Overview | Dosing information | Pharmacokinetics | Main
Cautions | Clinical applications | References | MDX Exchange

RACECADOTRIL

0.0 OVERVIEW

- A. Racecadotril is a selective enkephalinase inhibitor.
- B. **DOSING INFORMATION** : Oral doses of 100 to 300 milligrams (mg) three times daily have been given in the treatment of diarrhea.
- C. **PHARMACOKINETICS** : Data are limited. Racecadotril is a prodrug, and is hydrolyzed its active metabolite, thiorphan, following intravenous or oral administration; peak thiorphan plasma levels after oral doses occur in approximately one hour. Bioavailability data are lacking. Blood-brain barrier penetration of thiorphan has been negligible after oral doses.
- D. **CAUTIONS** : Adverse effects have not been greater than observed with placebo in most studies. Constipation occurs less frequently compared to loperamide. Racecadotril does not prolong gastrointestinal transit time.
- E. **CLINICAL APPLICATIONS** : Oral racecadotril is effective in acute diarrhea in adults and children, and may be safer than opioid derivatives. Efficacy has also been observed in chronic diarrhea in HIV-infected patients and those with AIDS.

1.0 DOSING INFORMATION

- **1.1 DOSAGE FORMS**
  - A. **SYNONYMS**

1. Acetorphan

- **1.3 ADULT DOSAGE**
  - **1.3.1 NORMAL DOSE**
    - A. **ORAL**
      - 1. Optimal doses for any indication have not been determined.
      - 2. In the treatment of acute DIARRHEA, the usual effective dose of racecadotril in clinical trials has been 100 milligrams (mg) three times daily, given before meals, for up to one week (Vetel et al, 1999; Matheson & Noble, 2000; Hamza et al, 1999). In one trial, racecadotril was effective when given in an initial dose of 200 mg, then 100 mg after each unformed bowel movement (maximum of 10 days) (Baumer et al, 1992).
      - 3. Oral doses of 100 to 300 mg three times daily have been given in chronic diarrhea related to HIV infection or AIDS (Matheson & Noble, 2000; Beaugerie et al, 1996).

- **1.4 PEDIATRIC DOSAGE**
  - **1.4.1 NORMAL DOSE**
    - A. **ORAL**
      - 1. Optimal doses for any indication have not been determined.
      - 2. In the treatment of acute DIARRHEA in children (3 months to 10 years),

the usual effective dose of racecadotril in clinical trials has been 1.5 milligrams/kilogram (mg/kg) three times daily until recovery, or for up to 5 days; the drug was given as an adjunct to oral rehydration (Cezard et al, 2001; Salazar-Lindo et al, 2000; Turck et al, 1999; Matheson & Noble, 2000).

2.0 PHARMACOKINETICS

- **2.1 ONSET AND DURATION**
  - **2.1.1 ONSET**
    - A. **INITIAL RESPONSE** :
      - 1. **PLASMA ENKEPHALINASE INHIBITION, ORAL** : 30 minutes (100 mg orally) (Lecomte, 2000).
    - B. **PEAK RESPONSE** :
      - 1. **ACUTE DIARRHEA, ORAL** : within 24 hours (Cezard et al, 2001; Lecomte, 2000; Hamza et al, 1999).
      - 2. **PLASMA ENKEPHALINASE INHIBITION, ORAL** : 60 minutes (100 mg orally) (Lecomte, 2000).
  - **2.1.2 DURATION**
    - A. **SINGLE DOSE** :
      - 1. **PLASMA ENKEPHALINASE INHIBITION, ORAL** : up to 8 hours (100 mg orally) (Lecomte, 2000).
        - a. The biological half-life of enkephalinase activity was approximately 3 hours following oral doses of 30 to 300 mg in healthy subjects (Matheson & Noble, 2000).
- **2.2 DRUG CONCENTRATION LEVELS**
  - **2.2.1 THERAPEUTIC**
    - A. **THERAPEUTIC DRUG CONCENTRATION** :
      - 1. In vitro data indicate that a thiorphan concentration of about 6 nmol/L is required for 50% inhibition of enkephalinase; this is 750 times lower than that required for the parent compound (Matheson & Noble, 2000). However, clinical correlations are unavailable, and clinical monitoring of plasma levels is not indicated.
    - B. **TIME TO PEAK CONCENTRATION** :
      - 1. **ORAL** : 1 hour (Matheson & Noble, 2000; Hinterleitner et al, 1997).
        - a. Represents time to peak levels of thiorphan following oral racecadotril 30 to 300 mg.
        - b. Following usual oral doses in adults and children, plasma levels of thiorphan have exceeded in vitro concentrations required for 50% inhibition of enkephalinase for up to 8 hours (Salazar-Lindo et al, 2000).
        - c. Pharmacokinetic parameters for thiorphan have been similar after single and multiple doses of racecadotril in healthy subjects (Matheson & Noble, 2000).
    - C. **AREA UNDER THE CURVE** :
      - 1. AUC values in arbitrary units of 1285 and 1049 have been reported after oral doses of 100 and 300 mg, respectively (Matheson & Noble, 2000).
- **2.3 ADME**
  - **2.3.1 ABSORPTION**
    - A. **BIOAVAILABILITY (F)**
      - 1. Bioavailability data for racecadotril are unavailable.

