ROTAVIRUS INFECTION - THE NEED FOR A VACCINE

Ruth Bishop and Graeme Barnes, Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Parkville, Victoria 3052

Abstract

Primary rotavirus infection in young children can cause severe acute diarrhoea requiring hospitalisation for treatment of dehydration. Morbidity and mortality rates in children throughout the world are sufficient to justify the development of a vaccine. Current strategies are aimed at the development of a live oral attenuated rotavirus vaccine to be given in the first two to three months of life, preferably in association with oral poliomyelitis vaccine.

Introduction

Acute diarrhoea in young children is one of the major world health problems, with an average incidence of 2.5, 2.3 and 3.9 episodes per child per year in Africa, Asia and Latin America respectively. In the United States of America, there are up to 2.3 episodes per child per year[1,2,3]. It has been estimated that diarrhoea results in up to 3.7 million physician visits and 220,000 hospitalisations of children under five years old annually in the United States of America. Rotaviruses are a leading cause of diarrhoea in young children throughout the world, with the peak age for severe disease varying between six and 12 months in developing countries and 12 to 24 months in developed countries.

Rotaviruses cause 20 to 40 per cent of the episodes of diarrhoea requiring hospitalisation of children in both developed and developing countries. It is not often realised that the disease can be as severe as cholera in adults, and that rotavirus infections cause the death of approximately one million children annually in developing countries. Mortality can be controlled by early access to rehydration therapy. It is unlikely that morbidity will be controlled by improvements in hygiene, water supply or sewage disposal, as the incidence of rotavirus diarrhoea is similar in developing and developed countries, despite high standards of community hygiene in the latter.

The World Health Organization has given a high priority to the development of a rotavirus vaccine for use worldwide[4]. Recent results of field trials make it likely that at least one candidate rotavirus vaccine may be licensed for use in the near future[5]. Decisions to use rotavirus vaccines must be based on the demonstration of the importance of the disease, the likelihood that it can be controlled by vaccination and the calculated cost effectiveness of a vaccine.

Clinical symptoms, transmission and sources of rotavirus infection

Rotavirus infections are ubiquitous in the young of all mammalian and avian species. Strains are adapted to infect individual animal species, and cross-species infections appear to be rare in nature. In humans, transmission is direct from person-to-person via the faecal-oral route. Rotaviruses can contaminate, and survive for long periods in sewage and water supplies, but these do not appear to be major sources of infection within most communities[2,3].

Rotaviruses are highly infectious. Excretion of high levels of infectious particles in faeces (10^6 tissue culture infectious dose, $TCID_{50}$ / ml) (tissue culture infectious dose), stability of the virus in the environment and the low dose needed to initiate infection (1-10 $TCID_{50}$ / ml) ensures that rotavirus infections can be transmitted and sustained over long periods of time in most communities. High levels of transmission of rotavirus within families have been recorded once infection is introduced by a family member. Mild to moderate symptoms of enteric infection can develop in most contacts, including older children and adult family members.

Rotaviruses infect the mature absorptive epithelial cell lining the villi of the small intestine, producing symptoms of enteric infection after a period of 24 to 48 hours. In young children undergoing primary infection, symptoms include acute onset of vomiting and watery diarrhoea, often accompanied by fever. Symptoms can persist for several days or weeks while the gut mucosal lesions heal. In rare cases, such as in immunocompromised children, virus infection persists, causing prolonged diarrhoea. In the majority of patients, dehydration from rotavirus diarrhoea can be readily corrected by early commencement of oral rehydration therapy (ORT). Nevertheless, for a variety of reasons, some young children still die from rotavirus diarrhoea, even in Australia, the United States of America and other developed countries. Antibiotics and antimotility drugs should not be used in treatment.

Epidemiology of rotavirus infection

Rotaviruses are one of the most common infectious agents encountered throughout life. Primary infection occurs early in life, and serum surveys imply that all children in both developed and developing countries have experienced rotavirus infection by five years of age. Repeated infections are common throughout life, and have the potential to cause disease at any age. In general, most rotavirus infections are only mildly symptomatic. However severe disease associated with rotavirus infections is not uncommon and accounts for between one-third and one-half of hospitalisations for severe diarrhoea in young children worldwide

The burden of rotavirus disease across a community has seldom been assessed. A longitudinal study of rotavirus infection and gastroenteritis in families regis-

tered with one paediatric medical practice involved a middle class suburban population in the United States of America[6]. This study produced evidence that rotaviruses infected one or more members in 51% of 65 families, including 28% (35 / 126) of children and 67% (16 / 24) of adults, during 29 months of surveillance. Rotavirus infection in both children and adults was symptomatic in 75 to 80% of cases. Similar results have been recorded in longitudinal surveillance studies involving 140 children and their families over three years in Melbourne.

