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Palivizumab: Use in the Prevention of Respiratory Syncytial Virus Infections

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Respiratory syncytial virus (RSV) infections are a significant cause of morbidity and mortality in the neonatal population. It has been estimated that RSV infections account for nearly half of all hospital admissions for bronchiolitis in children and 25% of hospitalizations for pneumonia. RSV disease has a considerable economic impact. A recent study from Canada documented nearly $18 million spent in one year on the treatment of children less than 4 years of age with RSV lower respiratory tract infections.[1,2]

RSV Immune Globulin

In 1996, polyclonal respiratory syncytial virus immune globulin (RSVIG or RespiGam®; MedImmune, Inc.) was approved by the Food and Drug Administration (FDA) for prophylaxis against RSV infection in susceptible patients.[3] The release of this agent marked a new era in the management of RSV; populations at risk could now be identified and given passive immunization throughout the winter months in an effort to avoid severe lower respiratory tract infections.

Two large multi-center studies comparing monthly infusions of RSVIG to placebo documented a reduction in the number of RSVIG treated children hospitalized with RSV infections and a decrease in the length of stay for those children who did require admission.[4,5] Based on these early studies, the American Academy of Pediatrics published recommendations that RSVIG prophylaxis be considered in children with bronchopulmonary dysplasia up to 24 months of age and infants born before 32 weeks gestation who are less than 6 months old at the onset of the winter season.[6]

Early reactions to RSVIG in routine practice were mixed. While some institutions saw a decline in hospitalizations of former neonatal intensive care unit patients, others found no significant difference when comparing to previous years.

The administration of RSVIG presented significant barriers to its use. As with other intravenous immune globulin products, RSVIG required establishing venous access and administering the infusion over several hours. The potential for infusion-related reactions and pulmonary edema resulting from fluid overload made close monitoring necessary. In addition, the product was often in short supply during the RSV season because of limitations in production. The cost of therapy, approximately $5,000 per year for each infant treated, further added to concerns over the wide-spread adoption of RSVIG. Despite these drawbacks, it achieved considerable use. In the 1997-1998 RSV season, sales of RespiGam® were approximately $70 million.

Palivizumab

In June 1998, a new RSV immune globulin was released to address some of the problems with RespiGam®. Palivizumab (Synagis®; MedImmune, Inc.) is a humanized monoclonal antibody to RSV.[7]

Palivizumab was developed to provide a more potent neutralizing antibody to the fusion protein of RSV than polyclonal RSVIG. The product is prepared using recombinant DNA technology with a murine monoclonal antibody, Mab 1129. It is then humanized by grafting the six variable regions of the murine antibody into an IgG human framework to avoid generating an anti-mouse antibody response.[8]

As a result of its higher potency (approximately 50 to 100 times that of RespiGam®), palivizumab

can be administered in a much smaller fluid volume, avoiding prolonged infusion times.

Clinical Trials

The safety and pharmacokinetics of palivizumab were defined in a phase I/II multicenter, randomized, double blind, placebo-controlled trial published in 1997.[9] A total of 62 babies were enrolled in the study from 10 different sites. All infants were either born at < 35 weeks gestation and < 6 months of age at enrollment or had documented bronchopulmonary dysplasia and were < 24 months of age. Patients were randomized to receive either placebo (normal saline), or 3 mg/kg, 10 mg/kg, or 15 mg/kg palivizumab given intravenously over 2 to 5 minutes. Doses were administered monthly. Fifty-seven infants completed the study; no infants withdrew because an adverse event.

The frequency of respiratory tract infections was comparable among the groups. RSV infections occurred in 4 of the placebo patients (20%), 3 of the patients receiving 3 mg/kg palivizumab (30%), 1 patient receiving 10 mg/kg (10%), and 2 receiving 15 mg/kg study drug (10%). Of these patients, 2 of the placebo-treated and 2 of the 3 mg/kg palivizumab-treated patients required hospitalization. None of the infants receiving higher doses required admission for RSV infection.

