

**NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN
DEVELOPMENT**

**BEST PHARMACEUTICALS FOR CHILDREN ACT (BPCA)
PRIORITIZATION MEETING**

Meeting Minutes

December 12, 2003

**Neuroscience Center—Conference Room C
Rockville, Maryland**

INTRODUCTION

George Giacoia, M.D., Coordinator, Pediatric Pharmacology Research Unit Network, National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)

Dr. George Giacoia stated that the purpose of the meeting was to select drugs that warrant revised labeling for pediatric use. The issue of feasibility must be considered because some drugs may seem like obvious candidates for study but might be extremely difficult to study for various reasons. The review process began with 179 drugs that were narrowed down to the 24 drugs under review at this year's meeting.

Dr. Giacoia remarked that a number of procedural improvements have been made in the review process since last year's meeting. The committee has been given guidelines, such as feasibility of study, as well as labels, to make its determinations.

Labeling Drugs for Pediatric Purposes

Dr. Shirley Murphy reported that, according to Food and Drug Administration (FDA) lawyers, the key question for reviewers is: "Is it labeled?" Last year, heparin (an anticoagulant) was on the list. The label said it was approved for children down to 1 kg; therefore, it was labeled from a literature review. According to the lawyers, only a significant safety concern or new science justifies breaking into a label. For instance, lithium was labeled down to age 12, but an examination of the FDA archives revealed that no children were ever studied. In addition, the science of bipolar disease had changed significantly in 20 years. Therefore, the lawyers approved going into the label and issuing a written request.

Dr. Jeffrey Blumer asked a question regarding the provision of information or guidance. During the course of the committee's deliberations, it might be determined that new science does exist that requires evaluation and compilation of the literature to revamp the label instead of new studies. If that situation develops, how should the committee provide that information or guidance in this context?

Dr. Murphy replied that if a safety issue is involved, FDA can review all the safety literature and tell the sponsor that the label must be changed. Dr. Murphy deferred to Dr. John Alexander of the FDA Anti-Infectives Review Division, who explained that if a group decides to change the labeling for dosing for particular children, the information along with its sources must be compiled. Either the group can approach the company that owns the data and ask that the data be changed or the group can file a citizen's petition with FDA.

Dr. Donald Mattison indicated that the NIH also is reviewing the legal issues of the BPCA. NIH attorneys are looking at the BPCA to determine how to engage the FDA in discussions around labeling and applications based on existing literature. According to the BPCA, studies are not encouraged if data are already available, from the literature for example.

Dr. Blumer raised a related question regarding the possibility of a fourth category—drugs for which a label change may be needed to ensure safety even if additional studies are not necessary. Dr. Alexander agreed with Dr. Blumer and stated that lindane is a case in point. This drug is on the list because labeling changes may be needed without further study. The following wording was proposed for a fourth category: “Data available supporting labeling and label changes needed. No further studies are necessary because data are available.”

Feasibility Obstacles

The reviewers discussed a constant problem in medical research, namely, finding a sufficient number of patients to conduct a study. Dr. Giacoia reiterated that feasibility is a major concern. Dr. Murphy referred to written requests from last year's list. Contracts were issued and individuals responded. The only exceptions were for very complicated indications, such as spironolactone combined with Diuril for chronic lung disease in children and infants, which has gone to the Neonatal Working Group. Dr. Wayne R. Snodgrass referred to other scientific issues, namely, that eplerenone and spironolactone probably should be compared head to head, something that has probably not even been done in adults.

ISOFLURANE

Jerrold Lerman, M.D., Department of Anesthesiology, Buffalo Children's Hospital

Thomas P. Green, M.D., Department of Pediatrics, Northwestern University School of Medicine

Primary Review

Dr. Jerrold Lerman made the following comments in his review of isoflurane:

- Isoflurane is used mainly for the maintenance of anesthesia. The current label for isoflurane does not mention children, so it is deficient, inadequate, and incomplete. In terms of the literature, basic data exist for clinical pharmacology. Most notably, the maximum acceptable concentration (MAC) of isoflurane is presented only to the age of 26 years. Well before 1998, when the label was revised, data were available down to premature infants. The MAC, a very important marker for clinical use, needs to be updated, and that is the major deficiency in the clinical pharmacology area. Many of the effects of isoflurane in adults and children are similar. However, when this drug is introduced to perform inhalation inductions, it should be

labeled like desflurane. Indications in the package insert state that it can be used in the induction and maintenance of anesthesia, but no one will use this agent for the induction of anesthesia in children because it stimulates airway reflex responses. The cardiovascular and respiratory responses are fairly predictable. This agent is used primarily for long-term maintenance of anesthesia, and the metabolic response of children is similar to that of adults.

- There probably is not a need for further studies. There is some substantive literature documenting irritability of the airway when inhalation inductions are performed with isoflurane. In addition, isoflurane studies are not necessary because there are two newer inhalational agents (desflurane and sevoflurane). Sevoflurane, used for induction in anesthesia, has replaced halothane. Desflurane, a more expensive cousin of isoflurane, is used for the maintenance of anesthesia. Information in the package insert is scant, and it is uncertain how much more it should be changed in terms of data available in the literature. Literature is available regarding the respiratory, cardiovascular, and cerebrovascular effect of isoflurane in children. Some peer-reviewed literature could be pulled to provide a framework for use of this agent and to get an indication in children of all ages. Even in the neonatal age range, there is a fair amount of data regarding cardiovascular depression.
- There is no ethical problem in doing more studies. The numbers are not adequate, but enough data exist to begin collating information for an indication in children. There are no ethical concerns regarding the administration of isoflurane in children for any research study.

Secondary Review

Dr. Thomas P. Green agreed with Dr. Lerman's review and added the following comments:

The summaries of the literature that the reviewers received did not include many of the studies on isoflurane. Several isoflurane studies not listed in the compendium cover pharmacokinetics (PK), efficacy, and safety in newborns, premature newborns, and older children.

The data suggest that usefulness in children is well documented and that the labeling could be changed based on the studies that are currently available.

Discussion

The following issues were raised in a discussion of isoflurane:

- Dr. Ralph E. Kauffman asked whether isoflurane was used frequently and extensively enough to be studied. Dr. Lerman responded positively and added that isoflurane is a ubiquitous pediatric maintenance agent, and it would be easy to recruit patients and centers to provide data if the literature does not already have sufficient data for a particular area.
- Dr. Kauffman asked whether specific age groups or types of studies are the highest priority. Dr. Lerman responded that the literature contains sufficient data about cardiovascular effects

with older children. The only group of interest would be neonates and infants, but this is not a high priority.

- In response to a question regarding whether the labeling for desflurane and sevoflurane includes children, Dr. Lerman responded in the affirmative. The desflurane label cautions against using it as an induction agent because of the airway reflex response, which the label for isoflurane does not state explicitly enough. For sevoflurane, extensive pediatric trials were conducted before it was approved, so Dr. Lerman felt certain that it has a pediatric indication or labeling. Baxter Healthcare Corporation/Pharmaceutical Products is now conducting a multicenter trial with desflurane in children, looking at it for maintenance and emergence of anesthesia and possibly to get pediatric labeling.
- Dr. Murphy confirmed that she had the label for isoflurane but not for desflurane or sevoflurane; studies in children have been requested for desflurane and sevoflurane. Dr. Lerman asserted that there is no desflurane labeling for children except to state that is not to be used for the induction of anesthesia. However, for sevoflurane, at least three large trials were conducted in which Dr. Lerman was involved and data were submitted to the FDA; he asserted that sevofluane is labeled for use in children.
- In response to a question regarding whether there are significant advantages of desflurane or sevoflurane over isoflurane in children, Dr. Lerman replied that sevoflurane is a smooth inhalational agent and the most common agent used to anesthetize children. In terms of maintenance of anesthesia, because sevoflurane is expensive, institutions switch to isoflurane during the maintenance phase of anesthesia. Desflurane is also costly, so for maintenance of anesthesia, most institutions pressure anesthesiologists to use isoflurane during the maintenance phase of anesthesia. Desflurane is the least soluble and most rapidly washed in and washed out agent available. It is possible to control the depth of anesthesia much more accurately with desflurane. For extended surgeries and in obese patients or individuals in which accumulation of an inhalational agent could occur, desflurane is the ideal choice because it is not soluble in the body; sevoflurane and isoflurane are second choices. In terms of advantages, sevoflurane is the induction agent of choice in children. Desflurane, although more costly, is theoretically and practically the maintenance agent of choice. From a cost standpoint, isoflurane is the most widely used maintenance agent.
- Dr. Lerman pointed out that isoflurane is a 25-year-old drug, and a thorough review of the literature indicates that few studies would need to be undertaken. Isoflurane has been adequately studied. However, most of the studies are not FDA-quality studies. Dr. Kauffman remarked that it may be possible to augment information for pediatric labeling from the literature and fill in some gaps. Dr. Lerman agreed and said that it is important to recognize that the yardstick by which the amount of inhalational agent is measured (i.e., the MAC), has been published even down to premature babies with isoflurane. Isoflurane has been used in premature babies, yet there is no indication or labeling for it. Even the package insert does not reflect its use in children, although it was updated in 1998.
- Dr. Murphy remarked that recent studies cite the possible implications of neuronal apoptosis in neonates and infants up to 3 months who were exposed to inhalational agents, ketamine,

and other agents. She asked Dr. Kauffman to comment on safety-related concerns and ethical implications that may come from these studies. Dr. Kauffman deferred to Dr. Lerman who referred to newborn rat studies that were published in *Nature*. A great deal of controversy exists about the relevance and validity of these studies, and there is concern about their relevance to human and clinical practice. Dr. Lerman denies that there are any ethical concerns for clinical application at this time.

- Dr. William J. Rodriguez from the FDA reported that currently there are studies in juvenile primates. Newborn primates will be exposed to ketamine, isoflurane, and nitrous oxide. The study results will be available in the next 12 months.

METOCLOPRAMIDE

Susan R. Orenstein, M.D., Professor of Pediatrics, University of Pittsburgh School of Medicine
Thomas P. Green, M.D., Department of Pediatrics, Northwestern University School of Medicine

Primary Review

Dr. Susan R. Orenstein offered the following information about metoclopramide:

- Metoclopramide is indicated for symptomatic gastroesophageal reflux and diabetic gastroparesis in adults. Metoclopramide's current label limits pediatric information to pharmacokinetic and safety information. The label lacks information on pharmacokinetics in premature babies, those aged 3 weeks and younger, and all children aged 6 months and older. It also lacks information on pharmacodynamics (PD) and efficacy in all pediatric age groups.
- Additional literature is available on PK. Pons et al. related dose to plasma concentration at 1 hour after dosing in 24 children 1 to 18 months of age. Kearns et al. studied 10 premature infants, identifying prolonged apparent plasma clearance in 30 percent of the infants and suggested that it might be due to pharmacogenetic variability (e.g., a poor metabolizer phenotype) for sulfotransferase isoforms responsible for 32 percent of the drug's metabolism in humans. He also proposed that enhanced clearance in some other infants might represent developmental variations in isoform-specific activity.
- Additional literature is available on PD relating drug dose or blood level to esophageal acid exposure, with the most useful parameter being the reflux index (RI), that is, percent of the study time during which the esophageal pH is less than 4. The RI improves in proportion to the 1-hour plasma concentration, but not so clearly in proportion to dose. Kearns et al. found the RI to improve by more than 75 percent in four of six infants by the steady state 10th dose, but not to improve significantly when all six subjects were considered together, nor when the RI after the first dose was considered, most likely due to underpowering of the study.
- Literature on effectiveness for gastroesophageal reflux disease (GERD) suggests a modest improvement in RI in infants under 12 months old orally dosed with 0.1 to 0.3mg/kg/dose tid-qid, but with unacceptable incidence of extrapyramidal effects appearing with single doses over 0.2mg/kg or cumulative daily doses more than 0.9mg/kg. The improvement compared with placebo was modest: placebo ~20 percent improvement; metoclopramide

~40 to 50 percent. Two studies suggest that although metoclopramide is effective in infant GERD, cisapride or domperidone are more effective.

- Literature on effectiveness for delayed gastric emptying (DGE), sometimes a component of GERD in infants, suggests that reflux-associated DGE or postsurgical DGE may respond to a single dose of intravenous metoclopramide 1mg/kg, whereas DGE in premature infants does not. Metoclopramide also has improved motility in GERD-associated DGE.
- Literature suggesting lack of efficacy of metoclopramide for GERD generally lacks power, sometimes lacks controls or blinding, and often includes older children or children referred for prior lack of responsiveness to pharmacotherapy.
- Several studies suggest the importance of correct diagnosis: unselected apnea in premature infants and esophagitis with prominent eosinophilia did not respond well to metoclopramide therapy in uncontrolled trials.
- Experience treating approximately 1,000 infants for GERD with metoclopramide suggests the importance of using adequate nonpharmacologic (“lifestyle” or “conservative”) measures for GERD. These measures were often lacking in the metoclopramide studies in the literature. Dr. Orenstein commented on the importance of engineering to prevent overdoses, such as limiting syringes with the oral formulation to 1 ml and perhaps including written material on the bottles to warn parents of hazardous dose levels. Pharmacists and medical residents have made prescription errors causing extrapyramidal side effects more often than parents have made dosing errors.
- It is possible to extrapolate adult efficacy studies to children to a degree, but less so for infants in whom the drug may be most useful.
- No similar drugs are currently approved. Domperidone, cisapride, and drugs in development may be more efficacious or have a wider therapeutic dosing window.
- In children above infancy, proton pump inhibitors generally are more effective for GERD, but those with more complex disease may benefit from the addition of a prokinetic agent. However, acid suppression with proton pump inhibitors or with histamine-2 receptor antagonists has not been proven to be as efficacious in infant GERD, where metoclopramide has been used the most.
- Especially needed is clarification of pharmacogenetic and metabolic variation, as suggested by Kearns et al. (1998), so that the narrow therapeutic window for dosing might be widened by administering effective doses while minimizing risks of extrapyramidal reactions.
- The effectiveness of chronic (weeks or months) oral use of metoclopramide for DGE in infants 1 to 12 months, with or without associated GERD, should be studied.

