

# Pediatric Pharmacotherapy

A Monthly Review for Health Care Professionals of the Children's Medical Center

Volume 5 Number 2, February 1999

## A New Rotavirus Vaccine: RotaShield<sup>®</sup>

Marcia L. Buck, Pharm.D., FCCP

- [Introduction](#)
- [Mechanism of Action](#)
- [Efficacy](#)
- [Contraindications and Precautions](#)
- [Adverse Effects](#)
- [Drug Interactions](#)
- [Dosing Reccomendations](#)
- [Product Availability](#)
- [Summary](#)
- [References](#)

### Literature Reviews:

- [Erythropoietin pharmacodynamics](#)
- [Macrolide comparison](#)
- [Measles vaccine](#)
- [Pharmacokinetic optimization in Cystic Fibrosis](#)
- [Risk-benefit of treating depression](#)

### Formulary Update

---

Rotavirus is a common cause of seasonal diarrhea in infants and young children, and sometimes is called "winter diarrhea." In children between the ages of three months and two years, rotavirus is the leading cause of viral gastroenteritis, producing up to 100,000 hospitalizations in the United States each year. Outbreaks frequently occur in places where small children gather, such as day-care centers and children's hospitals.<sup>1</sup>

Rotavirus is presumed to be transmitted by the fecal-oral route. The virus can survive for hours on human hands and for days on inanimate surfaces, resisting common disinfectants. Ingested virus particles infect the cells in the villi of the small intestine. Copious acute watery diarrhea occurs after an incubation period

of 1 to 2 days. Although there are many different strains of rotavirus, the majority of disease in the United States is caused by four G serotypes of rotavirus Group A.<sup>1,2</sup>

Until recently, there were no methods available for preventing rotavirus infection. Patients have traditionally been managed with supportive therapies. Although treatment with oral rehydration therapy has been adequate in mild cases, it does not affect the overall duration of illness. Severe cases have often required intravenous rehydration, requiring hospitalization of the infant or child.<sup>1</sup>

In 1998, the Food and Drug Administration (FDA) approved the first rotavirus vaccine. RotaShield<sup>®</sup> (Wyeth-Ayerst) is a live oral, tetravalent vaccine indicated for the prevention of rotavirus-associated gastroenteritis in infants.

## **Mechanism of Action**

The immune response to natural rotavirus infection is not completely defined. It is known that prior exposure to rotavirus provides incomplete protection from the virus; and therefore, infants and children can be reinfected from year to year.<sup>2</sup> Natural infection, however, may provide some protection from severe diarrhea during subsequent infections.<sup>2,3</sup> This may result from a virus-specific immune response generated at the intestinal mucosal surface.<sup>4</sup>

The rotavirus vaccine has been developed to mimic the immunologic responses stimulated by natural infection.<sup>5,6</sup> RotaShield<sup>®</sup> contains four live viruses, a rhesus rotavirus (identical to human serotype 3) and three rhesus-human reassortant viruses (serotypes 1, 2, and 4). The live vaccine virus generates IgG antibodies that neutralize these serotypes, as well as IgA antibody, which is thought to reflect a local immune response.<sup>7,8</sup>

## **Efficacy**

Just as natural rotavirus infection does not confer total immunity, the use of a live-virus vaccine does not yield complete protection against rotaviral infection.<sup>7</sup> However, like natural illness, the vaccine appears to provide protection against further episodes of severe illness.

The results of initial clinical trials demonstrate that more than 88% of infants respond by the third dose of the vaccine, as indicated by a fourfold or greater rise in serum IgA titers. Evaluation of the clinical efficacy of the vaccine has also been positive. In the first trial using RotaShield<sup>®</sup> in the United States, none of the infants in the vaccine group developed dehydration compared to 3% in the placebo group. In the same study, the number of infants requiring a visit to their physician was 11% lower in the vaccine group than in the placebo group.