In animal studies, a palivizumab concentration of 25 to 30 mcg/ml is needed to produce an average 2-log (99%) reduction in pulmonary RSV titers. Similar concentrations are believed to be needed to prevent infection in humans. Measurement of trough palivizumab serum concentrations 30 days after initial injection in the Phase I/II study were 6.8, 36.1, and 60.6 mcg/ml after the 3, 10, and 15 mg/kg doses, respectively. Serum concentrations rose slightly with repeated dosing. The authors concluded that the 15 mg/kg dose provided optimal serum concentrations. Pharmacokinetic analysis revealed an elimination half-life ranging from 19.3 to 26.8 days with a mean of 20 days, supporting the monthly schedule for drug administration.

Adverse reactions were comparable among the groups. The most frequently reported adverse events during treatment were fever, pneumonia, and infusion site infiltration. There were no significant alterations in serum chemistries, hematologic studies, or urinalyses with palivizumab use.

Two additional Phase I/II studies were completed during that time. Both were open-label, dose escalation studies of palivizumab administered intramuscularly (IM). The results of these trials supported the decision to continue research with the 15 mg/kg dose.[10]

The results of a Phase III clinical trial known as the "IMpact-RSV" study were just published in the September issue of *Pediatrics*. Over 1,500 infants and young children were enrolled in this randomized, double blind, placebo-controlled efficacy trial of IM palivizumab during 1996. The rate of hospitalization for RSV was 10.6% in the placebo group versus 4.8% in the palivizumab-treated infants ($p< 0.001$). Adverse events over the 5-month trial were similar in both groups, consisting of mild respiratory tract infection (50%), rash (20%), and pain at the site of injection (6-9%).[11]

FDA approval for palivizumab was based on the results of these studies. Like the previous polyclonal product, palivizumab is approved for use in premature infants and infants with bronchopulmonary dysplasia.[12]

Dose Administration

Palivizumab should be administered monthly during RSV season, typically November through March or April. The manufacturer expects to begin shipment to wholesalers on September 21, 1998. The recommended dose is 15 mg/kg given IM, preferably in the anterolateral aspect of the thigh. Administration into the gluteal muscle is **not** recommended. [12]

The drug is provided as a sterile lyophilized powder to be reconstituted with sterile water for injection to a final concentration of 100 mg/ml. Once mixed, the solution should be allowed to sit for approximately 20 minutes until it becomes clear. The single-use vial does not contain a preservative and should be used within 6 hours of reconstitution.[12]

Cost

The wholesale acquisition cost (WAC) of palivizumab is approximately $900/vial. Some purchasing groups will be able to receive palivizumab at a reduced cost. The cost of palivizumab is slightly higher than RespiGam®; however, the ability to give palivizumab IM

significantly reduces the cost of administration, providing an overall cost savings.

Summary

RSV immune globulin products are used to prevent infection in premature infants and infants with chronic lung disease, those patients most likely to suffer from severe bronchiolitis and pneumonia. Palivizumab offers distinct advantages over polyclonal RSVIG. Its increased potency may provide greater protection, and the availability of an IM dosage form allows this product to be easily administered in the clinic setting.

References

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12. Synagis® product information. MedImmune Home Page. URL: http://www.medimmune.com/products/synagispi.htm.

Pharmacology Literature Review

Azithromycin Update

The authors of this article present an in-depth review of the use of azithromycin in children. After a brief overview of the drug's antibacterial spectrum, the remainder of the paper deals with pharmacokinetic studies and clinical trials in different pediatric populations. The article contains several useful tables summarizing the results of American, European, and Asian trials. Since azithromycin use is likely to increase as a result of the new injectable form, this review would make a useful addition to any pediatric health care provider's files. Langtry HD, Balfour JA. Azithromycin: A review of its use in p(a)ediatric infectious diseases. **Drugs 1998;56(2):273-97.**