- Lacking other drugs for the indication, the effectiveness of chronic (weeks or months) oral use of metoclopramide for the indication of DGE in children aged 1 year and older, with or without associated GERD, possibly should be studied.
- There are no feasibility issues that would make the infant study difficult to perform. However, clinically important DGE is considerably less frequent in older children.
- Clinical outcomes of interest are increased tolerance of feedings, decreased emesis, and increased weight gain.
- There are no ethical issues that would make a clinical study difficult to perform, but adequate power, controls, patient selection, and blinding are crucial.
- In summary, metoclopramide is a moderately effective drug, with a narrow therapeutic window for a common disorder (infant GERD, and possibly for non-GERD DGE) with very limited options currently in the drug formulary. There is possibly a need for PK/PD studies of this drug if it is to be used in children greater than 1 year of age. It also would be most useful to know determinants of variability in PK/PD, that is, pharmacogenetic and metabolic variations. There is a need for efficacy studies of this drug for chronic oral use for delayed gastric emptying in infants, with or without associated GERD, and possibly for DGE in older children. There is no need for safety studies of this drug in children, but there is a need for engineering to fix the dosing error issues. There is a need to study more than one condition/indication, that is, chronic oral use for DGE for various ages. The drug should be studied unless better drugs for the indications will soon to be available.

Discussion

The following comments were made during the discussion of the review of metoclopramide:

- Dr. Green, the secondary reviewer for metoclopramide, commented that this drug has been used widely for a long time, but gastroenterologists have little enthusiasm for studying it. He asked whether metoclopramide would persist in the formulary as a primary drug in the future and whether better drugs are in the pipeline. Dr. Orenstein replied that she did not know about drugs in the pipeline. A couple of studies suggest that cisapride and domperidone are more effective, but they are not currently approved and indicated. The limitations of currently available prokinetic agents drive the use of metoclopramide for GERD. Metoclopramide does not need further study for GERD, but rather for chronic DGE. It is not an optimal drug, but a prokinetic agent is indicated for many children.
- Dr. Lewis I. Cooper from the FDA Review Division commented that the information supplied by Dr. Orenstein was in concert with what has been discussed at FDA. The studies currently available, which apply only to children aged 1 year and younger, involve a total of 16 patients in two separate studies, providing primarily PK and PD information. Other studies provided PD information primarily in infants. Concerns about the extrapyramidal and overdosing effects are real. There are no good studies in older children and only conflicting clinical anecdotes about extrapyramidal effects. Additional uses of the drug have been in

children with asthma who also have reflux. Studies of older asthmatic children found that their asthma is exacerbated by the reflux response, prompting physicians to turn to drugs such as metoclopramide to minimize the reflux and asthma problems.

- Dr. Blumer wondered whether the moderate efficacy seen with metoclopramide relates to not knowing the proper dose. In PK studies, variability in dosing is astronomical. He also observed that clinically relevant end points change with age. Dr. Orenstein agreed that dosing issues were important and responded that it would be useful to sort out the pharmacogenetic variability.
- Dr. Kauffman remarked that metoclopramide has a very narrow therapeutic range, a low therapeutic index, and high variability in the population. It was abandoned until cisapride disappeared. Is it a good idea to resurrect it, or should better drugs be found? Dr. Orenstein responded that both things should occur. If alternative drugs in the pipeline are not going to be rapidly available, more sophisticated use of metoclopramide is called for.
- Dr. Snodgrass pointed out that another genetic variation issue is the risk for tardive dyskinesia, which, while rare, is potentially permanent. Dr. Orenstein referred to a child who had been overdosed for a long period. The risk relates to duration of total dosing.

CEFPROZIL

*Ellen Wald, M.D., Chair and Professor, Department of Allergy and Infectious Disease,
Children's Hospital of Pittsburgh*

*John T. Wilson, M.D., Professor of Pediatrics, Louisiana State University Health Sciences
Center*

Primary Review

Dr. Ellen Wald offered the following information in her review of cefprozil:

- Cefprozil is a second-generation cephalosporin used predominantly for the management of respiratory infections (including pharyngitis, otitis media, sinusitis, and pneumonia) and skin and soft tissue infections.
- Although PK data seem sufficient, PD and efficacy data are absent. Experience suggests that cefprozil is inadequate in combating beta-lactamase-producing *Haemophilus influenzae*, which causes middle ear disease. Cefprozil also is not active against intermediate or resistant *Streptococcus pneumoniae*, especially for middle ear disease. Data are unavailable for children aged 6 months and younger who have acute otitis media or sinusitis, or for children aged 2 years and younger who have skin and skin structure infections.
- Further clinical studies of pediatric populations are needed, especially in the United States.
- Adult studies cannot be extrapolated to pediatrics because the prevalence of resistant *S. pneumoniae* in the two populations is not comparable. Adult studies of sinusitis also are

not adequate to approve use of the drug in children with sinusitis. Furthermore, there is no rationale for a lower dose recommendation for patients with sinusitis.

- Similar drugs in this class may make studying the drug irrelevant, but their liquid preparation is distasteful. Cefuroxime is actually a much more potent drug but harder to use because of its unpleasant taste.
- Cefprozil may be obsolete because it is not as potent as others, although its taste is superior.
- Cefprozil is of interest in children aged 5 to 6 years and younger because of its pleasant taste. It might be of interest to determine whether doubling the dose would improve efficacy if it has a reasonable safety profile. It also would be of interest to conduct studies looking at otitis media. This is not a high priority, however.
- More PK and efficacy studies are needed. In addition, safety studies might be needed because of reports of serum sickness-like reaction. Particular areas of study would focus on acute otitis media and sinusitis.

Secondary Review

Dr. John T. Wilson agreed with Dr. Wald's assessment of cefprozil and added the following comments:

- Cefprozil appears to be a second-choice drug and offers advantages in terms of cost, possibly safety, and formulation acceptability.
- Further study of the label indications in younger children would have to be supported by the need for the drug in those younger children.
- As a second-line drug, cefprozil does not deserve a high priority for study unless compelling evidence can be given regarding adverse effects, compliance based on fewer doses per day, and possibly cost and formulation acceptability.

Discussion

The following issues were raised during the discussion of cefprozil:

- Dr. Blumer asked Dr. Wald whether the studies she suggested would guide physicians in a more effective or safer use of the drug and wondered what the purpose of the studies would be other than to enhance the database on the drug. Dr. Wald responded that, in general, she would not recommend use of the drug in a patient who had not done well on a first-line drug. However, the drug might work better if dose were doubled, which would require a new study.

- Dr. Alexander commented that there is labeling for this drug down to 6 months of age. He questioned the usefulness of studying cefprozil. Regarding double dosing, it would be better to study other drugs where double dosing would be more appropriate.

CEFUROXIME (PARENTERAL)

*Ellen Wald, M.D., Chair and Professor, Department of Allergy and Infectious Disease,
Children's Hospital of Pittsburgh*

*Jeffrey Blumer, M.D., Ph.D., Professor of Pediatrics and Pharmacology, Case Western Reserve
University School of Medicine*

Primary Review

Dr. Wald made the following comments in her review of cefuroxime:

- PK and PD data are absent for pediatric patients. Cefuroxime is listed as indicated for the treatment of meningitis caused by strains of *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*. Published data suggest that meningitis due to *H. influenzae* should not be treated with cefuroxime. Likewise, it is probable that cefuroxime would be inadequate for meningitis due to *S. pneumoniae*, which is not susceptible to penicillin.
- Sufficient data are available for all the other proposed indications for cefuroxime.
- It is possible to extrapolate from adult efficacy studies to children for diagnoses such as pneumonia and urinary tract, skin, and soft tissue infections.
- There are not similar drugs in the same class that would make studying cefuroxime irrelevant; the drug is not obsolete. It is up-to-date for treating pneumonia. There are many other choices for treatment of urinary tract and skin infections. No off-label indications would be important to study.
- In summary, Dr. Wald noted that there is no need for more PK/PD data, no need for efficacy studies, and no need for safety studies of this drug in children. She recommended eliminating listing cefuroxime as a choice for central nervous system (CNS) infection and concluded that further study is not warranted at this time.

Secondary Review

Dr. Blumer agreed with Dr. Wald's assessment of cefuroxime and added the following comments:

Because reviewers were not given a specific indication as a guide, he pulled the package label for the oral form of cefuroxime because most of the pediatric indications are in that label and not in the parenteral label.

Cefuroxime will continue to be used, and no more information is needed because it is safe and effective.

Dr. Wald's recommendation to remove meningitis from the label is a little troubling, but in the face of other, more effective agents for bacterial meningitis, Dr. Blumer concurred with her recommendation.

Discussion

The following comments were made during the discussion of the review of cefuroxime:

- Dr. Kauffman asked whether sufficient information exists in the literature to justify the change in labeling in regard to meningitis. Dr. Wald commented that because there are so many superior drugs to cefuroxime, it would be inappropriate to use cefuroxime for meningitis.
- While acknowledging Dr. Wald's desire to eliminate the indication for bacterial meningitis from the label, Dr. Alexander cautioned that doing so would involve a protracted court process on the part of FDA. In any case, pediatricians have already stopped using cefuroxime for meningitis.
- Information about delayed sterilization is in the precautions section.
- Dr. Robert M. Ward asked about a use for the drug in the newborn and the preterm newborn. Dr. Wald responded that there are relatively few indications in that age group.

MORPHINE

Charles Berde, M.D., Ph.D., Professor of Anesthesia and Pediatrics, Harvard Medical School, and Chief, Division of Pain Medicine, Children's Hospital of Boston

Robert M. Ward, M.D., Professor of Pediatrics and Director, Pediatric Pharmacology Program, University of Utah

Primary Review

Dr. Charles Berde made the following comments in his review of morphine:

- Dr. Berde said he had reviewed the literature and wondered whether he should comment on all routes of morphine or just injectable. Dr. Murphy pointed out that the committee is discussing morphine because the written request was turned down for parenteral intravenous morphine.
- Morphine is indicated in the treatment of acute pain, cancer pain, and a combination of pain and distress in ventilated infants and children. A body of PK data exists for infants and children down to the neonate. Controversy exists about the patterns of clearance, specifically, the relative roles of glucuronidation to 6-glucuronide, 3-glucuronide, or sulfate in the neonate, but there is a strong consensus regarding diminished clearance in the preterm and term neonate, and there are a few disease states that modify clearance, particularly following surgery for congenital heart disease. A reasonable body of PK and PD data exist, but there is a role for more combined PK and PD study. A gap exists in knowledge of dosing in specific

nonintubated neonates. A number of studies cover dosing and comfort scores in intubated neonates and effective target plasma concentrations and infusion regimens for intubated neonates. A number of studies involve a mix of intubated and nonintubated postoperative neonates, but overall the body of safety data on respiratory effects in the nonintubated neonate is sparse. In many places showing the recommended dosing of morphine, especially for the bolus dose, there is growing consensus that the bolus dose in a nonintubated neonate should not be the traditional 0.1 mg per kilo but should start in increments of 0.025 to 0.05 mg per kilo. A body of literature suggests how morphine infusions should be scaled down in mg per kilo per hour in infants aged 6 months and younger. It would be appropriate to include those labels with the recommended starting infusion rate down to 0.025 mg per kilo per hour in infants aged 6 months and older without cardiac disease and 0.02 with cardiac disease.

- One of the questions to discuss is the role of nurse-controlled and parent-controlled analgesia. There is enough information to say that nurse-controlled analgesia is quite safe in both opioid-naïve and opioid-tolerant children. However, there have been a number of mishaps in parent-controlled analgesia, largely in community hospitals. Most physicians think parent-controlled analgesia is appropriate in palliative care, but there is more controversy regarding its use in the opioid-naïve child postoperatively.

Secondary Review

Dr. Ward made the following comments about morphine:

- The label specifically indicates that morphine should not be used in premature newborns, infants, and children and that they can be treated intravenously and with subcutaneous dosing. It also says that the single pediatric dose should not exceed 15 mg, which ignores the child with cancer who may be tolerant of the drug. A moderate amount of literature supports use of the drug, certainly in the premature infant and in the infant and the child being treated with the patient-controlled analgesia pump. Dr. Berde agreed that the labeling has to be changed to recommend intravenous use, not subcutaneous use.
- A robust dataset supports labeling in well-done trials, especially for the intubated preterm neonate.
- Dr. Ward agreed with Dr. Berde's comments about the nonintubated infant and the need for better guidelines based on appropriately controlled studies because the drug is being used that way in many settings. Another issue is that of oral dosing in the very young infant; the pharmacology is likely to be quite different from that in the older child. Dr. Berde agreed and guessed that the predominant oral use in the immediate newborn period is probably for the treatment of withdrawal as much as it is for a postoperative use. Labeling for intravenous use and for intubated preterm neonates—as well as a statement that dosing for intubated and nonintubated neonates may be different and should be smaller and more incremental in the nonintubated neonate—is important.

Discussion

The following comments were made during the discussion of the review of morphine:

- Dr. ShaAvhree Buckman from the FDA Review Division, who reviewed the literature and wrote the written request, reported that in its review of morphine, the Review Division noted several gaps in the label. Areas that were not adequately addressed included nonintubated neonates, younger children, long-term safety issues, and neurocognitive issues with long-term exposure. Difficulties involving morphine stem from the fact that it is an old drug that was grandfathered in by the Review Division. No adult efficacy studies were used to label morphine, which means that extrapolation from adults to children about safety and efficacy of the drug is difficult. The Review Division felt that having information on the safety and efficacy of morphine was of utmost importance, and the written request tries to address some of the gaps.
- Dr. Berde responded that the large postoperative infusion studies have established the safety and efficacy of infusion rates down to 6 months. There is some evidence for efficacy in intubated neonates, although ways of assessing adequacy are imprecise and there are huge gaps. Morphine ought to be studied with Government funding, not just pharmaceutical funding. Morphine is widely used off-label, and there is a lack of alternatives that have labeling for all settings. He called for an extension of the label, while recognizing that more information is needed.
- Dr. Buckman pointed out that the Review Division has a much higher burden to meet than the academic community in extending a label based on reviewed studies in the literature. More rigorous studies are needed to fill the gaps in the literature in order to extend the label.
- In referring to minimum effective dose in the written request in reference to nonintubated neonates, Dr. Stephen Spielberg thought that the standard was unrealistically high and not doable. Furthermore, the minimum effective dose itself depends on the infant's state and degree of pain. He warned that the panel must be very cautious about setting the standard for labeling where data are not ascertainable.
- Dr. Ward commented that the current label is irrelevant to the practice of pediatric medicine. To set the bar quite high and then not to have a sponsor for the studies defeats the goal.
- In defense of the Review Division's position, Dr. Buckman remarked that the written request is their best assessment of the information that is needed.
- Dr. Kauffman pointed out that significant gaps in the literature are in nonintubated infants, premature infants, and infants younger than 6-months—the most difficult age groups to study. With morphine, a drug used widely in these infants without labeling, he wondered if participants saw feasibility and/or ethical issues in conducting a study or if these considerations would be determined by the study design and conduct.

