



## Amoxicillin clavulanate vs. amoxicillin for treatment of UTI

Dear Editor,

I note in the "Antibiotics: Choices for Common Infections" booklet provided with the August 2013 edition of *Best Practice Journal*, that amoxicillin with clavulanic acid is recommended as an alternative agent for treating UTI in children. I would be interested in understanding the rationale for this recommendation, given the poor oral absorption and urinary excretion of clavulanic acid compared with amoxicillin.

In 1986, Horber, et al reported that the systemic bioavailability of oral amoxicillin was about 70% compared with that of clavulanic acid, which was about 50%. This team also demonstrated that: "In subjects exhibiting normal renal function the urinary excretion of unchanged amoxicillin and clavulanic acid following p.o. administration was 56 and 22%, respectively."<sup>1</sup>

Thus, rather than the proportion of clavulanic acid to amoxicillin present in urine being approximately 25%, as is present in oral formulations of amoxicillin/clavulanic acid combinations and as could be expected of serum concentrations, the proportion in urine is probably reduced to less than 10%.

This pharmacokinetic difference between the two beta-lactams won't be evident in the *in vitro* laboratory sensitivity testing where adequate concentrations of both agents are tested against bacterial strains. So it is understandable that sensitivity testing will indicate pathogen susceptibility to amoxicillin/clavulanic acid combinations. However, the significant reduction in clavulanic acid present in urine may be clinically significant *in vivo* and could increase the risk of treatment failure.

To consider this another way, given that the amount of clavulanic acid present in urine is likely to be significantly reduced, and as a consequence its therapeutic effect is likely to be significantly reduced, why isn't amoxicillin alone (rather than in combination with clavulanic acid) recommended as an alternative agent for treating UTI in children? Is clavulanic acid adding any value to amoxicillin in the treatment of UTI?

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The information in the "Antibiotics: Choices for Common Infections" booklet (Jul, 2013) was derived from expert consensus. In the booklet, it is recommended that the first choice antibiotic treatment for uncomplicated UTI in children is co-trimoxazole (due to the trimethoprim component). Cefaclor and amoxicillin clavulanate were listed as alternative treatment options. It is common practice for amoxicillin clavulanate to be used in the treatment of UTIs in children. In fact, current Starship Children's Health clinical guidelines list amoxicillin clavulanate as the most preferred oral treatment option (followed by co-trimoxazole then cefaclor).<sup>1</sup>

However, the question asked by the correspondent is whether amoxicillin clavulanate is superior to amoxicillin alone for the treatment of UTI. Amoxicillin has fallen out of favour as a treatment option for UTI due to increasing resistance to *Escherichia coli*, which accounts for the majority of uncomplicated urinary tract infections in children.<sup>2</sup> Clavulanic acid is a beta-lactamase inhibitor which works synergistically with amoxicillin to extend the spectrum of antibiotic susceptibility. In theory, this means that UTIs are less likely to be resistant to treatment with amoxicillin clavulanate than amoxicillin alone.

The objective of the Horber et al study, referred to by the correspondent, was to assess changes in the way amoxicillin and clavulanic acid are excreted with declining renal function.<sup>3</sup> Because of this, there were only six participants with normal renal function in the study. After oral administration of the drugs, lower urinary concentrations of clavulanic acid compared to amoxicillin were found in these six subjects. This suggests that the amount of bioavailable clavulanic acid

may be too low to make it clinically superior to amoxicillin alone.<sup>3</sup> However, the surrogate values in the study may not be representative of a large population.

Perhaps a more clinically relevant measure of antibiotic efficacy is resolution of infection. A 1986 study involving 52 elderly patients with urinary tract infection found that 87.5% of those treated with amoxicillin clavulanate had resolution of infection, compared to 43% of those treated with amoxicillin alone.<sup>4</sup> Five out of eight patients who did not initially respond to amoxicillin, responded to amoxicillin clavulanate. Although this study involved elderly subjects rather than children, and again, the number of included subjects was low, some interesting observations were made. The authors commented that:

“It has been suggested that, because of the high concentrations attainable in urine, amoxycillin [amoxicillin] is often effective in treating UTIs caused by organisms which are resistant to the drug in vitro. The results of our study, however, indicate that amoxycillin-resistant organisms do not respond to amoxycillin alone. Augmentin [amoxicillin clavulanate], on the other hand, is likely to cure urinary tract infection irrespective of the amoxycillin susceptibility of the organism in vitro. Of the patients infected with amoxycillin-resistant organisms, 80% were cured by augmentin. By contrast, only 10% of the patients with amoxycillin-resistant organisms were cured by amoxycillin.”

A small randomised controlled study in 1981 found that 11 out of 13 (85%) adult patients with penicillin-resistant UTI had an absence of bacteriuria after treatment with amoxicillin clavulanate, compared to 2 out of 8 (25%) patients receiving amoxicillin alone.<sup>5</sup>

Although both of these studies have limitations, and cannot necessarily be extrapolated to the treatment of UTI in children, they serve the purpose of demonstrating that medicines can have a clinically important treatment effect, despite their underlying pharmacokinetic profiles being less than ideal.

In summary, amoxicillin clavulanate is used as a second-line treatment for UTI in preference to amoxicillin alone, because most consensus-derived guidelines recommend this, and in

practice, it works. A recent Cochrane review concluded that although antibiotic treatment for children with UTI is effective, there is not enough evidence to answer the question of which antibiotic is superior.<sup>6</sup>

#### References

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