In a second trial conducted in the United States, medical visits for diarrhea and vomiting occurred for 9% of infants in the placebo group compared with 2% in the vaccine group.<sup>3,7</sup> None of the patients receiving the vaccine in this trial

required hospitalization. Both of these trials were conducted by the manufacturer, Neither has been published in the medical literature at this time. A third trial, conducted in Finland, produced similar results. Efficacy of the vaccine against severe gastroenteritis was maintained for at least 2 years following vaccination in both the U.S. and Finland trials.<sup>9</sup>

## **Contraindications and Precautions**

Hypersensitivity to any component of the vaccine, including neomycin, amphotericin B, or monosodium glutamate which are present during cell culture growth, is a contraindication to administration of RotaShield®.<sup>7</sup>

Infants with moderate to severe febrile illness should not receive the vaccine during their illness. Like other vaccines, the rotavirus vaccine can be given to an infant with a low grade fever.<sup>7</sup>

Since the rotavirus vaccine contains live virus, administration to infants known to be immunocompromised is contraindicated. The virus is shed in the feces.

However, studies have not demonstrated transmission of vaccine strains from vaccine recipients to non-recipients. Thus, the presence of an immunocompromised family member in the same home is not a contraindication to vaccine administration.<sup>3</sup>

## **Adverse Effects**

In clinical trials, a fever greater than 38° Celsius, decreased appetite, irritability, and decreased activity were reported more frequently in the vaccinated infants than in the placebo group during the first 5 days after the initial dose. Fever greater than 38° Celsius was the only adverse effect reported more often in the vaccinated infants than the placebo infants with the second dose. The frequency of fever was no different between the groups in the 5 days after the third dose.<sup>7</sup>

The rate of diarrhea occurring in the first 5 days following a dose of the rotavirus vaccine was not found to be significantly different than placebo. Other adverse effects were reported in similar frequencies for both the vaccine and placebo groups.<sup>7</sup>

## **Drug Interactions**

Coadministration of rotavirus vaccine with oral polio vaccine (OPV), diphtheria, tetanus and pertussis (DTP or DTaP), *Haemophilus influenza* B, and hepatitis B vaccines does not interfere with the immune response to any of these vaccines. Infants given OPV concomitantly with rotavirus vaccine may have slightly decreased serum antibody responses to the rotavirus antigens and serotype 1 poliovirus, but this interference is not evident after the third dose of either vaccine.<sup>10</sup>

## **Dosing Recommendations**

The immunization series consists of three 2.5 ml oral doses of RotaShield® administered to infants during the first year of life. The recommended dosing schedule is at 2, 4, and 6 months of age. In patients at greater risk for severe infection, the first dose may be administered as early as 6 weeks of age, with subsequent doses at least 3 weeks apart.

Because older infants and children may have an increased risk of fever after the administration of the first dose of vaccine, initiation of the vaccination series after the age of 6 months is not currently recommended.<sup>7</sup>

The vaccine may be given with or without food. It is not necessary to repeat the dose if the infant regurgitates vaccine. In order to reduce the risk of fecal-oral spread of live virus, parents should be reminded of the need to adhere to proper hand-washing techniques when changing diapers until 3 to 4 weeks after immunization.<sup>7</sup>

Infants who are breastfeeding may remain on their usual feeding schedule during vaccination. Although breastfeeding has demonstrated to decrease the immunogenicity of single doses of rotavirus vaccine, no overall effect has been noted on efficacy after administration of the complete three dose series.

Infants who develop a rotaviral infection during the vaccination process should complete the three dose series. Administration of the vaccine may provide additional protection against other serotypes and further reduce the severity of any subsequent infection.