- Dr. Blumer stated that if trials can be designed to provide information in the context of current care paradigms, the opportunity will exist to answer questions raised in the request. However, if the written request raises questions outside the realm of what would normally occur in the care of patients, then the situation is hopeless. The study is worthwhile and essential because the label is so old that it has no relevance to the current patient population. By looking at labeling as opposed to clinical use, they are essentially starting over. Dr. Berde concurred.
- Dr. Kauffman noted that the labels for the use of morphine in pediatric populations fall short because of inconsistencies in the labels.
- In a real-world clinical setting, Dr. Berde stated that an updated label that provides guidance for infants down to 6 months and the intubated neonate as well as one that describes the controversy and lack of information in the nonintubated neonate would be much better than the current label. It is important to try to extend the label to some degree. An extended label would prevent further harm and provide a better analgesia. Some information on how dosing is scaled and modified in the infant and some of the factors that modify it would be better than nothing on the label.
- Dr. Murphy pointed out that the labels and drugs belong to the companies, not to FDA. If a significant safety issue comes up, FDA can force the company to change the label. Otherwise, the public can pressure FDA to force the pharmaceutical company to change the label. She added that morphine is still on patent because there is an oral formulation, but the intravenous formulations are off-patent.

LINDANE

J. Routt Reigart, M.D., Department of Pediatrics, Medical University of South Carolina

Wayne R. Snodgrass, M.D., Ph.D., Clinical Pharmacology Unit, University of Texas Medical Branch

Primary Review

Dr. J. Routt Reigart offered the following comments in his review of lindane:

- Lindane is a potent neurotoxicant. Animal data suggest that at doses relevant to pharmaceutical use, it also is a testicular toxicant. Although it is labeled for use in children, present medical practice excludes it from use in children because of the availability of suitable alternatives. Because of delayed clinical response to treatment, it is highly likely that families dissatisfied with the initial response will apply secondary applications without recommendation of their physician.
- Dr. Reigart also remarked that the materials sent to him were for cream and lotion, not the shampoo. The cream and lotion are labeled for scabies, and the shampoo for lice.
- With regard to labeling, there is a general agreement that lindane should not be used in children under 50 kilos or 110 pounds, so it would be appropriate to consider adding this

information to the label. In the literature as well as clinical practice, people often treat without definitive diagnosis through specific microscopic visualization. To deal with the problem of repeated application, the label also should ensure that the quantity prescribed for use in children is sufficient for only a single application.

- In terms of sufficient available literature, efficacy studies are probably not necessary. The literature on absorption suggests that the drug is efficiently absorbed from the skin of children, although there is considerable variation. Further studies might improve understanding of the factors affecting absorption and also might better elucidate the difference between the distributive and clearance phases of the drug. Lindane is clearly toxic as used and presently labeled.
- There are no other drugs in the same chemical class, although there are alternative treatments. Alternative treatments are pyrethrins for lice and permethrin for scabies. Studies also suggest successful use of ivermectin for scabies. The efficacy of these treatments appears equal in the literature. However, general pediatric medical practice excludes the use of lindane in children.
- Because the accepted pediatric standard of care is to avoid use of this drug, further study of lindane is not recommended and would not be appropriate. There would be serious ethical issues in applying it to children for the purpose of further evaluating the PK, safety, or efficacy of the drug. Overall, it is a significantly hazardous drug that is not acceptable in children despite its label indications. Lindane should not be available at all.
- In summary, Dr. Reigart stated that there is no need for PK and/or PD studies of lindane in children or for efficacy studies of this drug in children. In regard to safety, it is well established that the drug is not particularly safe. The only difference might be in indications. When used in shampoo, the exposure is likely to be less than with total body exposure with the cream or lotion, so it is possible that the shampoo is safer, although there are no data to support that assertion. Overall, the drug should not be studied because of safety concerns.

Secondary Review

- Dr. Snodgrass agreed with Dr. Reigart's assessment of lindane and added the following comments:
- Lindane is a known animal and human carcinogen, so it would be unethical to suggest it should be used further.
- If the label contains any pediatric indications, perhaps a citizens' petition should recommend that it be removed.

Discussion

The following issues were raised during the discussion of the review of lindane:

- Dr. Rodriguez read some information about lindane provided by the Review Division in December 2002: Lindane has substantial use in the pediatric population. The therapeutic index for this drug is low, and if it is misused, there is the potential for serious adverse events. Lindane is only one of two drugs approved for the treatment of scabies. Because of the potential for the development of resistant scabies and the limited approved treatments for this condition, another form of treatment that would offer greater safety would have a broad public health implication. Dose/duration studies to improve the concentration and duration of therapy for lindane for the treatment of scabies in pediatric studies are recommended.
- Dr. Murphy reported that the label was updated this year with a safety warning. The written request called for looking at different durations of exposure of the drug. Lindane is not recommended as a first-line drug, but it is used as a second- and third-line drug.
- The only indication for a known carcinogen would be in children with cancer. This drug has a long body residence time and should not be used for the treatment of scabies.
- Dr. Snodgrass remarked that concentration studies show that absorption is very erratic, so even at a lower concentration, some children may be getting far more than others. Ivermectin is an alternative, but it is not labeled for this use. A recommendation prevalent in the pediatric community is to limit the use of lindane to children weighing more than 50 kilos, which is not in the label. The updated safety warning in the label is weak.
- Participants discussed frequency of use. Dr. Blumer said the scale of use may be larger than anticipated because of the lack of drugs labeled for scabies and because lindane has been around for a long time. It is hard to justify the use of the drug because of the safety issue, and he suggested that it be removed. There are significant hazards associated with use of lindane, and trying to manipulate it will expose more children to potential dangers.
- Dr. Green noted that patients with scabies come into his office in intense discomfort and want a therapeutic option; they want relief and they want it immediately, so removing the drug from the market may not be viable.
- Dr. Reigart commented on the need for a high diagnostic standard for scabies to ensure physicians are indeed treating scabies. He also pointed out that regardless of the agent used, there is no immediate relief from symptoms. The itching and discomfort are an allergic response to the mite, so early symptomatic relief is not a function of the drug.
- A participant pointed out that rapid diagnosis of scabies in the clinician's office is not in the near or foreseeable future. Although there is no immediate relief of symptoms with lindane, there is the promise of future relief.
- In regard to alternatives, permethrin for scabies has been studied and is more effective than lindane. Ivermectin also has been studied and is shown to be effective. The ivermectin option is not widely known among pediatricians.

- Looking at benefit-risk ratios, the question is why one would want to use a drug known to be a carcinogen. Dr. Reigart remarked on the reasonableness of using lindane as a second-line drug.
- The ethical issue involves enrolling children in a clinical trial for a well-known toxic agent. Institutional Review Board (IRB) approval would be difficult to obtain for such a study.
- Dr. Hari Sachs of FDA remarked that the written request said that lindane would be a second-line agent when another approved treatment failed with clear diagnostic confirmation of scabies.
- Dr. Kauffman asked Dr. Lisa Mathis, who has worked with lindane at FDA for the past 2 years, to share the FDA's perspective about lindane, which is seen as a very toxic agent that should not be approved for use in children. It would be helpful to know the basis for having lindane on the list and to know what the agency feels is missing. Dr. Mathis reported that FDA reviewed lindane recently to look primarily at safety issues. Analysis of the data determined that lindane has an extremely small therapeutic window. It is approved for second-line use only in patients in whom other therapies have failed. The current label contains a boxed warning, and a medication guide for parents tells them to confirm that their physicians use other drugs first; it also cautions them about safe use of the product. FDA's concern stems from the fact that only one other therapy (permethrin) exists for the indication of scabies. Because the pharmaceutical industry has failed to submit new drug applications or investigational new drug applications for other therapies, there are no second-line treatments for scabies, although permethrin and permethrin sulfate are used. FDA felt serum levels, which are related to serious adverse events, could be decreased with decreased contact time or decreased concentration. FDA's rationale for study was to find ways lindane could be used more safely, insofar as it is the only second-line treatment currently available.
- In response to a question from Dr. Reigart, Dr. Mathis said that lindane is being used even in infants. Close to 1 million prescriptions are written, many of them for first-line therapy, which is why the language in the new labeling has been tightened to ensure it is used only for second-line therapy.
- Dr. Snodgrass asked whether the label cites information from the Agency for Toxic Substances and Disease Registry (ATSDR) on human data for carcinogenicity and genotoxicity data in animal studies. Dr. Mathis said that some of the data are cited in the animal data section on the label, but ATSDR is not mentioned specifically. Dr. Snodgrass noted that the Red Book 2003 lists ivermectin as an effective therapy; it is not labeled for that purpose, but it is endorsed by the American Academy of Pediatrics (AAP) as an alternative therapy for scabies. Dr. Mathis questioned the data that this recommendation is based on and pointed to reports of deaths in older patients who have used ivermectin for scabies. She also said there are a myriad of reasons why a drug would not be approved for use in pediatric patients.
- Dr. Richard Gorman asked whether the new revised patient handout includes instructions to parents or caregivers about the need for clinical diagnosis of scabies, that is, a confirmed

visualization of the parasite. Dr. Mathis said the patient handout does not address that stipulation, but the package insert for physicians does.

- Dr. Spielberg commented on two issues: (1) the regulation of practice for a toxic compound and (2) whether to do additional studies of the compound. The solutions are very different. A study of such a toxic compound will not make it through the IRBs, and parents will not consent. On the other hand, very limited drugs are available to treat a significant problem. If lindane were studied and approved for use, there would be a need to balance issues of patient protection and physician and parent education to prevent toxicity.
- Dr. Kauffman commented that, even if studies of lindane were approved to investigate safety concerns, they would not be feasible because of ethical constraints.
- Dr. Gorman pointed out that similar issues were raised for studies of equally toxic substances for eczema, in which immune modulators that had known risks for carcinogenesis were tested in skin conditions for long-term use. Dr. Mathis added that thousands of parents are consenting to have their children use lindane, so parents would not necessarily refuse to enroll their child in a study. Lindane would be studied only as a second-line therapy, and thousands of patients already use the drug safely. Dr. Gorman pointed out, however, that most of the current patient usage does not involve informed consent. Another reviewer agreed and said that most parents would not consent to have their children treated with lindane if they were given a detailed informed consent form. If significant information is unobtainable, and if in the opinion of the committee it is unobtainable, where does that leave this compound? Dr. Kauffman interjected that one or two alternative treatments might be more effective for lice, if not for scabies.
- Dr. Reigart commented that permethrin shows promise—it is 85 to 90 percent effective. Some studies find that it is even more effective than lindane. Dr. Mathis agreed that there are alternatives for head lice but not for scabies. She said that there is a lack of good safety data on ivermectin at doses needed for the indication of scabies and questioned the AAP Red Book's recommendations for its one-time use. Dr. Mathis stated that the recommendation was questionable because scabies needs a blood meal; if there is an egg, it will not take a blood meal, so repeated dosing with ivermectin would be needed. Perhaps ivermectin should be studied rather than lindane.

AMPICILLIN/SULBACTAM

George McCracken, M.D., Department of Pediatrics, University of Texas Southwestern Medical Center

Richard Gorman, M.D., Chairperson, Committee on Drugs, American Academy of Pediatrics

Primary Review

Dr. George McCracken made the following comments in his review of ampicillin/sulbactam:

- Unasyn, which is the parenteral preparation of the drug, is an antibiotic with one approved indication in pediatrics, that is, for soft tissue/skin infections. It also has been used in the

intravenous form to treat intra-abdominal prophylaxis after surgery and for peritonitis, sepsis, complicated sinus infections, and complicated pneumonia. The PK are fairly well delineated in infants and children, especially in those with bacterial meningitis, for which there are a number of studies. Unasyn's spectrum of activity is similar to several other agents.

- Based on the limited use of this agent in pediatrics and the broad use in adult patients, it has a low priority for study in infants and children. Two potential areas of interest would be intra-abdominal sepsis alone and combined with aminoglycoside, and complicated sinus infections with or without CNS extension. The feasibility of performing these studies is moderate for intra-abdominal sepsis and difficult, if not impossible, for sinus infections because of insufficient numbers of patients.
- Dr. McCracken did not know if he was to review the oral preparation in addition to the parenteral form. A participant explained that the agent was put on the list to review because it was recommended in the AAP Red Book and the label does not reflect that recommendation. There is a need to coordinate AAP recommendations with labeling. Dr. McCracken would like to take the oral preparation of ampicillin/sulbactam out of the Red Book because this formulation is not available in the United States. When evaluated in pediatric patients several years ago, it was found to have an unacceptably high rate of diarrhea. It has no advantage over amoxicillin/clavulanate, and no studies are indicated.

Secondary Review

Dr. Gorman agreed with Dr. McCracken's assessment of ampicillin/sulbactam and added the following comments:

- Ampicillin/sulbactam has no clear advantage over other drugs. It has limited use in pediatrics.
- No extra study is needed of this drug; it should be moved to the bottom of the list of drugs to study.

Discussion

The following comments were made in discussion of the review of ampicillin/sulbactam:

- Dr. Rodriguez said that he conducted one of the oral studies of ampicillin/sulbactam and compared it to the clavulanate preparation, but the incidence of diarrhea was not that much greater in the pediatric population. However, for adults the increase in diarrhea resulted in the drug not being available in this country.
- Dr. McCracken commented that ampicillin/sulbactam has no advantage over amoxicillin/clavulanate. There is no need to do any studies in the United States. Dr. Alexander stated that because an oral preparation is not available in the United States, there is no mechanism for studies. Part of the reason for looking at ampicillin/sulbactam is its use in intravenous preparation for the treatment of intra-abdominal infections; therefore, it

has some value in particular settings, and efficacy studies could be done for additional indications.

- Dr. Blumer pointed out that this drug has been embraced by pediatric otolaryngologists for sinus infections and other airway infections as well as for off-label uses with sparse data. He suggested that ampicillin/sulbactam should be studied for these off-label indications. Dr. McCracken expressed reluctance to study the drug in that setting because of *Staphylococcus* and said it would be a low priority. He also would never recommend studying ampicillin/sulbactam alone for intra-abdominal sepsis. It would have to be combined with aminoglycoside as a minimum because of the enterics that are beta-lactamase producers and are not very effectively managed by ampicillin/sulbactam. For example, 30 percent of *Escherichia coli* cases would be unresponsive to this drug.
- Dr. Alexander (FDA medical reviewer in the Center for Drug Evaluation and Research Division of Anti-Infective Drug Products) remarked that none of the drugs in the Review Division are specifically labeled for conditions like retropharyngeal abscess. When asked by Dr. Alexander what drug he would study for the treatment of retropharyngeal abscess, Dr. McCracken picked clindamycin.