- **2.3.2 DISTRIBUTION**
  - **2.3.2.1 DISTRIBUTION SITES**
    - A. **OTHER DISTRIBUTION SITES** :
      - 1. **CEREBROSPINAL FLUID**
        - a. Available studies suggest no penetration of the blood-brain barrier following oral doses up to 20 mg/kg (based on plasma and CSF enkephalinase activity) (Lecomte, 2000; Farthing, 1999). However, intravenous doses have been shown to induce CNS activity (Hartmann et al, 1991). The oral-parenteral discrepancy may be related to low oral bioavailability of racecadotril; the bioavailability of this agent has not been determined. Further studies assessing actual drug concentrations in CSF/plasma are needed.
- **2.3.3 METABOLISM**
  - **2.3.3.1 METABOLISM SITES AND KINETICS**
    - A. TISSUES, extensive (Farthing, 1999; Hinterleitner et al, 1997; Matheson & Noble, 2000).
      - 1. Racecadotril is hydrolyzed in peripheral tissues to an active metabolite, thiorphan (R,S-thiorphan) (Hinterleitner et al, 1997; Matheson & Noble, 2000). Animal data suggest this conversion is complete (Matheson & Noble, 2000).
  - **2.3.3.2 METABOLITES**
    - A. Thiorphan, active (Hinterleitner et al, 1997; Farthing, 1999).
      - 1. Appears responsible for all activity of racecadotril.
    - B. Thiorphan thiomethylether, inactive (Hinterleitner et al, 1997; Farthing, 1999).

3.0 CAUTIONS

- **3.1 CONTRAINDICATIONS**

  - A. Prior hypersensitivity to racecadotril or ecadotril (sinorphan)

- **3.2 PRECAUTIONS**

  - A. Functional intestinal disorders (potential exacerbation)
  - B. Renal insufficiency (pharmacokinetic data unavailable)
  - C. Dysenteric syndrome with bloody stools/fever (antibiotic therapy required; racecadotril may be ineffective)
  - D. Presence of dehydration (rehydration therapy mandatory)
  - E. Pregnancy/breastfeeding period (animal/human data unavailable)

- **3.3 ADVERSE REACTIONS**

  - **3.3.3 CENTRAL NERVOUS SYSTEM**
    - A. **CENTRAL NERVOUS SYSTEM EFFECTS**
      - 1. Dizziness, malaise, and headache have accompanied therapy of acute diarrhea in a few patients (Hamza et al, 1999; Baumer et al, 1992), although causality is doubtful.
  - **3.3.4 ENDOCRINE/METABOLIC**
    - A. **METABOLIC EFFECTS**
      - 1. Persistence of hypokalemia has been reported infrequently in children with severe watery diarrhea receiving racecadotril (Salazar-Lindo et al, 2000); this was more likely related to the acute diarrhea.
  - **3.3.5 GASTROINTESTINAL**

- A. **GASTROINTESTINAL EFFECTS**
  - 1. Gastrointestinal adverse effects have been minimal, the incidence often not exceeding that of placebo (Hamza et al, 1999; Baumer et al, 1992; Cezard et al, 2001; Matheson & Noble, 2000). CONSTIPATION during treatment has been infrequent when placebo effects are eliminated, and less frequent than reported with loperamide (Vetel et al, 1999; Roge et al, 1993; Turck et al, 1999; Lecomte, 1999). In one trial in adults (n=157), rebound constipation (not passing a stool for at least 2 days during treatment) occurred in 19% and 10% of patients receiving loperamide and racecadotril, respectively (Vetel et al, 1999). In another study (Roge et al, 1993), the overall gastrointestinal tolerability of racecadotril was better than that of loperamide; constipation after diarrhea resolution was seen in 8% and 31% of patients, respectively.
  - 2. Abdominal distension has not been more common with racecadotril than placebo in available studies. Ileus has occurred rarely (Salazar-Lindo et al, 2000), although this was more likely related to the underlying condition.
  - 3. VOMITING has occurred in up to 50% of children treated with racecadotril, although a high incidence has also been seen with placebo (Turck et al, 1999; Cezard et al, 2001; Salazar-Lindo et al, 2000). Correcting for placebo effects, the incidence of vomiting in children is low (less than 10%).

