of bacterial proliferation with loperamide has been largely dispelled by clinical trials and large worldwide experience (93, 94). Even very high doses, administered to children with protracted diarrhea, failed to induce pathogen proliferation or bacteremia (65). Use in chronic diarrhea has not led to bacterial proliferation (66).

CLINICALLY EFFECTIVE DOSE AND EFFICACY IN ADULTS

The recommended doses and types of diarrhea studied are summarized in Table 2. In adults, racecadotril is recommended at a fixed dose regimen of 100 mg three to four times daily (12). This dose has been proposed based on the dose–response of enkephalinase inhibition in healthy volunteers: it results in a peak activity of 75% inhibition of the plasma enkephalinase, 1–3 hr after its oral administration (7–12). Clinical dose-findings during diarrhea are not available. In humans with castor oil-induced diarrhea, the dose eliciting more than 50% inhibition of the plasma enkephalinase for at least 6 hr was 11.2 mg/kg (about 8 times the 100 mg unit dose) and highly variable (standard error 4.2) (14). At this high dose, stool weight and stool number were significantly reduced.

TABLE 2. CLINICAL EFFICACY PROFILE OF RACECADOTRIL AND LOPERAMIDE FROM PLACEBO-CONTROLLED STUDIES AT CURRENTLY RECOMMENDED THERAPEUTIC DOSING SCHEDULES

Type of diarrhea	*Clinical efficacy**	
	Racecadotril	*Loperamide*
Infants and children†	1 mg/kg, every 8 hr)	0.08–0.1 mg/kg, extra dose only if loose stools, max 3/day
Acute diarrhea		
<2 years‡	++	not used
>2 years	?	+(+§)
Adults	100 mg three times a day	4 mg + 2 mg after each passage of loose stools, max 16 mg/day
Acute diarrhea		
Diarrhea (at home)	+	+++
Onset of action	24 hr	2 hr
Number of stools/ stool output	+	+++
Reduced duration of diarrhea	—	+++
Traveler's diarrhea	?	+++
In combination with antibiotics	?	+++
Comparison with other medications	?	+++
Adsorbents	?	>
Bismuthsubsalicylate	?	>
Probiotics	?	>
Antimicrobials	?	>
Chronic diarrhea	?	+++

*Clinical efficacy, as documented in trials with the currently recommended dosage, in: (+) 1 placebo- or comparator-controlled study; (++) at least 2 placebo-controlled studies; (+++) at least in 3 placebo-controlled studies;> : efficacy better than with the comparator medication; "?" : no clinical documentation available to date.

†WHO recommendations in infants and small children: only ORS as essential treatment, no routine medicinal treatment for acute diarrhea (113).

‡The enkephalin plasma concentrations in infants are more than 10-fold higher than in adults (31) and the half-life of racecadotril is longer in infants compared with adults (98). Average age was 13 months (98, 99).

§Older pediatric studies with loperamide usually include a broad range of ages in children, or, if >2 years, concern children with protracted or chronic diarrhea (not reviewed).

In acute diarrhea, flexibly dosed racecadotril significantly reduced the duration of diarrhea compared with placebo: a "mean" of twelve 100-mg capsules was consumed over three days, suggesting that some sufferers need more than 400 mg/day, the current maximum dose (14). One placebo-controlled study with 100 mg four times a day showed a mild reduction in stool output over two days, but no significant effects on diarrhea duration and stool number or volume during the first 2–24 hr (4). Medline searches did not reveal placebo-controlled studies in cholera (prototype toxin used in racecadotril's antisecretory models), traveler's and chronic diarrhea, or in combination with antibiotics. Although an initial open pilot study in chemotherapy-induced diarrhea suggested efficacy of racecadotril 300 mg/day (95), an open study including a control group showed that this dose had no significant antidiarrheal effects (96).

The dose of loperamide in adults is flexible: 2 capsules (4 mg) at start and 1 capsule (2 mg) after each loose bowel movement (maximum 8 capsules). It has been studied in acute diarrhea, traveler's diarrhea, and various forms of chronic diarrhea: it acts rapidly (within 2 hr) and significantly reduces diarrhea duration and number of unformed stools, when compared to placebo (16, 94). It is effective in combination with antibiotics (94). Although antisecretory effects against the cholera toxin have been shown (69), it is not used in cholera, with the rare exception in combination with an antibiotic (97).