AMPICILLIN

George McCracken, M.D., Department of Pediatrics, University of Texas Southwestern Medical Center

Robert M. Ward, M.D., Professor of Pediatrics and Director, Pediatric Pharmacology Program, University of Utah

Primary Review

Dr. McCracken made the following comments about parenteral ampicillin:

- Parenterally administered, ampicillin has been widely used in pediatrics for more than three decades. Although the two approved pediatric indications are bacterial meningitis and neonatal bacterial sepsis, its use has been far broader, especially in the treatment of premature and term infants, in which it is combined with aminoglycoside or cephalosporin for the treatment of sepsis.
- The PK of both the oral and parenteral preparations are well characterized, and the safety is well established even in newborns. The one population in which studies might be performed would be the premature infant with birthweight less than 1,500 grams. Additional studies in pediatrics are not needed beyond the one mentioned above. Ampicillin has been used safely and effectively for years, so there is no reason to study it further.
- The oral preparation was been used for several decades but has now been replaced by amoxicillin because it is better absorbed higher in the intestine with less frequent diarrhea. Therefore, there is no indication for additional study of the oral preparation.

Secondary Review

Dr. Ward offered the following comment about ampicillin:

- Even in the extremely low birthweight infant in whom the drug is used extensively, its safety and effectiveness profile are very well established from clinical experience. It would be an inappropriate use of limited resources to study the drug in that population.

Discussion

The following comments were made during the discussion of the review of ampicillin:

- Dr. Alexander remarked that the wording in labels for older drugs, such as ampicillin, is very different from what is done today. The labeling for ampicillin is far broader than just the indications of bacterial meningitis and sepsis that are listed for particular dosing. He suggested adding to the label the higher doses that are being recommended for bacterial meningitis for group B strep in the neonate.
- Dr. Ward commented that the recommended dosages in the label for sepsis and meningitis are 150 to 250 mg/kg per day. He was not aware of a justification for the common clinical practice of 400 mg/kg per day in the sicker infant. He also doubts the value of showing that 200 mg is as effective as 400 mg. Dr. McCracken stated that the lower dose is definitely effective. Dr. Ward commented that few practices reflect older recommendations of 50 mg/kg per day. Both Drs. Ward and McCracken agreed that as long as the label is up to 200 mg/kg per day, patients are being well served.
- Dr. Blumer said that the label does not define sepsis and asked whether FDA accepts an indication for sepsis. Dr. Alexander responded that at the current time, FDA does not have any guidance on how to approach sepsis.

AMOXICILLIN/CLAVULANATE

George McCracken, M.D., Department of Pediatrics, University of Texas Southwestern Medical Center

Ralph E. Kauffman, M.D., Director of Research, Children's Mercy Hospital, Kansas City, MO

Primary Review

Dr. McCracken made the following comments in his review of amoxicillin/clavulanate:

- Amoxicillin/clavulanate, or Augmentin, has been studied in infants and children. The PK are well characterized, except for newborns up to 2 months of age. The indications in pediatrics include infections of the acute otitis and sinusitis, for which it is commonly used, lower respiratory infections, urinary tract infections, and skin and skin structure infections. Additional indications are not required.

- Additional PK studies in infants aged 0 to 2 months are needed to be sure that the dosage is appropriate for treatment of acute otitis media.
- Efficacy data are not required because extensive data exist for the treatment of middle ear disease with the preparations discussed.
- It would be beneficial to have additional data in the younger infant.

Secondary Review

Dr. Kauffman offered the following comment about the use of amoxicillin/clavulanate:

- The label is ambiguous for infants younger than 3 months. There are not many infants studied in the first month or two of life.

Discussion

The following comments were made during the discussion of amoxicillin/clavulanate:

- Dr. Kauffman asked whether PK studies in the 0- to 2-month age group would be feasible for the indications mentioned. Dr. McCracken responded that they would be feasible and would not take long because otitis is seen in young infants. However, in an outpatient setting, studying very young infants in terms of birthweight could take time because they are less commonly studied. He commented that in a premature clinic followup at his medical center, antimicrobials are studied. A study of amoxicillin/clavulanate to treat otitis in very young infants could probably be done in 1 year at his medical center. If other institutions collaborated, a study could be done in approximately 6 months.
- Dr. Ward asked whether a 1-month-old prior preemie presented to Dr. McCracken's clinic with a fever and otitis would be treated as an outpatient or whether there would be an evaluation for other sources of infection and possibly admission to the clinic. Dr. McCracken responded that the infant would be admitted for 2 days and then would go home. If a full-term baby comes in at 2 weeks with otitis and looks good, the baby would not need to be admitted to the clinic and would be treated with amoxicillin/clavulanate.
- Dr. Kauffman commented that if studies are done, they should be very narrowly targeted to PK in this younger age group to ensure that the label is correct for the newborn who is less than 3 months. Additional efficacy studies are not needed.
- Dr. Alexander commented that PK studies alone are not sufficient if the drug is going to be extended to younger age groups; both PK and safety studies are needed. The number of children to be studied and possible adverse events must be determined. Adverse reactions and hematologic toxicities are a concern.
- Dr. Alexander also explained the need for care with amoxicillin/clavulanate as a combination product. Written requests are based on a particular active moiety, so a request for

amoxicillin/clavulanate would be based on amoxicillin, and outline studies on amoxicillin as well as amoxicillin/clavulanate or other formulations would be needed. The same would be true if the request is written for the active moiety of clavulanate. Therefore, there are complications in FDA generating a written request for this drug, and other drugs that might be affected must be considered.

- In considering a request for amoxicillin/clavulanate, Dr. Alexander said that studies of amoxicillin are feasible and should be done. The current dosing for amoxicillin is only for 25 to 40 mg/kg. The current recommendation for use in otitis media and community-acquired pneumonia is a 90 mg/kg dose, so it would be beneficial to compare higher and lower doses of amoxicillin to determine the clinical benefit of the new higher dosage regimen versus the risks.
- Dr. Rodriguez read what the label for Augmentin says for children less than 12 weeks and what the amoxicillin label says for neonates. The labels are similar, so it appears the augmentin label borrowed from amoxicillin.

KETAMINE

Charles Cote, M.D., Professor of Anesthesiology and Pediatrics, Northwestern University
Wayne R. Snodgrass, M.D., Ph.D., Clinical Pharmacology Unit, University of Texas Medical Branch

Primary Review

Dr. Charles Cote made the following comments in his review of ketamine:

- The current label is deficient in many areas. Children are mentioned only in passing. Doses are described as 1 to 2 mg/kg intravenous for children, which creates surgical anesthesia in adults. The intramuscular doses for children are 9 to 13 mg/kg. These doses are far higher than what would be used for procedural sedation. PK information for children of any age group is lacking. However, an important statement in the label is as follows: “Ketamine is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits outweigh the possible risks.” For many years, emergency medicine practitioners have believed that ketamine is without risk in patients with a full stomach; therefore, data are needed on the risk involved. Ketamine was originally designed as a general anesthetic, and the only two routes described were intravenous and intramuscular. Since the drug has been released, pediatricians have used the drug in other ways, including orally, rectally, nasally, and epidurally, by continuous long-term infusion in the intensive care unit, and by continuous infusion as an adjunct to opioid analgesia postoperatively. PK and PD data on these routes of administration are needed. Therefore, from a label standpoint, a great deal of information must be collected.
- In regard to feasibility, ketamine has such widespread use among a variety of specialists that it would not be difficult to design studies that are situation appropriate. In other words, the label only describes 1 to 2 mg/kg intravenous and 9 to 13 mg intramuscularly, but much lower or higher doses can be used in children depending on the situation. Bioavailability after different routes of administration needs to be examined, particularly if the drug is going to be

used for prolonged administration. Norketamine, which appears after 2.5 minutes of intravenous administration, also needs to be examined. This very rapid conversion to an active metabolite may not be of importance with single administration intravenously or even with continuous administration of short duration intravenously but may be of greater importance with oral, nasal, and rectal administration. Some studies suggest an equal degree of sedation with a lower plasma level of ketamine and norketamine than with just ketamine. Another safety issue that should be looked at is ketamine as a hypersialagogue agent. The literature on this usage is mixed. Studies could be done comparing ketamine with and without an antisialagogue and also comparing it with atropine and glycopyrrolate for emergence reactions. One study in the literature gave children ketamine and put dye in the pharynx to see if they would aspirate. Several children had spasms, so the study was cancelled. This suggests that although ketamine may preserve airway reflexes and the gag reflex, it increases airway irritability. Therefore, patients with passive regurgitation would likely develop laryngospasm. In relation to emergency medicine literature, a large body of literature describes a “dissociative” state, rather than deep sedation or general anesthesia, that does not require the same degree of monitoring as operating room anesthesia. However, the label needs to clearly state that dissociative anesthesia is deep sedation. There also is a need to look at the use of benzodiazepine as a means to reduce dreaming and emergence agitation. The literature is mixed on this point. In addition, there is a need to tailor the dose to the procedure.

- In regard to safety issues, a question is whether to give oxygen to prevent potential complications. A low but constant rate of laryngospasm, apnea, airway obstruction, vomiting, hallucinations, spasms, and aspiration associated with ketamine also must be looked at. Although ketamine has a very high safety profile, the drug has risks that must be precisely defined. The emergency room literature says that ketamine is very safe, with little need to worry about side effects. This may be true for emergency medicine, but not for orthopedic surgery. Another issue is how long it is necessary to fast before receiving ketamine. Some emergency room workers say it is not necessary to fast, but most of their papers say not to give ketamine to patients sooner than 3 hours after their last meal. This stipulation is much more liberal than the recommended fasting for general anesthesia. Aspiration is difficult to study. Data on use of ketamine for burn patients also are needed. Another safety issue involves epidural use.
- PD and PK studies are virtually absent. Another issue is the role of ketamine isomers. The two isomers of ketamine have been examined independently in the European literature; one has greatly reduced cardiovascular side effects with the same degree of analgesia.
- In terms of outcome variables, many situations can be looked at, such as the incidence of laryngospasms, apnea, hallucinations, vomiting, aspiration, and airway obstruction. Data are sparse in these areas.
- In regard to extrapolation from adult efficacy studies to children, virtually none of the data from adult studies applies to children.

- Ketamine is unique and very unusual and it should remain in the pediatric armamentarium. However, a great deal more information is needed about it.
- There would not be any ethical issues involved in studying this drug as long as the studies are designed appropriately and with the input of the specialists who use the drug.
- Ketamine should be at the top of the list of drugs to be studied because of the explosion of use by so many diverse specialists coupled with misinformation in the literature. Another issue to consider is dosing errors that result from the variable concentrations that are available. Should there be only one concentration?

Secondary Review

Dr. Snodgrass concurred with Dr. Cote's assessment and added the following comments about ketamine:

- The lack of dose response data for the several routes of administration is problematic, norketamine should be studied, and there are older adult data about analgesic effects at much lower serum concentrations.
- In regard to apoptosis, there is a need to compare slow infusions of 15 minutes or more versus a 1- or 2-minute infusion and to look at whether there would be the same increase in intracranial pressure. The adverse effect might be prevented by slower infusion.
- Another issue in regard to apoptosis is neuroprotection against anoxic encephalopathy. Ketamine might be the only drug available to decrease anoxic encephalopathy; therefore, it should be studied.

Discussion

The following comments were made during the discussion of ketamine:

- Dr. Cote pointed out that there are mixed data on intracranial pressure. Some studies have shown an increase in intracranial pressure thought to be due to an increase in blood pressure. An animal study looking at brain uptake of ketamine showed a decreased uptake when the animal's blood pressure dropped after sedation with ketamine. This might be a rate-of-administration issue. He added that a 15-minute loading dose time is too long.
- Dr. Cote commented that ketamine as currently supplied is neurotoxic. One study shows that it is the preservative that is neurotoxic, whereas plain, preservative-free ketamine is not. This needs to go on the label. If an epidural formulation is made available, it must be preservative free.
- Dr. Ward asked whether there is a need to study this drug in newborns and preterm newborns as an anesthetic or whether other agents would be used. Dr. Cote replied that he uses ketamine as an induction agent in children with cyanotic congenital heart disease regularly

and gives it to them intravenously or intramuscularly. He suspects that ketamine is used regularly in premature babies.

- Dr. Spielberg remarked that the drug definitely needs to be studied, but it will be necessary to make difficult decisions about what to study because of cost issues. Prioritization in the design of the study will be crucial.
- Dr. Cote commented on ketamine studies that found an incidence rate of laryngospasm and apnea of about 1 in 100.
- Dr. Snodgrass pointed out that there are three concentrations of ketamine, noting that the smaller the vial, the greater the concentration, which has led to dosing errors. Dr. Murphy added that different companies make different concentrations. Dr. Cote concluded that the reason for the high concentration dose is for giving the drug intramuscularly and said this issue will need to be studied.

BACLOFEN

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*Gilbert Burckart, Pharm.D., Professor and Chairman, Department of Pharmacy, University of
Southern California*

Primary Review

Dr. Jay Meythaler provided the following information in his review of baclofen:

- Baclofen, oral and intrathecal, is used in children to treat spasticity due to cerebral palsy and spinal cord injury. The current label for oral baclofen does not reveal indications for children. There are only open studies that look at cerebral palsy and a few small randomized trials that are too small to get an indication. Nevertheless, baclofen is used massively in children with cerebral palsy. There are no studies in regard to spinal cord injury. Those studies with acquired brain injury are often combined with cerebral palsy, and the data for the two have not been separated out. There is no dose tolerance evaluation, and the effects in both children and adults on upper limb spastic hypertonia have never been established. A paper is coming out looking at receptor effects of baclofen on the upper extremities. There are studies on the use of injectable baclofen, and they are much better done than the oral studies. Upper extremity effects are less with intrathecal baclofen. The intrathecal labeling is inadequate for children but does contain some material. Most people are using baclofen fairly comfortably, although intrathecal is much better established than oral baclofen.
- Most smaller children will not swallow pills, so the drug is compounded into elixirs or other carrier substances that have not been evaluated. This issue must be addressed.
- In regard to feasibility, there are clearly enough children available to perform studies on the use of oral baclofen in both spinal and cerebral disorders, which need to be studied separately. There is very little on spinal cord injury except for small case series. In adults,

there are two studies on stroke and none on head injury or the upper extremities. Baclofen is an old drug that was approved under the old guidelines. Considering the potential for baclofen to impede neurorecovery the first month following CNS injury and its cognitive side effects, studies are warranted. Furthermore, baclofen is a gamma-aminobutyric acid (GABA) agonist, and its effects on neurodevelopment and cognition as children get older has not been evaluated at all. Intrathecal baclofen does not get to the brain as much and its dose is much less than oral baclofen, so, developmentally, it may be less of a problem in regard to cognition and brain effects. It is not known what its motor effects are. Researchers are starting to look at these issues in regard to intrathecal baclofen.

