The Emergence of Rational Therapeutics from the Traditions of Clinical Practice

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Everyone actively engaged in the practice of pediatric medicine knows that the treatment of upper and lower respiratory tract infections in infants and children requires 10 days of oral antibiotic therapy. The past 4 decades have witnessed the emergence of more than a dozen oral antibiotics labeled for the treatment of upper respiratory tract infections in pediatric patients, and all of them have been introduced into clinical practice with a 10-day regimen.

It is interesting that the science is invariably in place from the outset. The *in vitro* potency of the agent against the common target pathogens is well described, along with the pharmacokinetic characteristics of the drug, including its bioavailability, protein binding, clearance, and area under the plasma concentration-versus-time curve. These characteristics also form the basis for meticulous comparisons with other drugs labeled for similar clinical indications, with notable differences forming the platform for elaborate marketing campaigns. Nevertheless, at the end of the day, clinical wisdom prevails and 10 days of treatment is prescribed for each and every agent.

Fortunately, thinking has begun to change during the past 5 or 6 years. Challenged by the looming threat of antibiotic resistance and the financial pressures imposed by managed formularies and the economic downturn, practitioners have begun to question the "one size fits all" mentality that has dominated clinical thinking. With little consideration given to the pharmacokinetic and pharmacodynamic characteristics of the agents targeted, attempts have been made to increase doses and to shorten the course of treatment for diseases such as acute otitis media and streptococcal pharyngitis. The wake of these attempts is littered with some predictable clinical successes, a large number of questions, and seemingly insufficient information to compel changes in clinical practice.

A number of beta-lactam antibiotics were shown to work as well using 5-day regimens as they did when used for 10 days. Upon further scrutiny, however, it appeared that the children under 2 years of age did not respond as well as their older co-sufferers. This odd, but reasonably consistent, observation has led to an air of caution surrounding the adoption of these radical short-course treatment regimens. It is also now common practice to use double the dose of amoxicillin

recommended previously in an effort to provide more effective coverage of antibiotic-resistant *Streptococcus pneumoniae*—an interesting practice with few clinical data to support its effectiveness. Finally, we have seen the emergence of a clinical trial paradigm in acute otitis media that has been rapidly embraced by the community of pediatric infectious disease experts: the “double-tap” protocol. According to this paradigm, the patient undergoes tympanocentesis at the time of diagnosis, before starting treatment, and again after 4–6 days on drug therapy. The effectiveness of treatment is gauged by the persistence of bacteria in the middle-ear fluid, regardless of the patient’s clinical condition or clinical outcome. No consideration has been given to the pharmacokinetic differences among the drugs compared that might account for the pharmacodynamic differences observed. Nevertheless, all of these forays into the therapeutic borderland suggest that the time is ripe for the emergence of science-based dosing strategies for the antibiotic treatment of upper respiratory tract infections in children.

In this supplement, we introduce a novel, but rigorously investigated, dosing strategy for the well-known azalide antibiotic, azithromycin. This drug has been an integral part of our therapeutic armamentarium for more than a decade, with indications for the treatment of acute otitis media and streptococcal pharyngitis. From the outset, it was unique in that its exceedingly long half-life (more than 40 hours in children) permitted the use of shorter treatment courses. However, these shorter courses were always presented in the context that, because of the longer half-life, the patient was *really* still receiving 10 days of therapy. In this supplement, we present a summary of the reevaluation of the unusual properties of this antibiotic molecule and their application to the development of a revolutionary new dosing strategy for the drug in the treatment of acute otitis media.

In the first paper, Dr. Constance Rothermel presents a review of the biodisposition of azithromycin, highlighting the structural features that determine its cellular uptake and its accumulation in inflammatory cells that are recruited to sites of infection, where the release of active drug is triggered by the presence of bacteria. She also reports the results from animal infection models, including models of acute otitis media, which demonstrate the superiority of single-dose administration over divided-dose regimens.

This is followed by a report of a brave undertaking by Dr. Adriano Arguedas and his colleagues in Costa Rica, where a study was designed to preliminarily test the hypothesis that the pharmacokinetics and pharmacodynamics of azithromycin would permit the delivery of a complete course of treatment with a single oral dose of drug. Almost 200 children were randomly assigned to receive a single 30 mg/kg dose of oral azithromycin, a 3-day oral regimen of azithromycin 10 mg/kg daily, or a single intramuscular 50 mg/kg dose of ceftriaxone. All patients underwent diagnostic tympanocentesis. The study data supported the effectiveness of the single-dose oral regimen, as would be predicted from the preclinical studies summarized by Dr. Rothermel. This work then led to a registration study, designed by Mary Murphy, MD, MPH, to whom this supplement is dedicated posthumously. The work, which was carried out at 9 centers in the United States,

demonstrated that a single 30 mg/kg oral dose of azithromycin was as effective as 10 days of standard dosing with amoxicillin/clavulanate in children with acute otitis media.

The work described in this supplement represents a true therapeutic triumph. For the first time in recent history we have been able to shed the bonds of conventional clinical practice and take a new look at how therapy is delivered for one of the more common pediatric infectious problems. This is made even more exciting because, instead of requiring the introduction of a new drug or class of drugs, both clinicians and the pharmaceutical industry have had the courage to go back and reexamine a drug already widely recognized for its safety and efficacy. The end result is a revolutionary new dosing regimen that establishes a new standard for the treatment of acute otitis media, and, perhaps even more importantly, a new freedom to ask hypothesis-driven questions about our therapeutic “sacred cows.”

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