The natural history of rotavirus infection supports the belief that effective active immunity could be achieved using a vaccine to protect against severe disease. Longitudinal surveillance studies in Melbourne and elsewhere show that primary rotavirus infection does not protect against reinfection, but is protective against the development of clinical symptoms on reinfection[2].

Rotavirus disease in Australia

Communicable Diseases Intelligence (CDI) publishes fortnightly reports on the diagnosis of rotaviruses made by contributing sentinel laboratories throughout Australia. It is apparent that rotaviruses, together with respiratory syncytial viruses (RSV), account for many of the laboratory reports to this scheme.

The seasonal occurrence of severe rotavirus infection varies from year to year and from State to State[7]. As observed in temperate countries worldwide, rotavirus enteritis occurs predominantly in the colder months of the year. Peak months can occur as early as May or June or as late as September. In any year, the peak of infection appears to occur earlier in Perth than in the eastern States. Peak months in the Northern Territory appear unpredictable and have even included the summer months.

A recent study published in the *Medical Journal of Australia* estimates that rotavirus is a major cause of morbidity among young children in New South Wales. The annual number of admissions to hospitals is approximately 3,700 children under five years of age, at an estimated cost of 4.6 million dollars[8]. The study concluded that routine infant vaccination against rotavirus could reduce this morbidity and the resulting health care costs. A further study of the direct and indirect costs of a rotavirus outbreak in a child-care centre in New South Wales suggests that large, indirect costs can also accrue from parents' lost work time and from illness due to secondary household cases[9].

The epidemiology of rotavirus disease in Australia and elsewhere is complex[2,3]. Rotaviruses comprise a genus within the family Reoviridae and can be subdivided into at least five antigenic groups (Group A, B, C, D and E). The majority of symptomatic infections in humans and other animals are caused by Group A rotaviruses. Group A rotaviruses are subdivided further into P and G serotypes based on identification of the two outer capsid proteins VP4 and VP7 respectively, both of which stimulate production of neutralising antibody in serum and intestinal contents post-infection. Antibodies to VP4 and VP7 have been shown to be protective in animal models. Although the protective response in humans is still not precisely identified, current hypotheses implicate involvement of neutralising antibody to VP4 and VP7.

In addition to recently developed specialised assays to determine G and P type, it is possible to study genetic variation in rotaviruses excreted by individuals. Rotaviruses contain a core of genetic material of doubled stranded RNA (dsRNA) that can be extracted and subjected to gel electrophoresis to reveal 11 distinct bands, each of which represents a gene that codes for a separate viral protein. The overall pattern formed by the 11 bands is designated the electropherotype of a particular strain. There appears to be an almost infinite variety of differing electropherotypes worldwide. The number coexisting in a particular location appears to be limited, with usually one or two patterns dominant. These dominant electropherotypes may persist, but are usually replaced in any one location after 12 to 18 months. Determination of electropherotypes provides a ready means of studying genetic variation in rotavirus strains, and of tracking transmission or spread of strains.

We have conducted comprehensive studies of the serotype and electropherotype of rotavirus strains causing severe enteritis in Australian children for the past three years, and earlier studies in Melbourne since 1973[2]. Results show that serotype G1 infections are common and persistent in all States as they are worldwide and show great genetic diversity. Unpredictable epidemics of G2, G3 and G4 strains have appeared in all States. At least one unusual strain that appears to be a combination of two pre-existing strains (by reassortment of genes) caused a widespread epidemic in children in Central Australia and the Northern Territory in 1994[10]. Rotaviruses of each major serotype have also been recorded as causes of endemic nosocomial infections in obstetric hospital nurseries in Melbourne and elsewhere, frequently for long periods of time[2].

The ability of one human serotype to cross-protect against disease due to other serotypes is the subject of continuing research. Longitudinal surveillance studies of Melbourne children infected as neonates with a G3 strain has shown that they were not immune to reinfection with rotaviruses of different serotypes one to three years later[11]. However, they were protected against moderate to severe disease on reinfection. This seminal finding has been confirmed in other developed and in developing countries. It provides the basis for an approach to vaccination using live oral attenuated vaccines derived from human rotavirus strains.

Vaccine development

Although rotavirus infection can occur in breast-fed infants, there is evidence that the use of oral immune supplements (passive protection) delays, but does not prevent, later rotavirus infection. Nevertheless there are numerous clinical circumstances in which passive protection could be advantageous, for example in prolonged nosocomial outbreaks, particularly among

young children requiring special care, children undergoing major surgery, and in day-care or other nursery situations.