- In regard to efficacy of the drug itself, outcome variables have been accepted by FDA. Effects on cognitive development and recovery have not been looked at carefully. In the clinical guidelines that will be coming out from NIH on traumatic brain injury, baclofen is not a first-line treatment orally because of its CNS side effects and potential for impeding recovery in the first 6 months after head injury. There is a fair amount of human and animal data indicating that GABA will affect recovery, and baclofen has affected recovery in animal models.
- In regard to available data, PK, safety, and efficacy data for oral baclofen in children is sparse. Elixirs are currently compounded, and, when they are added to baclofen, there are safety and absorption issues. Limited data exist on intrathecal baclofen, which is better established than oral. A significant amount of human data and extrapolation to adults has been done very well with intrathecal baclofen, which has fewer systemic effects. Motor issues at the brainstem and spinal cord as well as development and coordination issues for cerebral palsy need to be studied long term. A study coming out shows that 1 year after a head injury, there is an 18-percent incidence of cognitive deficit in adult patients given therapeutic oral doses of the drug. In children, no comparable studies have been performed.
- In regard to similar drugs in the same therapeutic group, baclofen is the only known GABA-B agonist with no equivalents, although other drugs are used to treat spasticity and spastic hypertonia. Most studied are the benzodiazepines. Tizanidine is used frequently in children; in adults, a study on head injuries and stroke found a 41-percent incidence of cognitive deficits with tizanidine. A similar study of tizanidine found a 46-percent incidence of cognitive effects in adults with spinal cord injury. Dantrolene sodium works peripherally and is the first-line drug clinical trial centers recommend for use in head injuries, but its effects have not been studied in children. There have been limited studies of gabapentin in adults but not children, and there have been a couple of case reports of spasticity. There have been case reports with tiagabine, vigabatrine, and clonidine in children, all of which have significant cognitive side effects. Except for benzodiazepines, PK parameters are not known for those drugs.
- Baclofen, a GABA-B agonist, is the only drug in its class available for systemic delivery. There are no substitutes for intrathecal baclofen for spastic hypertonia. Only two drugs are approved at all for intrathecal delivery—morphine and baclofen.

- In regard to indications and off-label uses, oral baclofen needs randomized controlled trials with dose escalation; the trials would not be expensive. Traumatic brain injury, cerebral palsy, and spinal disorders should be looked at separately. Some good open label data exist for cerebral palsy; however, a randomized trial is needed. Some work also is needed on dose escalation. It is not known how fast to escalate the drug dose in children because there is some tolerance with the drug. Acute withdrawal of both oral and intrathecal baclofen can cause seizures and fevers, which appears to be a serotonin syndrome. Intrathecal baclofen has been studied in cerebral palsy and traumatic brain injury, and withdrawal symptoms in children have been reported.
- Concerning ethical issues, studies for both oral and intrathecal baclofen could be performed easily with little risk of permanent side effects when taking the children off the drugs for a short period of time. The issue that needs to be studied is how soon after CNS injury the drug should be started and how it may affect development and cognitive function long-term.
- The drug should be included in the priority list.

Secondary Review

Dr. Gilbert Burckart added the following comments to the review of baclofen:

- From a pharmacologic standpoint, baclofen needs to be studied because of the wide variability of doses that are used.
- There have been reports of different responses in younger versus older children.
- In light of other emerging drugs, the question of whether baclofen has a future needs to be considered.

Discussion

The following comments were made during the discussion of baclofen:

- Dr. Buckman wrote the written request on oral baclofen, which was turned down by the pharmaceutical companies. Oral baclofen was on the list last year and has been referred to NIH. Dr. Buckman commented that oral baclofen is used widely throughout the United States in the 2- to 16-year age range. The written request asked for information on PK/PD, dose escalation, and tolerance as well as safety and efficacy studies and long-term studies on neurocognitive development. The request asked that cerebral palsy patients be looked at separately. FDA feels the drug still needs to be studied in pediatrics.
- Dr. Meythaler said that the control in a randomized controlled trial would be a randomized placebo. Children would need to be on baclofen orally for only 4 to 5 weeks. There will not be severe side effects in a research trial, so there is no detriment to using a placebo in the short term. However, it was pointed out that FDA had proposed a year on the drug for safety observations. Dr. Meythaler responded that efficacy could be studied in 4 to 5 weeks with a

placebo, but safety was another issue and would need up to a year. A concern in a long-term trial is the risk for contracture development, which would reduce range of motion and impede mobility. Dr. Buckman added that FDA had asked for a controlled PK/PD efficacy study for a shorter period of time and for an open-label safety study for 1 year.

- Dr. Spielberg asked how issues regarding stability and bioavailability of the formulation and consistency of formulation among study sites would be dealt with. Participants agreed that it is crucial to have consistent formulations. A sponsor also is needed.
- In regard to whether baclofen is a drug of the past or the future, Dr. Gorman commented that in his clinical area, the practice is changing to locally administered intramuscular medicines such as Botox for this issue, and he wondered if Botox was a potential controller without the cognitive side effects for these studies. Dr. Meythaler responded that focal dystonia with botulin toxin treatment combined with therapy may be useful. However, it does not have an indication for spastic hypertonia right now. It is a paralytic agent. It has a role but, because of FDA limitations on the amount that can be given, not enough Botox can be given. Therefore, systemic drugs must be used. Also, in human adult studies, baclofen has consistently shown fewer side effects than newer drugs.
- Dr. Buckman added that FDA was aware that Botox was used for localized spasticity as well as baclofen and wrote the written request so that use of an add-on therapy such as botox would be reasonable and subgroup analysis could be performed.

CYCLOSPORINE

William E. Berquist, M.D., Division of Pediatric Gastroenterology, Hepatology and Nutrition, Stanford University School of Medicine

Gilbert Burckart, Pharm.D., Professor and Chairman, Department of Pharmacy, University of Southern California

Primary Review

Dr. William E. Berquist made the following comments in his review of cyclosporine:

- Overall, the labels for the different versions of cyclosporine are quite good. However, in pediatrics, the PK data do not emphasize variability, and pediatric indications are not clearly specified. Safety and efficacy information is very good.
- In regard to sufficient available literature, PK data are very good, although the sampling groups are small; because of variability, clarification is needed. The data are limited because of the huge variability in PK. In regard to PD data, there is hardly anything.
- Extrapolation from adult studies has been done in transplant patients. Data on infants is sparse, but cyclosporine is not used much in infants and there may not be a need to pursue that age group very much, although liver transplants are done in infants down to about 3 to 6 months.

- There are similar drugs in this therapeutic class, most notably Prograf (tacrolimus). Although many centers still use cyclosporine as the main drug for liver and kidney transplants, the larger centers, especially for pediatrics, use Prograf. However, the increased use of Prograf does not make cyclosporine irrelevant because there are other uses of the drug. It is a fall-back drug when there are complications from Prograf.
- In regard to other treatments that would make use of this drug obsolete, even though Prograf is used, cyclosporine is not obsolete yet.
- In thinking about studies of this drug and indications for off-label uses, an area that needs to be looked at is ulcerative colitis because in patients with fulminant ulcerative colitis, there are few options for treatment. Cyclosporine has been studied in adults for this condition but needs to be looked at as a rescue drug for ulcerative colitis in the pediatric group. A problem in the pediatric group is the small number of children, which means it would have to be a multicenter study.
- In regard to clinical outcomes, a concern about both cyclosporine and Prograf is long-term neurotoxicity, which is hard to study. Children are often left on these drugs their entire lives, which has pushed concern about long-term toxicity.
- In summary, there is a need for PK and/or PD studies of this drug in children, especially for PD. The problem with PD studies is the parameter to use. Cyclosporine is a very dangerous drug, and PK information would need to be attached to the PD effect for proper dosing. Ideally, infants aged 3 months and older would be included in the study. Regarding efficacy studies, there are good studies of this drug for most indications except ulcerative colitis. In regard to safety, the labels are good, but neurotoxicity of the drug is an issue.

Secondary Review

Dr. Burckart agreed with Dr. Berquist's assessment and added the following comments about cyclosporine:

- Cyclosporine will continue to be used in pediatrics.
- In terms of labeling, the drug is used not only in ulcerative colitis but also in other autoimmune diseases that are not on the label.
- Adverse effects, one of the primary concerns with cyclosporine, have not been extensively addressed.
- Use of the drug has been studied extensively; it is carefully monitored with blood concentrations, and there are new improved formulations.
- Overall, there is good information on cyclosporine.

Discussion

The following comments were made during the discussion of cyclosporine:

- Dr. Blumer asked whether PK data can be related effectively to the profound adverse events linked to this drug and if the side-effect profile will be different in nontransplantation clinical arenas. Dr. Berquist replied that with the PK data and the experience of transplanters, it is possible to deal with the adverse effects. The drug has been used for more than 19 years, and those who have used it have a great respect for the drug and know how to use it. As far as moving into other indications, the concern is what level to look for to achieve the desired efficacy. A concern is that in moving into other autoimmune diseases, a number of patients will be hurt in the process by the lack of PK/PD data and experience. Dr. Burckart pointed out that when moving into other patient populations with this drug, there will be other drug interactions in patients on other regimens. However, sufficient information is available to use the drug safely in children with blood concentration monitoring, even though there may be some differences in drug interactions.
- Dr. Murphy cautioned about moving into other indications because it will require efficacy as well as safety data. Are enough patients eligible for a full-blown safety/efficacy study?
- Drs. Berquist and Burckart concluded that the current labeling and literature are adequate.

VINCRISTINE

*Michael Link, M.D., Department of Pediatrics–Pediatric Oncology, Stanford University
Gilbert Burckart, Pharm.D., Professor and Chairman, Department of Pharmacy, University of Southern California*

Primary Review

Dr. Michael Link made the following comments in his review of vincristine:

- Because of its use in a variety of pediatric cancers and its favorable toxicity profile, vincristine has become an established therapy for a majority of pediatric neoplasms, including acute lymphoblastic leukemia (ALL), Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, Wilms' tumor, Ewing's sarcoma, neuroblastoma, and some central nervous system neoplasms. The label is relatively complete, reflecting the fact that the drug has been well studied in a variety of tumors in children, and substantial PK data are available.
- There are some minor problems with the label. The label recommends against the use of doxorubicin in combination with vincristine and prednisone because of the risk of increased myelosuppression. Since this combination is considered standard for the induction of remission in childhood ALL, this statement in the label is disconcerting. Vincristine also has been implicated in causing veno-occlusive disease (VOD) of the liver in combination with dactinomycin with or without cyclophosphamide with or without irradiation. This toxicity is not adequately addressed in the label. Furthermore, the risk of VOD is highest in young children and infants. Although the role of vincristine in VOD is not clear, it should be

included in the label. The use of vincristine with doxorubicin and cyclophosphamide, with or without dactinomycin, for pediatric solid tumors (notably, Ewing's sarcoma) should be included in combination studies.

- The literature on vincristine is fairly robust. The administration of vincristine by continuous infusion is gaining popularity and may warrant further studies, including PK and drug disposition studies.
- In regard to extrapolation from adult efficacy studies, few adult tumor studies are useful as models for pediatric cancer, except adult ALL and the lymphomas. Much of what has been learned in the treatment of pediatric ALL has been extrapolated to treat adult ALL, rather than the reverse.
- Vincristine has a well-established role in the management of many childhood cancers. Its safety profile and lack of additive toxicities with many myelosuppressive agents make it ideally suited for combination chemotherapy. There are no drugs available that are likely to supplant vincristine as currently used.
- Indications for use of the drug are broad and include most childhood leukemias and solid tumors. Although novel schedules of administration are likely to be studied, these will probably be in combination with other agents in phase III trials.

In summary, vincristine is a well-established drug for use in childhood cancers. Much is known about its toxicity, except for its contribution to VOD, which needs further study in young children and infants. New schedules of administration are being explored, which may warrant supporting PK data. Further studies of this drug are a low priority given the abundant literature available.

Secondary Review

Dr. Burckart added the following comment about vincristine:

- The tumor biology has not been carefully explored and needs further study. Treatment in infant leukemias is not as beneficial as that found in older children and may be related to dosing.

Discussion

The following comments were made during the discussion of vincristine:

- Dr. Anne Zajicek of NICHD's Endocrinology, Nutrition and Growth Branch, Center for Research for Mothers and Children, referred to the dosing problem in children; it is unclear whether dosing should be on a mg/kg or mg/m² basis and whether dosage should be altered based on age. In infants, there is a poor response and a significant amount of neurotoxicity. Efficacy and safety studies are needed to clarify this issue.

DACTINOMYCIN

*Michael Link, M.D., Department of Pediatrics–Pediatric Oncology, Stanford University
John T. Wilson, M.D., Professor of Pediatrics, Louisiana State University Health Sciences
Center*

Primary Review

Dr. Link responded to the review questions as follows:

- This drug is one of the most effective treatments for solid tumors in children. Use of the agent alone or in combination with other agents has contributed substantially to improvement in outcome for selected localized and advanced-stage solid tumors in children.
- The current label has a number of shortcomings. Dactinomycin is particularly effective for the treatment of Wilms' tumor and rhabdomyosarcoma, which occur frequently in young children, and statements in the label recommending that the drug not be used in infants younger than 6 to 12 months of age are unfortunate. The label also provides insufficient emphasis on the risk of VOD of the liver, which has been reported when dactinomycin is used in combination with vincristine with or without irradiation and in combination with vincristine and cyclophosphamide. This toxicity may be the most devastating, and children younger than 3 years of age are reported to be at risk. Modification of dosage may ameliorate this risk. In addition, the vesicant nature of the drug and toxicities associated with extravasation are not emphasized sufficiently. The dosing guidelines recommend intravenous administration over 4 to 5 days, but most protocols use single daily dosing. According to the label, count suppression reaches a nadir at about 3 weeks, with recovery 3 weeks after the nadir. However, this experience is not usual. Dactinomycin used as a single agent is rarely associated with secondary leukemia or infertility, so warnings in the label about these toxicities may not be warranted. Of note, there are no published PK data.
- The drug is widely used, and reports related to its efficacy and toxicity are numerous. It is unlikely that further clinical studies are necessary except to address appropriate dosing in infants.
- The primary indications for dactinomycin are for embryonal solid tumors, which are rare in adults. Rather than extrapolating adult data to pediatrics, data from pediatric trials have been extrapolated to adults.
- Although other intercalating agents have demonstrated activity in tumors treated with dactinomycin, the safety profile of the agent makes it very attractive for use in young children, and it is unlikely to be replaced for these indications. In Wilms' tumor and rhabdomyosarcoma, combinations with dactinomycin remain "the gold standard."
- It is unlikely that new Phase 1 or Phase 2 studies of dactinomycin are feasible. The drug is well established as a first-line therapy for solid tumors, and it may be difficult to recruit patients for studies of novel schedules of administration. However, further study of drug

disposition in young children and further study of the role of dactinomycin in VOD are indicated.

In summary, dactinomycin is a well-established drug that has become a fixture in the management of pediatric solid tumors. The paucity of PK data is discouraging, but PK data may be needed in young children only when increased toxicity has been observed. The efficacy and safety of the drug are well established, except perhaps in infants when dactinomycin is used in combination with other drugs. Further study in infants would be attractive, but the number of available subjects and ethical concerns make it unlikely that such studies are feasible.