CLINICAL EFFICACY IN CHILDREN

In infants, the dose of racecadotril (1.5 mg/kg) corresponds to an average 100-mg dose in adults but would result in longer sustained levels of its active metabolites (98). In babies and infants (ages 3–48 months, average 13 months), this dose, given every 8 hr, was significantly effective in reducing stool output, diarrhea duration, and recovery within the first 24 and 48 hr, when compared to placebo (98, 99).

The effective dose of loperamide syrup in infants is 0.08–0.1 mg/kg, two to three times daily (no dose if no passage of diarrhea). In children older than 6 years, capsules are used, but the start dose is only one capsule instead of two. Loperamide was extensively studied in infants in the 1980s. A contraindication for those younger than 2 years was implemented after 15 years of usage in pediatrics, following rare reports of drowsiness, ileus, and central depression, mostly associated with overdose of concentrated drops (no longer marketed) in the very young (88). Efficacy in children older than 2 years has recently been reconfirmed (100).

COMPARATIVE EFFICACY

Four studies showed that racecadotril is as effective as loperamide (5, 6, 101, 102). The methodology, however, calls for caution in interpretation.

1. Three studies used a fixed instead of flexibly dosed regimen of low-dose loperamide (eg, 2 mg three times daily instead of 4 mg at start and 2 mg as needed, up to 16 mg/day) until "disappearance" of liquid stools, irrespective of prior liquid stool passage or until passage of two normal stools (6, 101, 102). Loperamide thus may have been underdosed in some, and overdosed in others. Repetitive unneeded doses of loperamide can slow transit (see "Effect on Gastrointestinal Motility and Transit") and may have induced the constipation and abdominal discomfort in some patients. Moreover, according to the baseline features in one study, some infants were "without" liquid stools prior to start of the study (24% in the loperamide group versus 11% in the racecadotril group) and hence, they received unneeded doses of loperamide (6). The fourth study used the recommended flexible loperamide dose regimen, but the maximum dose was not mentioned (5).
2. The duration of diarrhea prior to the study was not given (6) or allowed to last up to five days (5, 101, 102). Because acute diarrhea resolves in most patients within two to three days (94, 103, 104), spontaneous resolution of diarrhea can confound differences in clinical outcome in comparative studies, especially if long pretreatment periods of diarrhea are allowed. According to the authors' experience in reviewing clinical studies in acute diarrhea, the duration of the diarrhea prior to trial entry ideally should not exceed 48 hr, in order to allow consistent detection of statistically significant differences with placebo. According to FDA definitions, acute diarrhea is defined as lasting up to 96 hr only (105). Comparative trials allowing pretreatment durations of diarrhea beyond 48 hr should thus include a placebo group to validate conclusions.
3. The definition of recovery or duration of diarrhea was not given (101) or set as the time until "production" of "two" normal stools or until the first normal stool, followed by no stool during the following 12 hr (5, 102). This parameter is to be defined as "the time to the last unformed stool." The latter definition avoids confounding effects caused by the large intersubject variation in normal gut transit (two to four days) (106), and the time needed to replenish the bowel with nutrients (a function of diet taken).

One trial (with an appropriate design) compared racecadotril and loperamide oxide in acute diarrhea in adults (107). Loperamide oxide was found to be significantly superior to racecadotril in antidiarrheal and global efficacy ($P < 0.05$): fewer patients on loperamide had worsening of bloating when compared with racecadotril ($P < 0.05$). According to appropriate placebo-controlled studies, this prodrug of loperamide is as effective and as well tolerated as loperamide (103, 104).

There are no comparative studies of racecadotril in acute diarrhea with other antidiarrheal treatments, such as probiotics, adsorbents, or antimicrobials. Numerous studies in acute nondysenteric diarrhea show that loperamide is more effective than these agents, particularly with respect to its onset of action (94).

In chronic secretory diarrhea, comparative studies of racecadotril and loperamide are limited to open observations (108, 109). In delayed-onset diarrhea after irinotecan for colorectal cancer, 600 mg racecadotril did less well than 300 mg racecadotril plus six capsules of loperamide (no placebo and loperamide-only controls) (108). In an open study in AIDS patients, the number of stools was significantly lower with 100–300 mg of racecadotril three times daily than with 50–150 μg octreotide three times daily. The normal dose of octreotide in this indication is 100–250 μg, 3 times daily. Loperamide had previously unsuccessfully prescribed (dose not mentioned) (109).

