

Necrotizing Enterocolitis and Milk Protein Intolerance

Causes of Rectal Bleeding in a Term Infant

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Both necrotizing enterocolitis and severe milk protein intolerance causing grossly bloody stools are uncommon in the term infant. Necrotizing enterocolitis is a disease primarily of premature, low-birthweight infants who have been significantly stressed. Milk protein intolerance is a common disease with a variety of manifestations, but diarrhea with gross blood loss is uncommon. A case is reported of an infant suffering from both diseases.

CASE REPORT

A 7-day-old infant was brought to the Family Medical Center with a history of bloody diarrhea. The mother had had an uncomplicated prenatal course and an uncomplicated, planned repeat cesarean section at 39 weeks' gestation. Apgar scores were 9 and 9 at 1 and 5 minutes for this 2,900-g infant. Findings on newborn examination were unremarkable. Feedings with infant formula (SMA) were begun in the newborn nursery. Blood was noted in the stool on the second day of life but was attributed to an anal fissure, and the child was discharged on the third day of life with mother changing the formula to Enfamil. Persistent diarrhea with bloody mucus was noted by the mother. Family history was remarkable for the mother, the maternal grandfather and the three siblings of the maternal grandfather, and the mother's cousin all having had

milk protein intolerance and having required breast milk only or goat's milk.

On examination the infant was alert and responsive but had a 1-pound weight loss since birth, a pulse of 168 beats per minute, and bloody mucus on examination of the stool. The infant was admitted for further evaluation and treatment. The workup revealed necrotizing enterocolitis with right lower quadrant pneumatosis intestinalis visible on abdominal radiographs. Admission blood determinations included a white blood cell count of $35.0 \times 10^9/L$ ($10^3/\mu L$) with a differential of 0.35 polymorphonuclear cells, 0.02 band cells, 0.45 lymphocytes, 0.15 monocytes and 0.02 eosinophils. Room air blood gas results revealed mixed metabolic acidosis and respiratory alkalosis (pH 7.39, pCO₂ 16 mmHg, pO₂ 66 mmHg). Treatment included nasogastric suction, bowel rest, antibiotics, and hyperalimentation. The workup for sepsis was negative, and stool cultures did not reveal pathogens.

On the 11th day of hospitalization oral feedings were resumed beginning with glucose water and advancing to infant formula (Similac). On the second day of feedings, abdominal distention and bloody stools were noted. Feedings were changed to a second infant formula (ProSobee) without improvement. Workup at this time did not show evidence of pneumatosis but did show an eosinophil count of $7.8 \times 10^9/L$, 0.28 of all leukocytes. The infant's feedings were changed to an oral electrolyte solution (Pedialyte) followed by a formula of hydrolyzed protein (Nutramigen) and breast milk with resolution of symptoms. The in-hospital exacerbation was diagnosed as milk protein intolerance and not a recurrence of necrotizing enterocolitis. The patient was discharged at 22 days of life after 15 days of hospitalization. Follow-up barium enema showed no evidence of stricture or obstruction.

The infant did well until 28 days of age, at which time he presented to the Family Medical Center with emesis.

Submitted, revised, November 23, 1988.

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ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: **General:** 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocellular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Infectious: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

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Research Triangle Park, NC 27709
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Workup now revealed pyloric stenosis, which was treated with pyloromyotomy without complications.

DISCUSSION

Since its original description in 1891, the epidemiology of necrotizing enterocolitis has been studied and reviewed extensively.¹⁻⁴ The mechanism immediately responsible for the intestinal damage is probably ischemic necrosis precipitated by a variety of factors such as hypoxia, infection, and overfeeding. The majority of necrotizing enterocolitis cases occur in premature infants with newborns beyond 38 weeks' gestation comprising fewer than 5 percent of cases.⁵ The incidence is in the range of 1 per 1000 and mortality rate is in the range of 40 percent. The three essential components for the development of necrotizing enterocolitis described by Santulli et al² are (1) injury to the bowel mucosa, (2) presence of bacteria, and (3) availability of metabolic substrate. (Necrotizing enterocolitis, however, has been found in unfed infants.⁶ Term infants who develop necrotizing enterocolitis tend to do so in the first days of life in contrast to premature infants, who may develop the disease later.

Necrotizing enterocolitis may manifest itself with abdominal distention, emesis, and diarrhea with blood in the stools. Radiologic examination may reveal intramural air (pneumatosis intestinalis). The course may be fulminating and lethal. Breast milk may be protective, but Kliegman et al⁷ did not find human milk to be effective in lowering necrotizing enterocolitis in high-risk infants.

Staging criteria have been used so that the rational comparisons between groups of patients with necrotizing enterocolitis can be made.⁵ Hemorrhagic colitis may be part of the spectrum of necrotizing enterocolitis, but without other clinical or radiologic stigmata, necrotizing enterocolitis may be overdiagnosed in some instances.⁸ Loose labeling of the infants with no manifestation of necrotizing enterocolitis other than blood in stools may in part explain differences in the reported incidences of necrotizing enterocolitis. As demonstrated by the in-hospital exacerbation of bloody stools in this case and documented in published series, bloody stools may be a manifestation of intolerance to cow's milk.⁹⁻¹²

Milk protein intolerance afflicts between 0.5 and 7.5 percent of the population.^{13,14} Diagnosis is often clinical, but the presence of eosinophilia and confirmatory allergy testing may be helpful.¹³ Heredity plays a significant role, with 60 percent of infants with milk protein intolerance having a positive family history.¹⁵ Although the average age of presentation is 2 months, it has been noted as early as the first day of life.¹⁶ The gastrointestinal tract, respiratory tract, and skin are most commonly affected, with

symptoms ranging from rhinitis, asthma, and urticaria to diarrhea with blood loss.¹⁷

Gastrointestinal manifestations of milk protein intolerance can occur anywhere from the stomach to the small bowel and colon, and symptoms may be acute or delayed. Gastric and duodenal lesions present with vomiting and occult blood loss. Small bowel lesions cause a presentation similar to celiac disease with vomiting, malabsorption, and failure to thrive. Colonic lesions may present with blood and mucus in the stool, abdominal distension, and emesis. Symptoms regress on a milk-free diet, and recur following a repeat milk challenge.¹³ Soybean protein is recognized as having equal antigenicity with cow's milk protein, and infants having milk protein intolerance may at the same time have intolerance to soy-based formula.^{13,16}

The exact pathophysiology of milk protein intolerance is unknown. Direct toxicity to the gastrointestinal mucosa by milk proteins or an exaggerated immunological response to milk proteins or both have been postulated. In neonates, increased gastrointestinal absorption of antigenic material leading to sensitization may result from gut immaturity or ischemic or inflammatory damage to the epithelium.² In this child it is unknown whether colonic damage secondary to necrotizing enterocolitis contributed to the development of milk protein intolerance, or whether the milk protein intolerance contributed to the development of necrotizing enterocolitis. This child's course was further complicated by pyloric stenosis, which does not appear related to either milk protein intolerance or necrotizing enterocolitis.

In the term infant the diagnosis of necrotizing enterocolitis may initially elude the unsuspecting physician, who may attribute the bleeding to a more benign cause. The possibility of milk protein intolerance may also be missed in the child with bloody stools. Physicians must maintain an index of suspicion for both common and uncommon causes of bleeding in the neonate. Prognosis may be sig-

nificantly improved by early and aggressive therapy of these conditions.

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