DIAZOXIDE (HYPOGLYCEMIA)

Francine R. Kaufman, M.D., Division of Endocrinology and Metabolism, University of Southern California

Ralph E. Kauffman, M.D., Director of Research, Children's Mercy Hospital, Kansas City, MO

Primary Review

Dr. Francine R. Kaufman provided the following information about diazoxide for treatment of hypoglycemia in infants:

There is no label applicable to hypoglycemia even though this is one of the main uses for diazoxide. The current label would have to be changed to include the pediatric indication for use of diazoxide for hypoglycemia.

There is adequate data in the literature for the use of diazoxide for hypoglycemia. PK, PD, safety, and efficacy data include all age groups for which the drug is used, including the neonatal age group, which is where it is used primarily.

The main body of evidence is in the pediatric age range. Nothing needs to be extrapolated from the adult literature.

There is no other drug equal to or superior to diazoxide for this indication.

There is no need to design further studies of diazoxide. No other literature is needed on this subject.

In summary, Dr. Kaufman's opinion was that there is no need for PK and/or PD studies of this drug in children, for efficacy studies of this drug in children, or for safety studies of this drug in children. She concluded that the drug does not warrant further study. Furthermore, a randomized trial would be impossible for diazoxide in neonates.

Secondary Review

Dr. Kauffman's review of diazoxide for hypoglycemia included the following information:

Hypoglycemia is not a labeled indication for any age; therefore, there is no information in the label regarding use for hypoglycemia. Also, available PK/PD data are insufficient to provide generalizable pediatric information. Much of the literature consists of uncontrolled case series or case reports. Labeling for hypoglycemia as a pediatric indication would require a full clinical trial plan, including phase I, II, III, PK/PD, safety, and efficacy studies. Given established practice in using this drug for hypoglycemia, an extensive published literature, a relatively limited patient population, and the fact that diazoxide is used primarily as a second-line or adjunctive treatment, investment in studies that would support labeling must be given a low priority.

The available literature would not support labeling. Available PK/PD studies are inadequate. Most of the published papers are case reports or small case series. None of the studies are controlled, and many are retrospective descriptive reports. The case series include a variety of doses and duration of treatment, multiple different causes of hypoglycemia, and wide variation in concurrent treatment. Some safety information can be gleaned from some of the case reports, and several of the larger series could supplement well-controlled trials. There is a suggestion in several studies that neonatal-onset hypoglycemia does not respond well to diazoxide.

The response to diazoxide appears to be somewhat age-dependent and causes of hypoglycemia are different at different ages. Therefore, it is not possible to extrapolate adult efficacy studies to children.

There may be more effective and safer treatments, depending on the cause of hyperglycemia. However, most other modalities are used in combination with diazoxide, not as alternative therapy.

If this drug were to be studied, indication of short-term treatment of severe, persistent hypoglycemia unresponsive to diet or glucose infusion would be of interest.

Feasibility issues involved in study of this drug include the fact that hypoglycemia is a relatively rare condition, and diazoxide is typically used in conjunction with other treatment modalities. Because of this situation, recruitment for studies would be very difficult. In addition, hypoglycemia is an urgent or emergent condition, which makes screening, consenting, and enrollment difficult.

If this drug were to be studied, clinical outcomes of interest would be sustained euglycemia. Safety outcomes would include cardiovascular events, hyperglycemia, sodium retention, congestive failure, and the requirement for diuretics.

Ethical issues involved in the study of diazoxide for hypoglycemia revolve around the use of a placebo. It might be possible to compare diazoxide and placebo in conjunction with a standard background treatment with strict rescue criteria built into the protocol.

In summary, Dr. Kauffman's review concluded that diazoxide deserves a low priority for study.

Discussion

The following issues were raised regarding the labeling of diazoxide for hypoglycemia:

Dr. Kauffman stated that the pediatric studies of this drug include few children and that the data are insufficient to support the labeling based on current standards. He added that the efficacy and safety data are also deficient because much of the literature relies on uncontrolled series and case reports.

When asked whether she agreed, Dr. Kaufman said it would be impossible to do a randomized trial for hypoglycemia, which is a life-threatening condition in neonates. She said the drug either ameliorates the condition immediately or it does not. While acknowledging that much of the literature involves case reports, Dr. Kaufman stated that the experiential data over three decades with this agent are sufficient.

Dr. Kauffman responded that the studies have not been standardized and have used a different strategy of administration and duration. In many cases, newborns do not respond well.

Dr. Kaufman agreed with Dr. Kauffman's assessment but said that diazoxide is used for short-term amelioration to stabilize the child for an operative procedure or as an adjunct to another agent. Dr. Kauffman said he was looking for standards of studies, not published practice, to support labeling.

Dr. Ward asked the following question: "Would it be feasible to have a child controlled with a given infusion rate of glucose in specified mg per kg per minute and then add diazoxide with a monitoring of the serum glucose and determine the most effective dose for antagonizing that child's insulin secretion reflected by a rise in serum glucose?" He agreed that in a hypoglycemic child with an emergent condition, randomized trials would not be appropriate. However, it would still be feasible to study the appropriate dose regimen for a neonate who was already controlled with a glucose infusion.

Dr. Kaufman agreed that such a strategy could be pursued theoretically, but the dropout level would be high because the disease process is so severe. A second agent would be added over a 12- to 24-hour time period. In addition, even at a large center, only one or two cases are seen each year.

Dr. Kauffman asked whether there are enough hypoglycemic babies in North America to do such a study in less than 10 years to support labeling. How much would the study cost, and would it change practice? The reply was that it would take 5 years to get sufficient subjects at 40 to 50 centers, the study would be costly, and ultimately it would not change practice.

Dr. Snodgrass said the issue of changing practice depends on study design. With glucose control, the approach depends on the end point. It is an efficacy question and, despite the constraints, one could get an answer depending on the study design.

- Dr. Kaufman said that under current protocol, physicians generally turn to diazoxide for hyperinsulinism. The question is whether the disease is manageable with drugs or whether the only solution is eventual surgery. Physicians start with diazoxide and, if they can control low blood sugars, they add the second agent to avoid surgery. If the two agents do not work, then surgery is done. After failed pancreatic surgery, diazoxide can be used as a sole agent or a dual medication can be used. Another surgery might be necessary. Coronary artery spasm is another issue as well as risk of myocardial infarction, as reported in the literature.
- Dr. Jean Temeck, a pediatric endocrinologist from FDA, agreed with Dr. Kaufman that further clinical studies are unneeded. Enough safety and efficacy data exist in the literature to include this indication in the diazoxide label. Regarding efficacy in the neonatal onset form of hyperinsulinism/hypoglycemia, the literature supports the fact that with an early onset form of this disease, the efficacy is not as great as in older age groups. From a safety perspective, diazoxide is labeled generally for the treatment of acute severe hypertension, but repeated use of the medication over several days might lead to fluid retention, which can lead to cardiac failure in neonates. However, the benefit outweighs the risk if the drug can prevent the necessity of pancreatic surgery. Perhaps this caveat can be included in the label.
- Dr. Kaufman replied that one reason this drug does not work in newborn hypoglycemics is that the baby is born with a different disease process that calls for a pancreatectomy. Only infants with less severe pancreatic pathology can be treated medically. The differential depends on the underlying disease process. Another caveat about fluid retention is that physicians who use the drug for more than a day add a diuretic. Anecdotal evidence in the literature suggests that adding Diuril improves diazoxide's efficacy and mitigates the process of fluid retention. In addition, the metabolism of the drug can be affected by anticonvulsants prescribed because of seizures. Experienced practitioners are aware of these two safety issues (the drug's metabolism and the use of diuretics) despite what is on the label.
- Dr. Kauffman asked whether FDA could accept the published literature as a basis for adding the new indication to the label. Dr. Temeck reiterated that FDA has not had internal discussions on this issue and that the agency generally requires randomized controlled trials for drugs. However, because hypoglycemia is a life-threatening condition, it would not be feasible to test this drug in infants, and FDA would take that point into consideration.
- Dr. Kauffman concluded the discussion by stating that relying on published data would be the ideal solution given the lack of feasibility of conducting controlled trials because of the dearth of patients, excessive cost, and time required.

DIAZOXIDE (HYPERTENSION)

Ronald Portman, M.D., Department of Pediatrics, University of Texas Medical School at Houston

Ralph E. Kauffman, M.D., Director of Research, Children's Mercy Hospital, Kansas City, MO

Primary Review

Dr. Ronald Portman provided the following information about the use of diazoxide for hypertension in children:

Specific PK/PD data in pediatrics in the label are lacking, as is specific efficacy and safety information. However, the data presented in the label are germane to both adults and children. One excellent study of PK in children shows the drug to be slightly more rapidly metabolized in younger children than in adults. Pediatric dosing is included in the label at 1 to 3 mg/kg per dose to a maximum adult dose of 150 mg given by rapid intravenous injection due to immediate protein binding of the drug. Diazoxide can displace other protein-bound compounds such as bilirubin or warfarin. The dose may be repeated every 5 to 15 minutes until the desired effect is achieved. In adults, the desired effect is listed as a diastolic blood pressure of less than 100 mmHg, but there are no guidelines for the therapeutic target in children. Side effects of the medication include excessive hypotension, sodium retention often requiring concomitant administration of diuretics, hyperglycemia, and hyperuricemia. There are multiple contraindicated conditions such as those in patients with compensatory hypertension, patients who have received other antihypertensive agents, and patients with potential problems with cerebral or cardiac perfusion—all conditions frequently found in the pediatric intensive care unit. There have been reports in pediatric and adult literature of profound, irreversible hypotension, myocardial infarction, and neurologic complications.

The literature contains insufficient data about the use of diazoxide in pediatrics for the indication of hypertension. There are no randomized clinical trials in children with this medication. The literature review performed by the BPCA group found five citations. There were two 1-patient case reports, one 5-patient case series, and two nonrandomized clinical trials of 26 and 36 patients, both from the 1970s. The reports suggest that the drug is effective and safe in children with the same observed side effects as in adult patients. One paper reports a patient with an arrhythmia associated with diazoxide use. This experience is clearly inadequate to make a decision on the safe use of this medication as an antihypertensive for hypertensive crisis. However, from a practice and practical standpoint, the use of diazoxide has virtually disappeared for the indication of treating acute hypertensive crises in the past one to two decades because of an unacceptable risk-to-benefit ratio.

The experience in adults suggests that the drug is effective, but the side-effect profile is unacceptable in the face of the other available medications for the condition of hypertensive crisis. The same conclusion applies to use in children.

There are no other intravenous vasodilators in the thiazide class.

There are numerous other drugs that are safer and more effective, for example, nifedipine, clonidine, and minoxidil. The two drugs of choice are labetalol and nicardipine. Enalaprilat is also available in the patient with established ACE inhibitor use. Esmolol is not commonly used in children because of lack of information. Hydralazine also can be used intravenously but is not as effective. Fenoldapam, which has great potential, should be studied in pediatrics. Phentolamine, an alpha adrenergic blocker, also can be used, especially with patients with tumors that secrete large amounts of catecholamines.

In summary, Dr. Portman's opinion is that because many drugs have safety and efficacy profiles superior to diazoxide, further studies of this drug are unnecessary. In fact, such studies might be impossible because most pediatricians who treat acute hypertensive crises would be reluctant to enroll patients in such a trial.

Secondary Review

Dr. Kauffman supplied the following information about the use of diazoxide for hypertension in children:

Indications and usage include "children" without any specific age designations, inclusionary or exclusionary. Also, dose recommendations are weight based and could be used in children. Pediatric safety information includes neonatal hyperbilirubinemia, thrombocytopenia, hyperglycemia, and altered CHO metabolism following intrauterine exposure; hyperosmolar coma in an infant; and transient cataract in an infant. The inclusion of neonatal cautionary data implies that the general designation of "children" is intended to include neonates. However, no neonatal, infant, or pediatric-specific information is available. This old labeling does not include PK/PD data or any essential pediatric information in the label. Available literature is not sufficient to support labeling.

The available literature would not support labeling. There are two reports of severe adverse events (cardiorespiratory failure and development of heart block) associated with intravenous use of diazoxide in infants. These reports probably should be included in the label.

There are only four efficacy studies of diazoxide for hypertension, none of them randomized or controlled. These old studies include small numbers of subjects, a variety of diseases associated with acute hypertension, various doses and administration, and different outcome measures. The largest study is only 36 children aged 2 months to 18 years. Several of the studies show evidence of a dose-response relationship, but otherwise there are no meaningful PK/PD data. Taken together, these studies do not provide a basis for labeling. If the drug were to be studied, the strategy would have to include PK, PD, safety, and efficacy studies to support labeling at current standards.

It is unlikely that adult data could be extrapolated because of etiology and pathophysiology problems and acute hypertensive crisis.

Other potent vasodilators are available that are more likely to be used today for the same indication.

Better treatments for hypertension are minoxidil, alpha blockers, beta blockers, ACE receptor blockers, and ACE inhibitors.

Controlled studies in infants and children would be very difficult because of the rarity of the condition and the availability of preferred alternative treatments. Also, the indication is an urgent/emergent condition, and doing pediatric studies in such a setting is quite difficult. Positive control studies might be possible, but placebo-controlled studies would be impossible.

If this drug were studied, clinical outcomes of interest would be acute reduction and control of blood pressure.

Placebo controls or washout of concurrent antihypertensive drugs could not be ethically justified. Since the drug is approved for “children,” it would be difficult to credibly justify subjecting a child to a study protocol.

In summary, Dr. Kauffman stated that given the feasibility and ethical issues, the fact that diazoxide currently is labeled for children for hypertensive emergencies, the rarity of the condition in children, and the availability of superior drugs, he does not advocate studying diazoxide in children for hypertensive emergencies. He added that there might be a need to study diazoxide for hypoglycemia not responsive to other treatment modalities.

METOLAZONE

Ronald Portman, M.D., Department of Pediatrics, University of Texas Medical School at Houston

John Wilson, M.D., Professor of Pediatrics, Louisiana State University Health Science Center

Primary Review

Dr. Portman offered the following information about the use of metolazone for pediatric indications:

Many statements on the labeling are confusing. It is unclear whether some statements refer to Mykrox, which is the rapidly absorbed formulation, or metolazone. The indication lists for adults are applicable to children. No other information is provided, and the label is inadequate for pediatric patients.

There are five randomized clinical trials, three nonrandomized clinical trials, and two case series. The studies address different populations and different diseases. Six studies address edema due to liver or renal disease. Three studies address the use of metolazone for the removal of excess water for improvement of lung function in neonates. There are no pediatric dosage forms available.

