PIC QUESTION OF THE WEEK: 1/09/06

Q: Why is the maximum dose of Augmentin XR® so much greater than that of other Augmentin® dosage forms?

A: Augmentin XR® was marketed in 2002 and labeled for the treatment of bacterial sinusitis and community-acquired pneumonia due to beta-lactamase producing organisms (H. influenzae, K. pneumoniae, M. catarrhalis, H. parainfluenzae, or methicillin-susceptible S. aureus) and strains of Streptococcus pneumoniae that possess reduced susceptibility to penicillin (MIC = 2 mcg/ml). The product was specifically formulated for treating the increasing number of resistant S. pneumoniae species being reported in cases of sinusitis, pneumonia, etc. It is not indicated for S. pneumoniae whose MIC is ≥ 4 mcg. Resistance developed by S. pneumoniae is due to its ability to *alter the affinity of penicillin binding proteins on its cell membrane.* Increased doses of amoxicillin overcome this form of resistance. The other organisms cited above become resistant by *producing beta-lactamase (penicillinase).* The clavulanic acid doses incorporated into Augmentin XR® are typically sufficient to eradicate the beta-lactamase producing organisms (H. influenzae, M. catarrhalis, etc.). The XR formulation contains 1 g of amoxicillin and 62.5 mg of clavulanic acid. Resistant species of S. pneumoniae in children may require amoxicillin doses of 80-90 mg/kg/day. Some authors have suggested the need for possibly even higher daily doses with more resistant isolates. In children, this amoxicillin dose can generally be attained with the oral or chewable tablets, syrup, suspension, and Augmentin ES-600® suspension. With older children, this 90 mg per kg dose could result in dosage above the maximum recommended daily dose of 4 g of amoxicillin/ 250 mg clavulanic acid listed in the Augmentin XR® product literature. It is not unusual to see calculated doses of amoxicillin exceed 4 g per day. With the exception of Augmentin XR®, the other dosage forms suggest a maximum amoxicillin dose of 1750 mg per day. This higher maximum dose is undoubtedly due to the fact that clinical trials of Augmentin XR® used a much higher dose of amoxicillin for resistant S. pneumoniae. Because this was the only dosage form for which such data was submitted to the FDA, it is the only one that includes this higher maximum daily dosage recommendation. Using the ES formulation for older children and adults would simultaneously increase the clavulanic acid dose and the risk of diarrhea.

References:

- Anonymous. Augmentin XR. Med Lett Drugs Ther 2003;45:5-6.
- Augmentin XR (Amoxicillin/Clavulanate). Pharmacist's Letter/Prescriber's Letter 2002;18(11);181106.
- American Academy of Pediatrics. 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village:American Academy of Pediatrics;2003.

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