TOLERABILITY

In general, both racecadotril and loperamide appear to be well tolerated: in placebocontrolled studies, their adverse event profile is not significantly different from that of the placebo group. Clinically, constipation has occasionally been reported with loperamide. This adverse event is also mentioned in the label of racecadotril (11, 12). While its occurrence was similar with racecadotril and placebo in the trials using 100 mg three times daily, 11% of patients on racecadotril reported constipation versus 5% on placebo in the trial with flexibly dosed racecadotril (14).

A benefit proposed for racecadotril over loperamide is less constipation and abdominal distension (5, 6, 15, 102, 110). Some comparative studies in adults and children support these advantages, but the relevance of the findings can be questioned: they did not use the standard therapeutic loperamide dosages, but constantly and unnessarily prolonged dosing, thereby possibly inducing these untoward effects (see discussions of clinical efficacy above) (6, 101, 102), or they used a mathematical approach by calculating intervals (24 or 48 hr) without stools (5, 6). Following effective inhibition of secretions, it may take 24 to >48 hr for the bowel to replenish after a diarrhea episode (normal bowel transit takes two to four days) (106). "Pseudo" constipation is also observed with placebo and is likely to become more prevalent following fast and effective inhibition of intestinal secretions due to less rapid filling of the gut lumen. In this respect, it is noteworthy that the average duration of the mathematically calculated constipating intervals did not differ between the racecadotril and loperamide groups (5, 6). Induction of the observations by incorrect loperamide dosing is further supported by the consistent finding that in well-controlled double-blind trials of acute diarrhea, normal dosing schedules of loperamide do not differ from placebo in the incidence of constipation and bloating (100, 103, 104, 111) and loperamide provides faster complete relief of gas-related abdominal discomfort (including cramps, gas pressure, and bloating) than placebo (111).

DISCUSSION

This evidence-based analysis presents an update on the antidiarrheal action and efficacy of racecadotril and loperamide. It shows that the selection of study conditions can have a significant impact on the outcome of pharmacological and clinical studies of diarrhea.

Although inhibition of toxin-induced secretion was demonstrated with highly dosed racecadotril *in vivo*, the antisecretory selectivity of its antidiarrheal action proposed via the intestinal δ-opiate receptors can be challenged: (1) there is no *in vitro* documentation of antisecretory efficacy or reduction of mucosal cyclic AMP (2) *in vivo* antisecretory models allowed prior systemic absorption (2, 67, 68), (3) the μ-receptor antagonist naloxone reversed the antisecretory and antidiarrheal action of racecadotril (2, 42, 67), and (4) none of the models allowed us to exclude the possibility that racecadotril or its resulting enkephalins acted across the blood–brain barrier at the enkephalinase-rich cerebral membranes (10–12, 77). Further, enkephalins also bind the μ-opioid receptors and exert potent centrally mediated antidiarrheal actions (21, 22). In addition, several centrally mediated pharmacological effects of racecadotril have been described (45, 79, 81). The inefficacy of oral thiorphan (not crossing the blood–brain barrier) even suggests that penetration into the brain is a prerequisite for racecadotril's antidiarrheal action (13, 42, 45). Rigorous standardization of the pharmacological test conditions for differentiation of peripheral and central actions, applying the same doses ranges and routes of administration within the same species, is desirable, in order to get a coherent image of the exact mechanism of action of racecadotril. The use of the peripheral μ-receptor antagonist naloxone-methiodide, which does not pass the blood–brain barrier (112), may also be

helpful in elucidating the selectivity of its antidiarrheal action. Theoretically, racecadotril can also exert pharmacological actions by inhibiting the degradation of a number of other neuropeptides, such as substance P, neurokinin A, neurotensin, neuropeptide Y and endothelins (13).

Conversely, loperamide binds both the δ- and μ-opioid receptors in the human gut (57, 70), acts as an antidiarrheal at doses lower than those affecting gastrointestinal motility or transit (49, 50, 60–66) and exerts antisecretory and transit-normalizing properties at therapeutic doses (72–74). It can thus be proposed as an antisecretory antidiarrheal, exerting its effects mainly via the enhancement of absorption and the inhibition of secretion, rather than via the inhibition of the intestinal motor activity. Nonetheless, the antidiarrheal action of the drugs discussed in this analysis can be the result of integrated antisecretory and motility-inhibiting effects, whether these are brought about directly by interaction of loperamide with the opiate receptors or indirectly by the racecadotril-induced increase in endogenous enkephalins interacting with these receptors.

