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Global Poliovirus Eradication and the Inactivated Poliovirus Vaccine Marcia L. Buck, Pharm.D., FCCP

In 1988, the World Health Assembly, the directing council of the World Health Organization (WHO), passed a resolution committed to the elimination of poliomyelitis. The resulting Global Polio Eradication Initiative has become the largest international public health program ever conducted. The program has been very successful. Between 1988 and 2003, the number of polio-endemic countries was reduced from 125 to six: Afghanistan, Egypt, India, Niger, Nigeria, and Pakistan. The number of cases of wild poliovirus infection reported annually decreased from approximately 350,000 to 682.^{1,2}

Despite these successes, there is still much work to be done before global eradication can be assured. On January 15, 2004, the WHO published an update of the program goals, the Global Polio Eradication Initiative Strategic Plan 2004-2008, which highlights the steps needed to achieve the following objectives:

- to interrupt poliovirus transmission globally,
- to achieve certification of polio eradication in all six WHO regions, including assurance of adequate disease surveillance measures and laboratory containment programs,
- to prepare for cessation of the use of oral poliovirus vaccine in children, and
- to develop long-term plans for disease control.^{1,3}

At this time, only three of the six WHO regions have been certified as polio-free. Certification is determined by an international commission, and requires three consecutive years without report of wild poliovirus transmission. In addition, all laboratories in the region with poliovirus materials must have adopted standard

containment measures. The Americas Region was the first to be certified, on August 20, 1994. The Western Pacific Region was the second area to be declared free of poliovirus, with certification on October 29, 2000, followed by the European Region on June 21, 2002. The three regions not yet certified include Africa, Eastern Mediterranean, and South East Asia.¹⁻³

In the last two years, there has been a significant increase in wild poliovirus cases in Nigeria, predominantly in the northern state of Kano. This increase is believed to be linked to the boycott of polio vaccination by leaders in several Nigerian states, who have falsely claimed the vaccine causes sterility and spreads acquired immunodeficiency syndrome (AIDS). During the 2002-2003 reporting period, the number of confirmed cases in Nigeria rose from 202 to 355. In response to this outbreak, supplemental immunization programs supported by the Nigerian government have been implemented which target children less than 5 years of age. Educational programs have been provided to reinforce the importance and safety of vaccination. Intensified immunization programs are also planned in India and Pakistan this year.^{2,4,5}

Poliovirus Vaccines

There are currently two forms of poliovirus vaccine, the oral, live virus vaccine and the inactivated vaccine which can be given subcutaneously or intramuscularly. Both vaccines contain the three known serotypes of poliovirus (Mahoney, MEF-1, and Saukett) and are given in a four-dose series at 2, 4, 6-18 months, and 4-6 years.

Oral poliovirus vaccine has been the mainstay of immunization in the United States since its

licensing in 1963. The oral vaccine was initially favored because of its superior ability to produce mucosal immunity and concerns over the safety and immunogenicity of the original inactivated product. Reformulation of the inactivated poliovirus vaccine (IPV) in 1987 produced a more potent product, as equally efficacious as the oral vaccine. In children given the new IPV product during clinical trials, seroprevalence rates for detectable serum neutralizing antibody were 95 to 100% for the three poliovirus strains after the first two doses were administered.^{6,7}

Conversion to IPV

On January 1, 2000, the Advisory Committee on Immunization Practices (ACIP) made the recommendation to discontinue use of the oral poliovirus vaccine and begin exclusive use of IPV for routine childhood immunization in the United States.⁸ This announcement followed a three year transition period, beginning in January 1997, where the two vaccines were administered in sequence.

The conversion to IPV was spurred by continued reports of vaccine-associated paralytic poliomyelitis (VAPP) with the oral vaccine. Administration of a live virus vaccine carries the risk of inducing the disease, with immunocompromised individuals being at greatest risk. Between the years 1980 and 1995, 132 cases of VAPP were reported to the Centers for Disease Control and Prevention (CDC). The majority of cases occurred in children under one year of age. Fifty-two cases were reported in previously healthy vaccine recipients, 41 cases involved healthy household contacts of the recipient, and seven occurred in healthy community contacts. The remaining 32 cases were reported in immunocompromised individuals who were either vaccine recipients or their close contacts.⁸

Based on these numbers, the estimated incidence of VAPP is one case per 2.4 million doses of oral live virus vaccine administered.⁸ While paralytic poliomyelitis was still endemic in the United States, this risk was considered justified in relation to the risk for wild poliovirus infection. With the eradication of wild poliovirus in the United States, however, the risk of VAPP became unacceptably high.