Eicosanoid Research in Children

This brief review discusses the current and potential role for eicosanoids (e.g. prostaglandins, thromboxane, and leukotrienes) and their antagonists in treating pediatric illnesses. The author addresses the role of prostaglandins in treating congenital cardiac defects, pulmonary hypertension, and preventing gastric lesions. He also theorizes on its use as a peripheral vasodilator for treating burn wounds. The use of specific cyclo-oxygenase (COX-2) inhibitors as anti-inflammatories is also briefly reviewed, as well as the use of thromboxane and leukotriene inhibitors in asthma. This rather eclectic approach covers a wide range of disease states, but provides the reader with a better understanding of the potential of this group of compounds. Shimizu T. The future potential of eicosanoids and their inhibitors in p(a)ediatric practice. **Drugs 1998;56:169-76.**

Ibuprofen Overdose

The case of a 15 year old boy who ingested seventy 200 mg ibuprofen tablets is presented. On admission, the patient's blood and urine studies were within normal limits; however, renal function began to deteriorate within the first day of hospitalization. The peak serum creatinine reached was 199 micromol/L (2.3 mg/dL) on hospital day 2. All laboratory monitoring parameters returned to normal within 72 hours. This case serves as a reminder of the potential for prostaglandin inhibition to result in acute renal failure and highlights the risk of overdose of an over-the-counter medication. Bhangoo P, Choonara I. Transient acute renal insufficiency following an overdose of ibuprofen. **J Pediatr Pharm Pract 1998;3:163-5.**

Midazolam in Infants and Children

Midazolam has become one of the most frequently used sedatives in the management of hospitalized children. This review covers both the pharmacodynamics and pharmacokinetics of the drug in children, as well as dosing, drug interactions, and methods for administration. Several useful tables are included. For example, Table 1 presents a comparison of midazolam half-life and clearance values from several studies in infants and children, as well as adult values. Blumer J. Clinical pharmacology of midazolam in infants and children. **Clin Pharmacokinet 1998;35:37-47.**

Pharmacists' OTC Recommendations

The results of a survey of retail pharmacies are presented in this article. Of those pharmacists surveyed, 195 (16%) responded. In the category of children's cough and cold preparations, Dimetapp®, PediaCare®, and Triaminic® were each recommended by nearly 1/3 of the respondents. Fifty percent of the pharmacists recommended Desitin® for diaper rash, followed by A&D ointment by 35%. Nix® was the leading pediculicide, recommended by 87% of the respondents. Choice of oral rehydration solutions was nearly unanimous with 95% recommending Ross's Pedialyte® brand. Recommendations for children's vitamin preparations were more diverse, with 60% of respondents favoring Bayer's Flinstones® brand, and 32% Centrum Jr®. Anon. Pharmacists' top choices in OTCs for 1998. **Drug Topics 1998; Supplement: 8s-22s.**

Risk-Benefit Assessment of Surfactants

This extensive review covers the efficacy and adverse effects associated with the administration of exogenous surfactants to premature neonates. The authors present an interesting discussion of potential adverse effects not yet identified, such as the long-term impact of exogenous surfactants on immunologic function. While this article provides a very thorough review of the data published on surfactant use to date, very little emphasis is given to economic concerns or comparisons among preparations. Walti H, Monset Couchard M. A risk-benefit assessment of natural and synthetic exogenous surfactants in the management of neonatal respiratory distress syndrome. **Drug Safety 1998;18:321-37.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 8/28/98:

1. Mirtazapine (Remeron®), a tetracyclic antidepressant, was added to the formulary.
2. Fenofibrate (TriCor®) was also added to the formulary for the management of patients with Type IV or V hyperlipidemia.
3. The intravenous form of azithromycin (Zithromax®) was added to the formulary. The oral form was previously approved.
4. Quinupristin/dalfopristin (Synercid®) was added to the formulary, in anticipation of final FDA approval, for management of patients with vancomycin-resistant bacterial infections. It is considered a resticted (category A) drug and orders require approval of an attending physician in infectious disease.
5. Pramipexole (Mirapex®) was added for the treatment of Parkinson's disease.
6. All restrictions were removed from budesonide.
7. The following drugs were removed from the formulary: Actifed w/ Codeine® syrup, promethazine with codeine syrup, aspirin with codeine #3 tablets, stanozolol, and secobarbital (injectable and oral forms).
8. The quarterly report of the Adverse Drug Reaction Reporting Program was presented. For more information, please contact Dr. Michelle McCarthy at 934-8034.

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