## **Product Availability**

RotaShield® is supplied in single-dose vials as a lyophilized preparation, pink in color. The solution appears yellow-orange to purple when reconstituted with the manufacturer-supplied diluent and may contain a fine precipitate. The diluent contains citrate-bicarbonate 9.6 mg/ml and sodium bicarbonate 25.6 mg/ml to neutralize stomach acidity and protect the acid-labile rotaviruses from degradation. The lyophilized vaccine and diluent are stable at room temperature and under refrigeration.<sup>7</sup>

The average whole sale price (AWP) for RotaShield® is \$30.00 per dose, making it one of the most expensive vaccines in the routine childhood immunization schedule.

## **Summary**

The rotavirus vaccine offers the benefit of reducing the severity of rotaviral gastroenteritis in infants, with the potential to reduce the need for hospitalization and intravenous rehydration in severely affected patients. In addition, it may reduce the need for physician office visits and parental time lost from work. The true value of the vaccine, however, remains to be proven. While the adoption of

this vaccine into the routine childhood immunization schedule in the United States appears likely, its benefits must be weighed against the high cost of the available product.

## References

1. Glass R, Kilgore P, Holman RC, et al. The epidemiology of rotavirus diarrhea in the United States: Surveillance and estimates of disease burden. *J Infect Dis* 1996;174 (Suppl 1): S5-11.
  2. Bishop RF. Development of candidate rotavirus vaccines. *Vaccine* 1993;11:247-9.
  3. Committee on Infectious Diseases, American Academy of Pediatrics. Prevention of rotavirus disease: Guidelines for use of rotavirus vaccine. *Pediatrics* 1998; 102:1489-91.
  4. Offit P. Host factors associated with protection against rotavirus disease: The skies are clearing. *J Infect Dis* 1996; 174 (Suppl 1):S59-64.
  5. Ward R. Mechanisms of protection against rotavirus in humans and mice. *J Infect Dis* 1996; 174 (Suppl 1): S51-8.
  6. Estes M. Advances in molecular biology: Impact on rotavirus vaccine development. *J Infect Dis* 1996;174 (Suppl 1):S37-46.
  7. RotaShield product information. Wyeth Laboratories, 1998.
  8. Orenstein W, Hadler S, Kuritsky JN, et al. Rotavirus vaccines-from licensure to disease reduction. *J Infect Dis* 1996;174 (Suppl 1): S118-24.
  9. Joensuu J, Koskenniemi E, et al. Prolonged efficacy of rhesus-human reassortant rotavirus vaccine. *Pediatr Infect Dis J* 1998;17: 427-9.
  10. Rennels MB, Ward RL, et al. Concurrent oral polio and rhesus-human reassortant rotavirus vaccination. *J Infect Dis* 1996; 173:306-13.
- 

## Literature Review

### Erythropoietin pharmacodynamics

Serial hemoglobin levels were measured in eight children between 8 and 15 years of age who were receiving erythropoietin for anemia due to renal failure. Patients received weekly SC injections of erythropoietin with doses ranging from 1,700 to 6,800 units. The increase in hemoglobin levels was linear until steady-state was reached. The average time to reach steady-state was 103 days. The rate and extent of increase in hemoglobin were not correlated to body weight. The authors provide a detailed description of the model they have developed from these patients and discuss its use in predicting hemoglobin concentrations. Port RE, Ding RW, Fies T, et al. Predicting the time course of h(a)emoglobin in children treated with erythropoietin for renal an(a)emia. **Br J Clin Pharmacol** 1998;46:461-6.

---

## **Macrolide Comparison**

The risk for adverse effects with macrolide use is the focus of this review. The authors attempt to weigh the differences among erythromycin, clarithromycin, and azithromycin. Based on their review of the literature, they conclude that the risk for adverse gastrointestinal effects, allergic reactions, hepatotoxicity, ototoxicity, neurologic and dermatologic reactions, and laboratory abnormalities are roughly equivalent within the macrolide group. They suggest, however, that the potential for serious drug interactions with erythromycin and clarithromycin may make these agents less appropriate for routine use in children. Principi N, Esposito S. Comparative tolerability of erythromycin and newer macrolide antibacterials in p(a)ediatric patients. **Drug Safety 1999;20:25-41.**