Efficacy and safety are similar in children and adults, but it is difficult to draw conclusions when dose ranges are not scientifically established and the experience is less than 100 patients. The therapeutic dose is determined arbitrarily in a study with very small numbers and is quoted in

pediatric drug manuals. Medication with quicker and more complete absorption may be valuable, but there are no ethical, safety, efficacy, or PK studies.

Chlorothiazide can be used instead of metolazone, but Zaroxolyn is the most potent of the diuretics.

There are no other, better treatments for the indicated use that make the use of metolazone obsolete.

Four studies could be carried out with different study designs: (1) a PK study with pharmacodynamic measures, (2) treatment of edema, (3) treatment of hypertension, and (4) treatment of excess lung water resulting in decreased lung compliance. From the PK/PD studies, the use of metolazone requires a formal PK study, alone or in combination with Lasix. It would be important to assess the diuretic effect of metolazone in relation to plasma concentration. It also would be important to assess oral absorption in patients with severe edema. Most of the antihypertensive studies would require placebo, but it would be impossible not to know who was receiving the drug, so another FDA-approved design would have to be chosen that does not require a placebo. Studies of diuretic efficacy are the most important and would not require placebo.

There are no feasibility issues that would make a study difficult to perform.

The value of metolazone as a diuretic is the most important clinical outcome.

There are no ethical issues that would make a clinical study difficult or impossible to perform.

In summary, Dr. Portman's opinion is that there is a need for PK and/or PD studies of metolazone in children, for efficacy studies of this drug in children, and for safety studies of this drug in children. These studies should be done in all age groups.

Secondary Review

Dr. Wilson concurred with Dr. Portman's comments. He provided the following information:

The label for metolazone is miserably inadequate for children.

Studies of this drug are feasible because subjects of all ages are available, and outcome variables can be easily measured.

PK data are lacking for all ages, and PK studies in all ages are needed, especially for testing alone or in combination.

Extrapolation is possible but has not been tested, and safety and PK may be different in children. Care must be exercised in choice of the preparation for testing regarding the more rapidly absorbed form.

Other diuretics are available. The advantages of metolazone are not substantiated in children. Its primary use is in combination therapy. The advantage in the combination of two agents is that each acts on different sites, which creates a synergistic effect.

There is uncertainty about a pediatric formulation, especially for young infants. This question must be evaluated very thoroughly.

The off-label indications for edema and blood pressure are for all ages.

The ethical issues are minor; overall, the drug needs further study in children, including young infants.

Discussion

The following issues were raised during the discussion of metolazone:

Dr. Green noted that both reviewers commented that metolazone is primarily useful in combination. The efficacy data should reflect how well metolazone combines with a diuretic.

A representative from FDA raised the question of using combination therapy, specifically a diuretic and an antihypertensive, which complicates the situation. FDA regulations require the demonstration that the components of the combination therapy have an additive effect. Therefore, a minimum of three arms are required. Another FDA representative agreed with this assessment. What is needed is to test metolazone alone for efficacy and then in combination to show an additive effect.

Dr. Portman stated that traditionally this drug is studied in combination; however, metolazone has not had adequate study as a single agent. He would opt for a basic safety and efficacy trial before considering a more complicated approach. Metolazone is a potent diuretic that has not been studied alone.

One reviewer stated that not enough is known about the ideal dose; therefore, a basic safety and efficacy trial with a wide range of doses is needed to determine the dose response. In a child with severe renal disease, up to 20 mg may be needed.

Dr. Blumer stated that using the PK approach does not lend itself to classic PK and PD studies. There are ways to look at concentrations in urine with prior exposure and the concept of diuretic efficiency. He expressed optimism that the results of PK studies could lead to refinement of dosage.

MEROPENEM

Charles G. Prober, M.D., Division of Pediatric Infectious Disease, Stanford University Medical Center

Thomas P. Green, M.D., Department of Pediatrics, Northwestern University School of Medicine

Primary Review

Dr. Charles G. Prober offered the following information about the use of meropenem in children:

Although the current label does not provide specific PK data for children, it does indicate that the PK of meropenem has been studied in pediatric patients 2 years of age or older and is essentially similar to that in adults. The material summarizing the studies done on meropenem supports this statement. Analyses have been conducted in 53 infants/toddlers younger than 2 years of age, 39 children 2 to 6 years of age, 36 children 6 to 12 years of age, and 63 additional children of nonspecified ages. The PK studies are sufficient to inform the correct dose of meropenem in children aged 2 years and older.

The label states that the safety and effectiveness of meropenem have been established for children aged 3 months and older. Clinical adverse reactions are adequately described in the label and supported by ample literature. The literature reports on the safety of meropenem in 750 pediatric patients and 42 additional patients in the toddler age range. Therefore, there is a fair amount of information related to safety.

Specific data regarding the efficacy of meropenem for children between 3 months and 17 years of age with bacterial meningitis are provided in the label; 396 of the 446 subjects studied in randomized clinical trials comparing meropenem with cefotaxime or ceftriaxone were children. There are more data in children than in adults. Specific data regarding the efficacy of meropenem in the treatment of intra-abdominal infections are not provided in the label, but it is stated that the use of meropenem for this indication is derived from adequate and well-controlled studies with adults with additional data from pediatric PK and controlled clinical trials in pediatric patients. The literature describes about 295 children enrolled in evaluations of meropenem for intra-abdominal infections.

In summary, the current label has sufficient information regarding the pharmacokinetics, safety, and efficacy (for meningitis) of meropenem in children. The label extrapolates the efficacy of meropenem for intra-abdominal infections from adult subjects. The label lacks data regarding PK in children with renal dysfunction (including those on dialysis) and hepatic dysfunction. There also is a lack of information regarding the PK, safety, and efficacy of meropenem in neonates, but it is unlikely that it will be used extensively in this population.

Meropenem has potential therapeutic advantages under certain clinical circumstances, including isolation of pathogens resistant to alternate agents and hypersensitivity to drugs of first choice.

In children (and adults), meropenem is likely to be used most often under circumstances when multiply-resistant pathogens are suspected or proved by culture (e.g., nosocomial infections

in intensive care environments) or in the presence of hypersensitivity to the drugs of first choice in the management of severe or recalcitrant infections. Efficacy studies in these populations are difficult because of heterogeneity and multiple confounding variables; therefore, these studies should not receive high priority.

In summary, Dr. Prober's opinion is that there is no need for PK studies of this drug in children beyond those that have already been done, for efficacy studies of this drug in children, or for safety studies of this drug in children. There is sufficient information in the literature to make further studies unnecessary. Drug labeling should be changed to reflect use in children, supported by the current literature.

Secondary Review

Dr. Green added the following points to Dr. Prober's comprehensive review:

Meropenem is a well-studied drug for indications in children.

Appropriate extrapolations can be made from adults where there are good PK data in many populations.

Meropenem is a very important drug and will continue to be so, especially where drug resistance is prevalent. For children with cystic fibrosis, meropenem is the most effective drug.

Discussion

The following issues were raised during a discussion of meropenem:

Dr. Ward commented that he prefers the use of meropenem in neonate patients with resistant gram-negative organisms. However, there are not adequate PK studies in this area. A clinically important niche exists for meropenem for the preterm neonate with necrotizing enterocolitis.

Dr. Blumer agreed that more data are needed to guide dosing in the neonate. Meropenem is largely not used for the indications for which it has been studied, namely, the treatment of bacterial meningitis in infants and children or for intra-abdominal infections. He stated that meropenem is used in patients with cystic fibrosis and in patients in intensive care units where pathogens have not been isolated. Meropenem is used for serious infections in combination therapy.

Dr. Rodriguez said he has used meropenem successfully in the nursery with extended spectrum beta-lactamase (ESBL) infection.

Dr. Alan Shapiro of the FDA's Division of Pediatric Drug Development is doing a review of meropenem. Especially in the neonate, the data for PK and safety are very important. Meropenem should be studied to fill in all the gaps.

Dr. Rosemary Higgins of the NICHD Pregnancy and Perinatology Branch echoed Dr. Ward's sentiments about emerging resistance in the neonatal intensive care unit. It would be beneficial to know meropenem's effects for renal and hepatic-compromised infants in that setting and to have the drug in the arsenal for those with multiple gram-negative organisms.

FDA's Dr. Alexander commented on the lack of feasibility of getting PK data on the renal- and hepatic-compromised pediatric patient. Dosing pediatric patients with antibiotics would be difficult, and finding such a population would take years. The label is for meningitis and intra-abdominal infections, but there are also hospital-borne infections, such as pneumonia or other respiratory infections. These indications could be studied under a written request. For 0- to 3-month-old infants, Dr. Alexander agreed that studying the antibiotic for treatment of those extended spectrum gram-negative organisms would be of interest despite the small population. Dr. Alexander stated that although there is little PK information for pediatric patients with renal and hepatic impairment, infections such as hospital-acquired pneumonia or other respiratory tract infections could be studied under written request.

Dr. Prober said that although meropenem is used for pneumonia or other infections in a number of centers, the end points in the intensive care unit around nosocomial pneumonia are basically unmeasurable. If studies were to be done, they should focus on the kinetics of the drug, which could incorporate renal and hepatic dysfunction patients as well as microbiologically documented infections, such as systemic infection, as firm end points. End points in the intensive care unit and patients with multiple organ dysfunction are virtually impossible to study in a comparative trial. It also is impossible to study necrosis of the bowel to determine therapeutic efficacy.

Having the PK data on children who are in the intensive care unit for various infections is not enough for FDA to label the drug for uses in that population. Full-blown efficacy studies would be needed, not just PK data.

PIPERACILLIN/TAZOBACTAM

Charles G. Prober, M.D., Division of Pediatric Infectious Disease, Stanford University Medical Center

Stephen Spielberg, M.D., Ph.D., Dean, Dartmouth University School of Medicine

Primary Review

Dr. Prober supplied the following information regarding piperacillin/tazobactam (pip/tazo):

The label contains no information regarding the PK, safety, or efficacy of this antibiotic in children. The data provided in the literature indicate that PK data are available from 24 children aged 0 to 2 years, 12 children aged 2 to 6 years, and 11 children aged 6 to 12 years. In addition, more than 400 children have received the drug for a number of indications from whom safety information could be derived, and more than 300 children have participated in studies designed to evaluate the efficacy of the drug in children with intra-abdominal infections (mostly appendicitis).

Based on the data summarized above, additional studies to define the PK, safety, and efficacy of this antibiotic in children are necessary.

After the correct dosage has been defined on the basis of additional PK studies, there can be some degree of extrapolation from adult efficacy trials for some infections of pip/tazo.

There are drugs with substantial therapeutic overlap (e.g., ampicillin plus sulbactam and ticarcillin plus clavulanic acid); however, pip/tazo has sufficient therapeutic distinction to warrant independent study.

In children, pip/tazo is likely to be used most often under circumstances when multiply-resistant pathogens are suspected or proven (e.g., nosocomial infections in intensive care unit environments) or when polymicrobial infection is suspected (e.g., intra-abdominal infection). Efficacy studies in these populations are difficult because of the heterogeneity of the population and multiple confounding variables.

In summary, Dr. Prober's opinion is that there is a need for PK and/or PD studies of pip/tazo in children. Efficacy studies of pip/tazo in children will not be needed if adequate PK studies are conducted. Safety studies of pip/tazo are not needed. Dr. Prober's overall rating of this drug is that it is potentially useful for treatment of serious infections in children; at least PK studies should be conducted.

Secondary Review

Dr. Spielberg added the following comments to Dr. Prober's review.

The PK database down to 2 months is fairly reasonable; however, specific information in the neonate is lacking. Sufficient data on piperacillin in neonates are available to provide a rationale for dosing.

Sufficient data on comparator drugs are available in adults, which together with pediatric PK and clinical studies provide a basis for rational use of the drug in the pediatric population.

Discussion

The following issues were raised in the discussion of the review of pip/tazo:

Dr. Ward stated that his group uses pip/tazo in necrosis for intra-abdominal infections. The problem is a broad spectrum of disease in which the entire bowel may be necrosed and the child moribund.

Dr. Blumer commented that a number of pip/tazo studies were published, but they are not in the database. He also remarked on the disconnect between dosing in pediatrics and the pediatric PK data that are available. Pip/tazo is a drug used in various serious infections in patients who are at great risk. The effectiveness or utility of the drug might be compromised by

spreading out the dosing interval—pip/tazo is cleared very rapidly in young children. The data may be there, but they have not been connected well.

Dr. Alexander stated that pip/tazo has wider indications and that the labeling indicates it is not safe or effective in children younger than age 12; therefore, additional PK information and additional safety information are needed.

The current dosing in pediatric practice may be wrong. There should be a written request for PK, safety, and efficacy studies to extrapolate the adult indications down to children.

CLONAZEPAM

Tracy Glauser, M.D., Professor of Neurology, University of Cincinnati School of Medicine
Stephen Spielberg, M.D., Ph.D., Dean, Dartmouth University School of Medicine

Primary Review

Dr. Tracy Glauser provided the following information about clonazepam:

The current label for clonazepam is based on use for seizure and panic disorders. The label uses terms no longer in use for the treatment of epilepsy. Many of the articles reflect the same older terminology, making their application to current usage difficult to translate. No specific age ranges are given. One PK study used a total of 4 patients, while 11 trials were poorly done with unacceptable outcome variables using outdated terminology. There are deficiencies in the PK data and in the safety and efficacy data.

Benzodiazepines are used for subacute management of epilepsy and for acute treatment. Other drugs are used in the chronic management of epilepsy.

Except for seizure and panic disorders, there is not a large off-label usage of clonazepam in other pediatric neurologic conditions.

The feasibility of study is questionable because of limited populations of patients.

Outcome variables that would be studied have been well defined and are verifiable, reliable, and objective. Theoretically, studies could be done. Missing PK data would be of greatest use to the clinician. Safety data are also missing. Efficacy data would be difficult to collect for epilepsy.

The ethical issues that would be difficult to surmount concern the tolerance that develops. Conventional wisdom holds that clonazepam will work for 6 to 9 weeks and then loses efficacy. A theoretical and practical issue arises about how to design trials that study efficacy and not tolerance.

In summary, Dr. Glauser believes that there is a need for PK studies of this drug in children. Efficacy studies of clonazepam in children would be of less value.

Secondary Review

Dr. Spielberg added the following comments to the review of clonazepam:

The drug is available only in tablet form. The smallest tablet is 0.5 mg. Most formulations are extemporaneous and none are validated with respect to safety and bioavailability, which makes PK/PD study difficult.

Efficacy studies will be difficult. Clonazepam has numerous side effects, is typically titrated, and is used for short periods of time. Additional PK information might not be helpful in either optimizing the efficacy of the drug or in minimizing the side effects or changing the utility in the long run.