- **3.3.12 OTHER**
  - A. **PHYSICAL DEPENDENCE**
    - 1. Animal studies suggest that racecadotril has minimal potential for abuse (Lecomte, 2000).
  - B. **OVERDOSE**

4.0 CLINICAL APPLICATIONS

- **4.1 MONITORING PARAMETERS**

- **4.1.1 THERAPEUTIC**
  - A. **PHYSICAL EXAMINATION**
    - 1. Abatement of diarrhea and associated symptoms (eg, abdominal pain/distension, anal burning, nausea, anorexia)
      - a. Duration of diarrhea from treatment onset and stool number and/or weight have been primary efficacy criteria in clinical studies
- **4.1.2 TOXIC**
  - A. **PHYSICAL EXAMINATION**
    - 1. Signs/symptoms of adverse effects (eg, constipation, vomiting)

- **4.3 PLACE IN THERAPY**

- A. Racecadotril appears to be an equally effective and less toxic alternative to antimotility agents (eg, loperamide, diphenoxylate) in the management of acute diarrhea. The lack of antitransit effects with racecadotril may obviate the potential for bacterial colonization, abdominal distension, and toxic megacolon, which are concerns with antimotility agents (although worsening of bacterial diarrhea has seldom been seen clinically with these drugs); constipation may also be less with racecadotril. CNS effects appears minimal, reducing chances of respiratory depression or physical dependence; however, clarification of CNS activity with oral versus intravenous racecadotril is in order.
- B. Racecadotril should be considered first-line or second-line therapy of acute diarrhea, particularly in children and the elderly.

- **4.4 MECHANISM OF ACTION/PHARMACOLOGY**

- A. **MECHANISM OF ACTION**
  - 1. Racecadotril (acetorphan) is an enkephalinase inhibitor indicated primarily in the treatment of diarrhea. It is a prodrug, being rapidly hydrolyzed to an active metabolite (thiorphan) after oral doses, which appears to account for all enkephalinase-inhibitory activity (Matheson & Noble, 2000; Farthing, 1999).
  - 2. Enkephalinases are membrane-bound metallopeptidases found in the gastrointestinal tract, CNS, and other tissues, and degrade endogenous opioids (enkephalins) (Matheson & Noble, 2000; Bergmann et al, 1992). Thiorphan-induced inhibition of enkephalinase in the gastrointestinal tract results in prolongation of the antisecretory effects of enkephalins, with a reduction in water/electrolyte secretion into the intestinal lumen (Hinterleitner et al, 1997; Bergmann et al, 1992; Lecomte, 2000; Matheson & Noble, 2000). Naloxone-reversible antidiarrheal activity of racecadotril has been observed in animal studies, attributed to protection of endogenous enkephalins (Bergmann et al, 1992). The drug has reduced diarrhea induced by castor oil in healthy subjects (Baumer et al, 1992).
  - 3. Unlike mu-receptor agonists, racecadotril does not increase intestinal transit time (Bergmann et al, 1992; Lecomte, 2000), and appears less likely to promote bacterial colonization or fluid pooling in the distended bowel lumen, or to induce constipation. Racecadotril (thiorphan) reportedly does not cross the blood-brain barrier when given orally (Farthing, 1999; Lecomte, 2000), although intravenous doses of racecadotril have been shown to induce CNS activity (Hartmann et al, 1991); the intravenous drug has been investigated in the treatment of opioid withdrawal symptoms. The oral-parenteral discrepancy may be related to low oral bioavailability of racecadotril
  - 4. Ecadotril (sinorphan) is the S-enantiomer of racecadotril (racemic acetorphan); it is under investigation for the treatment of heart failure (Dussaule et al, 1991; Cleland et al, 1998; O'Connor et al, 1999).
- B. **REVIEW ARTICLES**
  - 1. Clinical patterns, causes, and treatment of diarrhea (Farthing, 2000).

- **4.5 THERAPEUTIC USES**

- A. **DIARRHEA - ACUTE**
  - 1. **OVERVIEW** :