To date vaccine development has centred around the development of live oral vaccines capable of conferring protection against clinical disease on reinfection. At present this is most likely to be achieved by the use of a live oral attenuated rotavirus vaccine capable of stimulating a mucosal immune response (or other immune response) effective against the four major human rotavirus serotypes. Since rotavirus disease can occur under six months of age and is most common between six and 24 months of age, the vaccine should be given within the first few months of life, preferably in association with oral poliomyelitis vaccine[12].

The first candidate oral vaccine to have completed phase 1 and phase 2 field trials is a mixture of four live viruses derived from an animal rotavirus strain. This includes a G3 simian rotavirus (RRV) together with three reassortant viruses in which the gene coding for VP7 of human G1, G2 and G4 serotypes has replaced the corresponding simian gene coding for G3. This tetravalent vaccine (RRV-TV) has been tested in children in 23 centres in the United States of America and shows a relative efficacy of 57% against all rotavirus diarrhoea, and of 82% against very severe rotavirus enteritis[4]. Incorporation of this vaccine into immunisation schedules in the United States of America has been assessed as likely to be cost effective[13].

Rotavirus was first discovered in 1973 by scientists at the Royal Children's Hospital (RCH) and Melbourne University. Research since then at the Royal Children's Hospital has focussed on the epidemiology of rotavirus infection, together with the immune response observed after natural infection. This research has led to the identification of a candidate oral rotavirus vaccine by adapting to culture the strain of human rotavirus (RV3) shown to immunise newborn babies after natural infection[2,4]. Early results of phase 1 trials in adults, children aged three to four years and infants aged three months have shown no adverse symptoms after one dose of virus (6×10^5 $TCID_{50}$/ml), and have resulted in immune responses in a proportion of recipients. It is hoped that funding for further testing of this candidate vaccine will be made available.

Alternative approaches are also being explored in Australia and elsewhere. This includes the use of virus-like particles incapable of replication but bearing the major outer capsid proteins of rotavirus serotypes, genetically engineered vaccines using avirulent *Salmonella* species or other bacteria or viruses as vectors for genes expressing rotavirus proteins[3].

It now seems within our grasp to control this common life-threatening 'cholera' of young children. Efforts to do so deserve wide support from scientists and funding bodies.

References

1. Brandt C, Glass RI. Impact of diarrheal diseases worldwide. In: Kapikian AZ, ed. Viral infections of the gastrointestinal tract, 2nd ed. New York: Marcel Dekker, 1994:1-26.
2. Bishop RF. Natural history of human rotavirus infection. In: Kapikian AZ, ed. Viral infections of the gastrointestinal tract, 2nd ed. New York: Marcel Dekker, 1994: 131-167.
3. Kapikian AZ, Chanock RM. Rotaviruses. In: Fields BN *et al*. Field's Virology, 3rd ed. Philadelphia: Lippincott-Raven, 1996:1657-1708.
4. Bishop RF. Development of candidate rotavirus vaccines. *Vaccine* II: 1993;247-254.
5. Bernstein DI, Glass RI, Rodgers G *et al.* Evaluation of rhesus rotavirus monovalent and tetravalent reassortant vaccines in US children. *JAMA* 1995; 273:1191-1196.
6. Rodriguez WJ, Kim HW, Brandt CD *et al.*Longitudinal study of rotavirus infection and gastroenteritis in families served by a paediatric medical practice: clinical and epidemiologic observations. *Pediatr Infect Dis* 1987;6:170-176.
7. Masendycz PJ, Unicomb LE, Kirkwood CD, Bishop RF. Rotavirus serotypes causing severe acute diarrhoea in young children in six Australian cities 1989 to 1992. *J Clin Microbiol* 1994; 32:2315-2317.
8. Ferson MJ. Hospitalisations for rotavirus gastroenteritis among children under 5 years of age in New South Wales. *Med J Aust* 1996; 164:273-277.
9. Ferson MJ. Direct and indirect costs of a rotavirus outbreak in child care. *Comm Dis Intell* 1995;19:4-6.
10. Palombo EA, Bugg HC, Masendycz PJ. Multiple gene rotavirus reassortants responsible for an outbreak of gastroenteritis in central and northern Australia. *J Gen Virol* 1996 (in press).
11. Bishop RS, Barnes GL, Cipriani E, Lund JS. Clinical immunity after neonatal rotavirus infection. A prospective longitudinal study in young children. *N Engl J Med* 1983;309:72-76.
12. Crawley JMS, Bishop RF, Barnes GL. Rotavirus gastroenteritis in infants aged 0-6 months in Melbourne, Australia: implications for vaccination. *J Paediatr Child Health* 1993; 29:219-221.
13. Smith JC, Haddex AC, Teutsch SM, Glass RI. Cost-effectiveness analysis of a rotavirus immunization program for the United States. *Pediatrics* 1996; 96:609-615.