The conversion to IPV, initially limited to the United States and several European countries, is gradually spreading to other areas of the world. Assurance of adequate vaccine stock and the higher price of IPV compared to the oral vaccine have been cited as the major impediments to

implementation of routine IPV use in some countries.⁷⁻⁹

As a result of the conversion to IPV, oral poliovirus vaccine is no longer commercially available in the United States. A stockpile is maintained by the CDC for use in the management of an unexpected polio outbreak. In addition, this supply can be used for immunization of unvaccinated individuals who will be traveling in less than 1 month to an area where polio is endemic, since the oral vaccine produces higher seroconversion rates after a single dose.⁹⁻¹¹

Contraindications

Inactivated poliovirus vaccine should not be given to patients with a history of hypersensitivity to any component of the vaccine, including streptomycin, neomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde. Although purification of the IPV vaccine removes most of these substances, trace amounts may remain. Patients who experience anaphylaxis or anaphylactic shock within 24 hours of receiving IPV should not receive additional doses.^{6,7}

Immunization with IPV should be postponed in patients with acute, febrile illness. The presence of a minor illness, including upper respiratory tract infection, does not require a delay in vaccine administration.⁶

Adverse Effects

The most frequently reported adverse effect following IPV administration in clinical trials was fever > 100.6° F. Since most infants and children are receiving other vaccines at the same time as IPV, causality has been difficult to establish. Guillian-Barre Syndrome has been reported after use of an IPV product that is not available in the United States, but no link between the vaccine and the syndrome has been established.^{6,7} Adverse reactions potentially associated with IPV administration should be reported to the manufacturer or through the Vaccine Adverse Event Reporting System (VAERS).¹²

Availability and Dosing

Inactivated poliovirus vaccine is available individually and in a combination vaccine product. The single product (IPOL®, Aventis Pasteur) is available in 0.5 ml single-dose syringes for subcutaneous or intramuscular administration and a 5 ml multidose vial. A pentavalent combination product containing diphtheria, tetanus, acellular pertussis, (DTaP) hepatitis B, and IPV (Pediarix®, GlaxoSmithKline) is also available for

administration at 2, 4, and 6-18 months. It is packaged in both 0.5 ml single-dose vials and syringes and is administered intramuscularly. Both products must be kept refrigerated prior to administration. Vaccine that has been frozen must be discarded.^{6,7}

Combination vaccine products have proven to be very popular among pediatric health care providers, as they reduce the number of injections required during well baby visits. It is expected that additional combination vaccines will be available in the United States within the next two to five years.¹³ A hexavalent combination product, which contains DTaP, IPV, hepatitis B, and *Haemophilus influenzae* type b vaccines, is currently available in Europe.⁷

Cost

The average wholesale price (AWP) of IPOL[®] pre-filled syringes is \$31.49 per dose. The multidose vial, which provides 10 doses, costs \$270.58. The AWP for Pediarix[®] is \$82.54 per single-dose vial, slightly less than the combined cost of the individual components.¹⁴

Summary

Routine childhood immunization with poliovirus vaccine has resulted in the elimination of wild poliovirus infection in most areas of the world. It is anticipated that complete global eradication will occur within the next year. With the risk of wild poliovirus eliminated, several countries, including the United States, have turned their efforts towards improving the safety of polio immunization. Over the past decade, IPV has replaced the oral live virus vaccine in an effort to eliminate cases of vaccine-associated paralytic poliomyelitis. Continued surveillance will be needed to determine the long-term safety of IPV and its efficacy in maintaining poliovirus eradication.