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FDA APPROVAL:  Adult, no; pediatric, no
EFFICACY:  Adult, effective; pediatric, effective
DOCUMENTATION:  Adult, good; pediatric, good
```

  - 2. **SUMMARY** :

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- Oral therapy has been effective in treating acute
  diarrhea in adults and children, and comparable
  in efficacy to loperamide

- A reduced requirement for rehydration has been
  seen during racecadotril therapy
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  - 3. **ADULT** :
    - a. Oral racecadotril has been superior to placebo and as effective as oral loperamide in the treatment of ACUTE DIARRHEA of presumed infectious

origin in randomized, double-blind studies (Baumer et al, 1992; Matheson & Noble, 2000; Vetel et al, 1999; Roge et al, 1993; Hamza et al, 1999; Lecomte, 2000). The usual dose in these studies was 100 milligrams (mg) three times daily.

- b. In one study (n=70), using stool weight as the criterion for antisecretory activity, the mean stool weight during the first day of treatment was 355 g with racecadotril 100 mg three times daily compared to 499 g in the placebo group (29% decrease with racecadotril). The frequency of diarrheic stools after the first day was reduced significantly by racecadotril (Hamza et al, 1999). A further study (n=193) reported that the incidence of diarrhea was reduced by 30% with racecadotril compared to placebo; racecadotril significantly reduced diarrheal-associated symptoms, such as abdominal pain, anal burning, abdominal distension, and nausea (Baumer et al, 1992).

- 4. **PEDIATRIC** :
  - a. Oral racecadotril 1.5 milligrams/kilogram (mg/kg) three times daily has been effective as an adjuvant to oral rehydration in the treatment of acute diarrhea in infants and children (3 months to 4 years of age) in placebo-controlled studies (Cezard et al, 2001; Salazar-Lindo et al, 2000; Matheson & Noble, 2000). Efficacy of the drug was comparable to loperamide in one trial involving children 2 to 10 years of age (Turck et al, 1999).
  - b. In one study involving hospitalized children 3 months to 4 years of age, therapy with oral racecadotril and oral rehydration significantly reduced stool output during the first 2 days of treatment; stool output was approximately 60% of that in children receiving placebo/rehydration. The need for oral rehydration was reduced in the racecadotril group. The drug was efficacious regardless of rotavirus status (Cezard et al, 2001).

- B. **DIARRHEA - HIV-RELATED**
  - 1. **OVERVIEW** :

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FDA APPROVAL:  Adult, no; pediatric, no
EFFICACY:  Adult, effective
DOCUMENTATION:  Adult, good
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  - 2. **SUMMARY** :

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 - Effective in the chronic diarrhea observed
   in these patients
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  - 3. **ADULT** :
    - a. Racecadotril has been effective for treatment of chronic diarrhea in patients with HIV INFECTION or AIDS, including those refractory to conventional antidiarrheal therapy (Beaugerie et al, 1996; Matheson & Noble, 2000). In one large study (n=174) involving patients with HIV infection and chronic diarrhea, significantly more patients receiving racecadotril (100 or 200 milligrams (mg) three times daily) experienced a one-third reduction in stool number than those treated with placebo (36 versus 23%). Efficacy was greater with racecadotril in patients without cryptosporidium infection (Matheson & Noble, 2000).

- C. **DIARRHEA - IRINOTECAN-INDUCED**
  - 1. **OVERVIEW** :

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FDA APPROVAL:  Adult, no; pediatric, no
EFFICACY:  Adult, effective
DOCUMENTATION:  Adult, fair
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- 2. **SUMMARY** :

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- Racecadotril was effective when combined with
  loperamide  for treatment; racecadotril
  monotherapy was ineffective as prophylaxis
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- 3. **ADULT** :
  - a. Prophylactic administration of oral racecadotril had no effect on the delayed-onset diarrhea associated with irinotecan chemotherapy in 5-fluorouracil-resistant colorectal carcinoma patients in one study. Racecadotril was given in a dose of 100 milligrams (mg) three times daily for 15 days, beginning the day of irinotecan infusion (350 mg/m(2) every 3 weeks) (Ychou et al, 2000).
  - b. However, combined administration of racecadotril and loperamide has demonstrated efficacy in treating this complication in small studies (Matheson & Noble, 2000).

- D. **OPIOID WITHDRAWAL**
  - 1. **OVERVIEW** :

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FDA APPROVAL:  Adult, no; pediatric, no
EFFICACY:  Adult, possibly effective
DOCUMENTATION:  Adult, poor
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  - 2. **SUMMARY** :

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- Intravenous racecadotril appeared to prevent
  opioid withdrawal symptoms in a small study;
  confirmation of these results is required
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  - 3. **ADULT** :
    - a. One small study (n=19) suggested the efficacy of intravenous racecadotril (50 milligrams (mg) twice daily for 3 days) in preventing objective signs of opioid withdrawal, primarily from heroin; the drug was at least comparable to oral clonidine, although baseline initial withdrawal symptoms were more severe in the clonidine group (Hartmann et al, 1991). No further studies have been published, and a larger comparison is needed to clearly establish efficacy.

- **4.6 COMPARATIVE EFFICACY**
  - A. **CLONIDINE**
  - B. **LOPERAMIDE**
  - C. **OCTREOTIDE**

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7.0 AUTHOR INFORMATION

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