There is a desperate need for anticonvulsants in neonates, but there is no intravenous formulation. Clonazepam is not an optimum drug to study in this population.

Clonazepam is used primarily by pediatric neurologists who are familiar with its dosing, efficacy, side effects, titration, tolerance, and withdrawal issues. It is unlikely that additional formal studies leading to labeling will contribute a public health benefit to use of the drug.

In summary, Dr. Spielberg commented that there is not a great deal of enthusiasm for studying clonazepam at this stage.

Discussion

One comment during the discussion session was that clonazepam is not used in neonates.

ETHOSUXIMIDE

Tracy Glauser, M.D., Professor of Neurology, University of Cincinnati School of Medicine

Jeffrey Blumer, M.D., Ph.D., Professor of Pediatrics and Pharmacology, Case Western Reserve University School of Medicine

Primary Review

Dr. Glauser provided the following information about ethosuximide:

All the deficiencies identified in the review may be answered by a National Institute of Neurological Disorders and Stroke (NINDS)-funded study, which is a double-blind, three-drug, randomized controlled trial at 20 sites, with 473 patients. The trial will look at the PK, efficacy, and safety of ethosuximide and two other drugs in the disease process of absence epilepsy.

Ethosuximide is indicated for the control of pediatric absence epilepsy, which accounts for 10 percent of all childhood epilepsy. The drug is not used in children younger than 3 or older than 15. The current label is brief and to the point; it does not mention age groups.

The feasibility of doing studies on absence epilepsy to gain more pharmacologic data is very positive; the label is not adequate for PK data on dosing or to identify the PK/PD relationship.

A significant amount of PK/PD, safety, and efficacy information is missing in the literature. None of the children in the trials were in the 0- to 2-year-old range. Eleven trials in the efficacy area do not have breakdowns for PK/PD relationships and methodology to answer the basic questions. Gaps exist in the available data.

Extrapolation from adults to children would not be done because this is a pediatric disease process.

Similar drugs in the same therapeutic class are more toxic. Ethosuximide is the least toxic and the most efficacious. Therefore, there is no me-too drug. Ethosuximide is not used for any off-label indications.

In summary, Dr. Glauser noted that the need for more information about ethosuximide will no doubt be fulfilled by the NINDS study that is under way.

Secondary Review

Dr. Blumer agreed with most of Dr. Glauser's statements and noted that two items may not be addressed adequately in the NINDS study:

Very focused dose-ranging studies may still be needed because neither the literature nor the label makes clear what limits the efficacy of ethosuximide in monotherapy. Dr. Glauser's study may not fully cover this gap in knowledge.

Ethosuximide tends to be used frequently in combination with other anticonvulsants, which is a kinetic nightmare confounded by age-related differences in drug disposition. Studies of drug-drug interactions in pediatric patients receiving ethosuximide along with another drug will be important in terms of ensuring its safety and efficacy in children.

Discussion

The following issues were raised in the discussion of ethosuximide:

A question was raised about the impact of the NIH-funded study on the BPCA process.

Dr. Murphy stated that FDA would have to look at the data and the studies. She said that the agency has been trying to design studies with NIH. Congress intended that BPCA result in new information and labels. Ethosuximide is labeled for absence seizures and Lennox-Gastaut syndrome down to 3 years of age; therefore, legally breaking into the label will be difficult for FDA because it is labeled.

Dr. Blumer stated that the label gives the clinician no idea of how to use the drug or what to expect from the drug. Ethosuximide is labeled for children, but there are real deficiencies in

the label. If the advisory panel decides that the label is inadequate, how can this problem be handled? Dr. Murphy replied that an FDA advisory committee would have to look at the problem. Sponsors own the labels, and they do not want to add a pediatric indication because it increases their liability. This is a matter for a citizen's petition. Dr. Blumer noted that the final wording is a negotiated outcome between FDA and the sponsors, with FDA giving significant input to the sponsors. Dr. Murphy stated that if there are new safety data, then FDA has the authority to go into the label, but so far this is a territory that has not been explored. The intent of the BPCA is to get more information into the public domain.

Dr. Wilson remarked that the timing of the negotiations between FDA and the sponsor is unknown. FDA is limited in its expected scope of authority.

Dr. Gorman said that the AAP sees great benefit in holding meetings to inform stakeholders about labeling.

Dr. Kaufmann said that the BPCA contains a provision that if a study uses public funds, FDA has the mandate to change the label and negotiate it with the sponsor. If the sponsor disagrees, FDA can declare the drug misbranded. Dr. Murphy stated the importance of labeling disputes being done publicly at the advisory committee level.

The agency is currently working on a guidance for dispute resolution, which addresses the issue. An advisory committee will be involved so that experts and the public will be brought into the process under the new BPCA law.

RIFAMPIN

Jon S. Abramson, M.D., Division of Pediatric Infectious Diseases, Wake Forest University School of Medicine

Robert M. Ward, M.D., Professor of Pediatrics and Director, Pediatric Pharmacology Program, University of Utah

Primary Review

Dr. Jon S. Abramson offered the following comments about rifampin:

The current label indicates that children of all ages are in need of study. The specific issue raised concerns about CNS shunt infections. More PK, efficacy, and safety data are needed.

The current label is inadequate, incomplete, and insufficient.

It is feasible to do these studies.

Outcome variables are suitable for labeling studies.

There are no similar drugs in the same therapeutic group.

There are many indications for off-label use.

Better data are needed for the use of rifampin for methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis and CNS shunt infections.

Secondary Review

Dr. Ward added the following comments about rifampin:

The label currently applies only to tuberculosis and meningococcus. In the PK data, the youngest child was listed as 3 months old, and the entire PK database consisted of 12 children.

Rifampin is being used in neonates whose infections fail treatment with other drugs. This drug is important in clinical practice.

The only caution concerns hepatic dysfunction.

Rifampin also is used for resistant *S. aureus* infections that are related to catheters and that do not clear with other drugs.

Discussion

The following issues were raised in a discussion of rifampin:

Dr. Blumer commented on conditions that call for long-term therapy. Resistance development must be looked at; with continued exposure, a change in susceptibility results if the organism is not eradicated. In addition, rifampin is one of the few well-documented drug metabolism inducers in humans. It is used in complex patients who are on chronic therapy with other drugs that are metabolized. This circumstance deserves close attention in regard to adjusting doses. Looking at the PK of rifampin poses a significant challenge.

It might be valuable to pursue uses that are not part of the current label, but doing so will involve efficacy studies in a pediatric population. Dr. Abramson stated that a full-blown efficacy study would not be necessary to determine how often shunt infections are eradicated and how often the result is culture-negative disease. Rifampin is intended for use in combination.

A clinical study could start patients on a typical therapy and then randomize them to receive rifampin or not rifampin. The bacteriology needs to be tied to some clinical benefit for patients.

Dr. Spielberg asked if extrapolation in some conditions is possible from adults to children to arrive at a PK strategy for children without having to do full-blown efficacy trials.

Dr. Abramson replied that adult endocarditis is very different from pediatric heart disease and results in very few shunt infections.

A study of endocarditis could use adult and pediatric patients.

MRSA is increasing, many centers are using rifampin blindly, rifampin use raises the resistant rate, and most centers remove the shunt hardware between 40 and 72 hours, expecting the cultures to be negative.

CLARITHROMYCIN

Jon S. Abramson, M.D., Division of Pediatric Infectious Diseases, Wake Forest University School of Medicine

Richard Gorman, M.D., Chairperson, Committee on Drugs, American Academy of Pediatrics

Primary Review

Dr. Abramson provided the following information about clarithromycin:

Clarithromycin is a me-too drug.

Colleagues who treat HIV infections have switched to azithromycin.

The only other advantage in using clarithromycin is for *Helicobacter pylori*.

Secondary Review

Dr. Gorman agreed with Dr. Abramson's assessment with no elaboration.

PROMETHAZINE

Cheston Berlin, M.D., Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine

Richard Gorman, M.D., Chairperson, Committee on Drugs, American Academy of Pediatrics

Primary Review

Dr. Cheston Berlin offered the following information about promethazine:

Information in the package insert for the injectable form of promethazine is sparse and imprecise for pediatrics. For example, it says that the dosage should not exceed half that allowed for adults. No allowance is made for weight or age. The information about how to administer the drug together with a narcotic is confusing. Also lacking in the label are PK and PD data and efficacy and safety information, particularly for other conditions. There is no mention of using promethazine for other causes of nausea and vomiting in the pediatric population. The current major use of promethazine has been for vomiting due to gastroenteritis. The label discusses only the injectable form but not the oral or suppository form. The PDR has extensive dosage information for these forms, but there is no indication that this is the official label.

PK, PD, safety, efficacy, and age group information is missing. The inadequate data warrant further studies. If the label for injectables were to be extended to the pediatric population, these studies would be needed.

It is not possible to extrapolate adult efficacy studies to children. These studies are insufficient to change the labeling. The number of patients is small, with dental patients receiving multiple drugs plus general and local anesthesia.

There are similar drugs in the same therapeutic class that are equal/superior to promethazine, which would make studying promethazine irrelevant.

Intravenous fluids or clear fluids by mouth are better treatments for the indicated use and make the use of promethazine obsolete.

There would be serious issues involved in a study using promethazine.

In summary, Dr. Berlin's opinion is that if someone wants to study promethazine for a reason he has not elucidated, there would be a need for PK and PD studies of this drug in children, for efficacy studies of this drug in children, and for safety studies of this drug in children.

Secondary Review

Dr. Gorman echoed Dr. Berlin's comments and added the following information about promethazine:

There have been no studies of promethazine's major use in pediatrics, which is for vomiting from infectious disease.

Its second use is in the treatment of cough, which it is not labeled for. It has been combined with codeine in an oral formulation for use in the treatment of cough.

Discussion

The following comments were made regarding promethazine:

- Dr. Buckman said there would be a major problem in getting a study on promethazine approved by an IRB.
- FDA is looking at changing the label based on safety data.

LITHIUM

Barbara Geller, M.D., Professor of Psychiatry, Washington University in St. Louis

Jeffrey Blumer, M.D., Ph.D., Professor of Pediatrics and Pharmacology, Case Western Reserve University School of Medicine

Primary Review

Dr. Barbara Geller offered the following information about lithium:

- The main indication for use of lithium is for manic depressive illness, currently known as bipolar disorder, where it has the following indications in individuals older than 12 years: treatment of the acute phase of this lifelong illness and prophylaxis against recurrence of bipolar disorder episodes. Lithium also has been shown to be prophylactic against completed suicide.
- According to the current label, lithium is not approved for use in children aged 11 years and younger. This is grossly deficient. Increasing National Institute of Mental Health (NIMH)-funded work over the past decade has established the existence, characteristics, and longitudinal validation of bipolar disorder in children aged 11 years and younger, yet there is not a single double-blind, placebo-controlled study of children aged 11 years and younger for any of these indications.
- Regarding feasibility, the potential number of subjects to conduct studies of lithium in children is more than sufficient. NIMH-funded ongoing studies of pediatric bipolar disorder successfully recruited children with bipolar disorder, and an advocacy group called the Child and Adolescent Bipolar Foundation includes 15,000 families, 60 percent of whom have children aged 11 years and younger with bipolar disorder.
- Outcome variables for indication are available.
- Further PK data are unlikely to be informative.
- Safety and PD data in children need further work.
- The pathophysiology of bipolar disorder is unknown across the age span, and there are no neurobiological or other clinical or research examinations that are specific to bipolar disorder. Therefore, similarity of pathophysiology between children and adults is not known at this time.
- There are no me-too lithium drugs.
- There are currently no indications for lithium in children aged 11 and younger; however, lithium is commonly used for children with bipolar disorder.
- There is no ethical issue to prevent study of lithium.

In summary, Dr. Geller's opinion is that there are no factors that preclude inclusion of lithium in the priority list.

Secondary Review

Dr. Blumer added the following information regarding lithium:

- There may be some value to further PK evaluation because in the age ranges under consideration, drugs that are renally eliminated tend to show differences from adult clearance, so that extrapolation may not be possible.
- The plasma concentrations relative to therapeutic effects and toxicity in the treatment of acute episodes, as well as prophylaxis, need to be studied for possible differences.

Discussion

The following issues were raised during the discussion of the review of lithium:

Dr. Kauffman asked whether there is a lower age limit of children to be included in the studies. Dr. Geller responded there is not enough data to know. The ongoing NIMH study begins at age 6. Once studies now under way profile the characteristics of preschool bipolar disorder, efforts will be made to study lithium for children between ages 3 and 6.

Dr. Snodgrass asked whether there is any indication that children younger than age 6 can have bipolar disorder. If so, what would that age be? Dr. Geller responded that a study at Washington University in St. Louis will systematically study the characteristics of bipolar disorder in 3- to 5-year-old children. Anecdotally, there are many case reports of children in that age range. When more systematic information becomes available in the next 3 to 5 years, PK data on lithium in the preschool age range will be needed.

Drs. Snodgrass and Geller concurred that age 3 could be determined as the lower age limit for bipolar disorder.

Dr. Sachs wrote the written request going down to age 10 on treatment of acute mania. Amid the controversy, the data are clear that lithium is being prescribed to children as young as age 2. Some people felt that a controlled placebo trial for acute mania in children younger than age 10 might be ethically problematic, especially in a maintenance setting. Existing bipolar disorder PK data are probably deficient because the data include many children with conduct disorder. The biggest problem in the dosing of lithium is to get to a therapeutic range without achieving toxicity; the therapeutic margin seems to be very narrow. Toxicity is seen in children and adolescents who were on doses that should not be considered toxic. The indication is now from ages 10 to 17; data on use of lithium in adolescence are also lacking.

Dr. Geller stated that the Consensus Conference on Lithium ignored all the key data that emerged in the past decade. At that time, Dr. Geller said she was already studying children as young as age 7, and now the multisite early-age mania study includes 6-year-olds. She

contended that age 10 is a number not based on any data. Doing placebo in maintenance calls for a study design that accounts for the ethical issues. More recent equipoise strategy designs are well suited for children and elicit informative data. In terms of toxicity, Dr. Geller said that her group has seen none in early-age mania studies. One of her group's studies shows that the same algorithm for predicting single doses also can be applied to children. The toxicity issue has not been seen in the systematic study.

Dr. Murphy said the drug was labeled down to age 12 but actually not a single child had been studied. Therefore, she recommended doing the legwork to check the FDA label. Dr. Geller said that data do exist on adolescents. The general feeling in the field now is that children and early and young adolescents form one group from the point of view of diagnosis and treatment whereas mid- and older adolescents fit into the adult group. Further research should be done in the prepubertal and early adolescent age group.

A participant asked whether children are being treated with other drugs besides lithium. Dr. Geller replied that in the absence of data on how to treat these children, treatment has been based on extrapolation from adult data. Poly-pharmacy is used.