References

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Pharmacology Literature Review

Antifungals in Neonates

This extensive review covers the pharmacology, efficacy, and toxicity of antifungals used to treat neonatal candidal infections. The article focuses on amphotericin, both standard and lipid formulations, flucytosine, and fluconazole. The potential role for echinocandins, such as caspofungin, is also addressed. Frattarelli DAC, Reed MD, Giacoia GP, et al. Antifungals in systemic neonatal candidiasis. **Drugs 2004;64:949-68.**

Insulin Update

This concise article provides an overview of the current research in insulin therapy, including novel delivery routes. The author begins with a discussion of the currently available injectable insulin products, then focuses on non-invasive administration methods, including transdermal, intranasal, oral, and inhaled products. An extensive bibliography is also included. Cefalu WT. Evolving strategies for insulin delivery and therapy. **Drugs 2004;64:1149-61.**

Safety of Rectal Diazepam

Diazepam rectal gel has been shown to be an effective means of controlling periods of increased seizures. It is often prescribed in children with seizure disorders that have been difficult to control, as part of the management strategy developed by the parents and health care

providers to deal with an increase in seizure frequency until the patient can be brought to a medical care facility. This review addresses the safety of the rectal formulation, after administration of a single dose and after repeated doses. Pellock JM. Safety of Diastat®, a rectal gel formulation of diazepam for acute seizure treatment. **Drug Safety 2004;27:383-92.**

Tobramycin Pharmacokinetics

The pharmacokinetic profile of tobramycin was evaluated in 60 children (0.6-17.4 years of age) with febrile neutropenia who were undergoing stem cell transplantation. This analysis was performed as part of a prospective study comparing once-daily tobramycin administration to traditional dosing every 8 hours. Serum tobramycin concentrations were obtained at 2 and 8 hours after the first dose. Pharmacokinetic parameters were similar between the groups. The mean rate of elimination was $0.34 \pm 0.09 \text{ hr}^{-1}$ in the 8 hour group versus $0.43 \pm 0.12 \text{ hr}^{-1}$ in the once-daily group. Average volume of distribution was $0.48 \pm 0.12 \text{ L/kg}$ in the 8 hour group and $0.43 \pm 0.26 \text{ L/kg}$ in the once daily group. As anticipated, tobramycin volume of distribution varied with age. Using the variables derived in this analysis, the authors recommend initial once-daily tobramycin doses of 10 mg/kg in children 6 months to 9 years of age, 8 mg/kg in children 9 to 12 years of age, and 6 mg/kg in patients 12 years and older. Dupuis LL, Sung L, Taylor T. Tobramycin pharmacokinetics in children with febrile neutropenia undergoing stem cell transplantation: once-daily versus thrice-daily administration. **Pharmacotherapy 2004;24:564-73.**

Vancomycin in Neonates

This extensive review covers the pharmacokinetics of vancomycin in neonates, as well as its antibacterial spectrum, the development of bacterial resistance, toxicities, and dosing recommendations. The authors include specific information on the elimination of vancomycin in patients with patent ductus arteriosus (including the effects of concurrent indomethacin treatment) and during extracorporeal membrane oxygenation (ECMO). They conclude with a discussion of the utility of monitoring vancomycin serum concentrations in this population. De Hoog M, Mouton JW, van den Anker JN. Vancomycin: pharmacokinetics and administration regimens in neonates. **Clin Pharmacokinet 2004;43:417-40.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 5/28/04:

1. The olanzapine orally disintegrating tablet formulation (Zyprexa® Zydis®) was added to both the Inpatient and Outpatient Formularies for use in patients who are unable or unwilling to swallow tablets.
2. Risperidone long-acting injection (Risperdal® Consta™), the first long-acting atypical antipsychotic, was added to both Formularies.
3. Eplerenone (Inspra®), a selective aldosterone antagonist derived from spironolactone, was also added to both Formularies. It is indicated in the management of hypertension and in patients with left ventricular systolic dysfunction and evidence of congestive heart failure after an acute myocardial infarction. Its use is restricted to patients unable to tolerate spironolactone.
4. As a result of the annual Formulary review, chlorpheniramine, bethanechol, and propantheline were deleted from the Inpatient Formulary because of lack of use. Trihexyphenidyl was added to the Outpatient Formulary.

A Note of Thanks

With this issue of Pediatric Pharmacotherapy, we say good-bye and good luck to Dr. Anne E. Hendrick. Anne has been a member of our editorial board since 1995, and has consistently provided our authors, including myself, with thorough, balanced, scientific reviews. She has set high standards for the quality of the clinical studies cited in our articles and the depth of the study results presented to our readers. In addition, she has taught me a great deal about the process of scientific writing. We are honored to have worked with Dr. Hendrick and wish her all the best in her new career path.

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