There may, however, be a difference in potency and reliability of the antidiarrheal action of both drugs. Loperamide is flexibly dosed as a function of diarrhea severity and, thus, according to the patient's individual need. Racecadotril is dosed at a constant regimen of 100 mg three or four times daily. This dose, resulting in a peak of 75% plasma enkephalinase inhibition in healthy volunteers, however, is much lower (on average eight fold) than the highly variable doses needed for a therapeutically effective 50% inhibition for 6 hr in humans with castor oil-induced diarrhea (14). These observations, together with the established high variability in enkephalin levels and their degrading enzymes as well as their fast turnover in humans, support investigation of flexible dosing of racecadotril. In addition, the high doses of racecadotril used in antisecretory models (2, 68) and the relatively poor documentation of clinical efficacy of racecadotril 100 mg three times a day in adult acute and chronic diarrhea (14, 108, 109) suggest that higher and individually adapted doses may be needed for adequate antidiarrheal control in adults. Whether flexible and/or higher doses will prove to be more effective [as suggested by one study (14)], and equally well tolerated, or whether the antidiarrheal potency of racecadotril in adults is limited during diarrhea, due to fast depletion of the enkephalin stores, is not known.

Fast, consistent efficacy of racecadotril, however, is seen in young infants with acute diarrhea (98, 99). Possible explanations include: (1) the longer half-life of active racecadotril metabolites in infants, (2) their much higher enkephalin levels in the plasma and the brain, and (3) the more enkephalin-permeable blood–brain barrier when compared with adults. The drug was well tolerated, but ileus was observed in a 7-month-old infant on racecadotril (98). Although this ileus was attributed to hypokalemia, a role of high peripheral and central enkephalin concentrations in infants, further elevated during enkephalinase inhibition with racecadotril, cannot be excluded. A possible advantage of racecadotril in very young infants may nevertheless be a low risk potential for central depression, an adverse event that formerly has been observed in rare cases of overdosing of opiate agonists; in principle, such risk would be minimized by the limitation in natural stores of endogenous enkephalins.

Ileus is an adverse event that also has been reported very rarely with loperamide. In infants, this and rare CNS adverse events were mostly associated with overdosing of concentrated drops (no longer marketed) (88). It took more than 15 years of widespread usage to recognize the potential risks and contraindications of its use in the very young (younger than 2 years). In young infants, an immature liver and blood–brain barrier can annihilate the normal pharmacokinetic and pharmacodynamic protections, which account for the well-established lack of central effects of this opiate agonist. The decision was also prompted by the new guidelines of WHO, which specified that infants with acute diarrhea should only be treated with oral rehydration solution (ORS) and not be exposed to the risks of routine medicinal treatment (113). In adults, loperamide has built up a remarkably good efficacy and safety record in the symptomatic treatment of acute and chronic diarrhea. It is not to be used in cases of dysentery or severe (pseudomembranous) colitis.

The comparative studies of racecadotril and loperamide do not allow us to draw conclusious on equal efficacy and/or benefits of racecadotril over loperamide. As summerized in Table 1 and shown throughout the review. They have problems with regard to the selection of the loperamide dose (fix, too low, too high or even lethal in experimental settings), the models (germ-free versus normal conditions) and clinical trial design (long pretreatment periods, inappropriate definitions of diarrhea and tolerability parameters). In fact, they have flaws in their design, which are similar to those in comparative studies of loperamide and adsorbents, showing equal efficacy of the latter agents (94). Yet, the superior efficacy of loperamide compared to adsorbents is well-established today (16, 94). Better comparative studies are warranted.

In conclusion, based on the clinical findings and physiology of enkephalins, racecadotril may have a better efficacy in infants when compared to adults. Whether racecadotril truly offers benefits over loperamide in terms of antisecretory properties, antidiarrheal efficacy, or tolerability in the treatment of acute and chronic diarrhea

warrants more study with validated methodology and correct doses and further experience in clinical practice.

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