---

## **Measles Vaccine**

This review focuses on the adverse reactions that have been reported following administration of the measles vaccine. Anaphylaxis, encephalopathy and seizure disorders, optic neuritis, subacute sclerosing panencephalitis, transverse myelitis, Guillain Barre syndrome, thrombocytopenic purpura, ulcerative colitis, Type I diabetes, and autism are included. The authors address each topic individually, reviewing first the cases documented then evidence supporting or refuting the claim of causality. Toward the end of the review, a very useful table contrasts the risks of complications from natural measles with those of the vaccine. Duclos P, Ward BJ. Measles vaccines: a review of adverse effects. **Drug Safety 1998;19:435-54.**

---

## **Pharmacokinetic optimization in CF**

These authors present an interesting discussion of the use of models which predict pharmacokinetic variables to optimize therapy in children and adults with cystic fibrosis. The article focuses on the use of antibiotics and the role of pharmacokinetics to predict desired serum concentrations. A Bayesian model is used to highlight the ability of mathematical equations to accurately target desired concentrations. Touw DJ, Vinks AATMM, Mouton JW, et al. Pharmacokinetic optimisation of antibacterial treatment in patients with cystic fibrosis: current practice and suggestions for future directions. **Clin Pharmacokinet 1999;35:437-59.**

---

## **Risk-Benefit of Treating Depression**

This review discusses the merits of a variety of therapeutic agents used in the treatment of depression in children and young adults. The clinical studies of

antidepressants in children completed to date are addressed, as well as issues related to the treatment of comorbid states and the management of resistant depression. The last section of this review may be the most important; the authors conclude with an insightful discussion of developmental factors affecting treatment. Special consideration is given to compliance issues in adolescents and the effect of noncompliance on assessing therapy. Renaud J, Axelson D, Birmaher B. A risk-benefit assessment of pharmacotherapies for clinical depression in children and adolescents. **Drug Safety 1999;20:59-75.**

---

## Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/22/99:

1. Daclizumab (Zenapax® ) was added to the formulary for prevention of organ rejection in patients following renal transplantation. Daclizumab is administered in a 1 mg/kg dose given intravenously over 4 hours perioperatively and then every 14 days for a total of five doses.
2. Leflunomide (Arava® ) was approved for use in adult patients with active rheumatoid arthritis. It is considered a second line agent and is restricted to the Rheumatology service.
3. Midazolam syrup (Versed® ) also was added to the formulary. The syrup is cherry-flavored and provides 2 mg midazolam/ml.
4. Granisetron (Kytril® ), a 5-HT<sub>3</sub> receptor antagonist, was removed from the formulary. Ondansetron remains on the formulary.
5. The 3rd and 4th quarter and the 1998 annual reports of the Adverse Drug Reaction Reporting Program were presented. For more information about these reports, please contact Dr. Michelle McCarthy in the Drug Information Center at 924-8034.

All health care providers are encouraged to report adverse drug reactions (ADRs). If you are unfamiliar with the procedures for reporting and ADR through MIS, please contact a pharmacist in your area or call the Drug Information Center. The Center staff will assist you with completing all necessary documentation.

---

*Contributing Editor: Marcia L. Buck,  
PharmD*

*Editorial Board: Anne E. Hendrick,  
PharmD*



*Michelle W. McCarthy, PharmD*

*Production manager: Stephen M. Borowitz*

*If you have any comments or would like to be on our mailing list, please contact Marcia Buck by mail at Box 274-11, University of Virginia Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to [mlb3u@virginia.edu](mailto:mlb3u@virginia.edu).*



[Return to the Children's Medical Center Home Page](#)

---



[Send comments to Witz@Virginia.edu](mailto:Witz@Virginia.edu)

All contents copyright (C) 1995, Stephen M. Borowitz, M.D., Children's Medical Center, University of Virginia. All rights reserved. Last Revised: March 15, 1999