Gatifloxacin Therapy for Children: An Antibiotic Still in the “Back Room”

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(See the article by Pichichero et al. on pages 470–8)

The emergence of drug-resistant pathogens in the 1990s—particularly *Streptococcus pneumoniae* resistant to β-lactams, macrolides, lincosides, and trimethoprim-sulfamethoxazole—posed increasing challenges for clinicians treating infants and children with acute otitis media (AOM), especially children with persistent symptoms during antibiotic therapy and those with recurrent infection. There were a number of parallel responses to these challenges. Campaigns to reduce antibiotic use were initiated, and there has been decreased per capita use of antibiotics for children [1]. Guidelines for treatment of AOM recommended the use of drugs with greater activity against drug-resistant pathogens for children at high risk for AOM, whereas amoxicillin is still recommended for initial therapy of children at low risk [2]. Finally, pharmaceutical manufacturers initiated clinical trial programs with quinolones that have antibacterial activity against drug-resistant pathogens. One of these manufacturers, Bristol-Meyers Squibb, sponsored trials of gatifloxacin for AOM, and this experience is described by Pichichero et al. [3] in this issue of *Clinical Infectious Diseases*. Gatifloxacin eliminates middle-ear pathogens at rates comparable or superior to those achieved by other antibacterial agents, and as a result, high clinical response rates are achieved [3, 4]. Clinical trials comparing gatifloxacin with the comparator amoxicillin-clavulanate also uncovered no clinically important adverse events [3]. At this point, it would be reasonable to conclude that a new agent for treating difficult cases of AOM will soon be available.

However, development of quinolone antibiotics for use in children has been under a black cloud for several decades. Cartilage abnormalities in young, growing experimental animals raised concerns about the use of these agents in children. However, public discussions, as well as accumulating data showing no increased risk of joint abnormalities associated with use of quinolones in pediatric patients, eventually allowed some clinical trial programs to move forward [5]. Gatifloxacin trials in persons with AOM were performed, some of the data were presented and published, and a meeting of the Anti-Infective Drugs Advisory Committee of the US Food and Drug Administration (FDA) was scheduled for 10 May 2004, to review the clinical trial data before reaching a decision regarding licensure. At the eleventh hour, before public viewing of the data, the meeting was cancelled [6]. It was reported that “Bristol withdrew its sNDA [new drug application] for the gatifloxacin oral solution because it could not come to an agreement with FDA about a risk management program for use of the drug in the pediatric indication” [7]. For the purpose of this commentary, I will assume that the foregoing quotation is an accurate description of the reason for cancellation of the FDA Advisory Board meeting and thus, apparently, for calling a halt to further development of gatifloxacin for pediatric use. Were there new data showing that gatifloxacin has risks that we do not know about? In the discussions of risk management, what risks were considered? Real risks of gatifloxacin in humans? Risks associated with other members of the quinolones class? Risks known only in experimental animals? Theoretical risks? We may never know what was discussed or not discussed “in the back room.”

Unfortunately, access to a promising therapy for children with difficult-to-treat AOM appears to have been quashed in the back room. If the report by Pichichero et al. [3] is a full description of all the safety data available, then this appears to have occurred without new data demonstrating real—rather than imagined—concerns about the safety of gatifloxacin. Yes, the safety data reported by Pichichero and colleagues involves <1000 children, hardly enough to conclude that gatifloxacin is...
safe. But the solution to this uncertainty is to obtain more pre- and/or postlicensure safety data, not to create barriers that result in a halt to the development of a promising antibacterial agent.

The FDA has a clear mandate to weigh safety and efficacy before drug licensure and to monitor safety thereafter. Treating clinicians have a similar obligation to weigh safety and efficacy for individual patients. The public at large also has a stake: just as the public has an interest in timely knowledge of newly discovered risks of drugs, the public also has an interest in whether potentially efficacious drugs are being withheld without any data indicating that they are associated with unacceptable risks. This could be addressed by considering the following 3 recommendations: the safety data on gatifloxacin use in children should be reviewed in a public forum, such as the Anti-Infective Drugs Advisory Committee; if there are no data indicating increased risks of side effects with gatifloxacin, compared with other licensed antibiotics, then recommendations for further safety studies should be put forward; and the nature and basis for a risk-management program should also be exposed to public scrutiny and discussion.

As this case illustrates, some general recommendations should be considered regarding the safety, efficacy, and licensure of drugs. First, all human clinical trials data from investigational new drug–regulated studies should become available in the public domain, or else a full assessment of safety and efficacy will be impossible, because not all trial results are published in peer-reviewed journals. This should apply both to licensed products and to products that do not achieve licensure. Data on human experimentation with pharmaceutical agents is potentially too important to be kept in locked files. Second, important decisions regarding the assessment of the balance of safety and efficacy should also be discussed in a public forum.

Acknowledgments


References