The comparative efficacy and safety of teicoplanin and vancomycin

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Sir,
In the recent review published in your journal (Wood, 1996) that compares the efficacy and safety of teicoplanin and vancomycin the author concludes that teicoplanin is as efficacious as vancomycin. The review consists of a meta-analysis of eleven clinical trials in which both drugs are compared. By adding all the cases treated with both drugs the author does not find differences between the drugs. We believe that, before accepting this conclusion, it should be considered that a disproportionate number of trials with teicoplanin have focused in neutropenic patients with fever. In fact, more than half of the patients included in the meta-analysis belonged to this category. Clinical trials of glycopeptides in neutropenic patients with fever are very difficult to interpret and deserve careful analysis since other drugs are used (β-lactams and aminoglycosides), such infections are frequently associated with catheters and are often not documented by culture. For example in the trial with the highest sample size (Menichetti et al., 1994) it was necessary to enrol 635 patients (527 evaluable) in order to obtain 102 patients with documented Gram positive bacteraemia. Only 23 of the infections were caused by bacteria resistant to the non-glycopeptide antibiotics used in the trial. If the objective of Wood’s review was to determine whether teicoplanin has the same efficacy, in general, as vancomycin, an imbalanced distribution of the conditions in clinical trials causes a considerable bias. Interestingly, only 45 so-called deep-seated infections were recorded among more than 1000 cases included in the meta-analysis. Although there were no statistically significant differences between teicoplanin and vancomycin when evaluating this group of infections, there was a trend of more failures among patients treated with teicoplanin (11 out of 21; 52%) that those treated with vancomycin (9 out of 24; 37%). A matter of concern is the lack of efficacy of teicoplanin in staphylococcal endocarditis (Gilbert, Wood & Kimbrough, 1991; Fortun et al., 1995). Among all the types of infections, endocarditis is one of the most challenging situations in order to test the efficacy of an antibiotic due to the absence of local mechanisms of defence and the high density of bacteria in vegetations. In this context any favourable response can be attributed to the effect of the drug. The same can not be assured when evaluating less serious infections.

We think that a more critical approach considering every potential indication is needed to reach conclusions about the efficacy of a new drug.

Among other advantages of teicoplanin, Wood emphasizes that there is no need for the routine serum monitoring which is required for vancomycin. As is pointed out in a recent review and editorial (Cantú, Yamanaku-Yuen & Lietman, 1994; Moellering, 1994) it is not necessary to routinely monitor the levels of vancomycin since the plasma levels are predictable, and it is only recommended in some situations such as changing renal function, combination with an aminoglycoside and haemodialysis. Finally, if other potential advantages of teicoplanin like the intramuscular use or once daily bolus administration are considered, we should not forget potential disadvantages like the easier selection of resistant strains among coagulase negative staphylococci (Maugein et al., 1990) and the anecdotal but qualitatively important report of the development of resistance to teicoplanin during the treatment of S. aureus endocarditis (Kaatz et al., 1990).

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The localization of the gene bla<sub>ESP</sub> on *P. aeruginosa* plasmid pMS350, we cloned bla<sub>ESP</sub> in *Escherichia coli* K-12 /1037 from pMS354, a segregant plasmid derived from *P. aeruginosa* plasmid pMS350 of clinical origin, and determined the nucleotide sequence of the gene with its flanking regions.

The *Bam*HI fragment cloned on vector plasmid pHSG398 conferred resistance to both imipenem and sulphanilamide. Fine physical mapping of the fragment showed that bla<sub>ESP</sub> was inserted into the integron (In0) structure (Figure). In0 is an ancestor integron identified on a *P. aeruginosa* plasmid, which contained both the integrase gene (*int*) and an unoccupied integration site where the integrase acts, ORF4, and the sulphanilamide resistance gene (*sul1*) (Bissonnette & Roy, 1992). The In0 sequence is separated by the GGT triplett into two parts, respectively called the 5'-conserved and 3'-conserved sequences. GTT is a recombination crossover point, within or on either side of which the antibiotic resistance genes are usually inserted as cassettes. The promoters for the gene cassette inserted into the GGT site are localized at the sequences near the 3' end of the *int*.

We sequenced 4032 bases from the 5'-*Bam*HI site to the *PstI* site of the bla<sub>ESP</sub> segment, in comparison with the nucleotide order of In0 starting from *Bam*HI (n1) to *PstI* (n2017). The bla<sub>ESP</sub> segment showed a 5'-conserved sequence identical to that of In0, except for a single base substitution at position n1064 in *int*, without change in the amino acid sequence.

The bla<sub>ESP</sub> cassette was found to be inserted after the GGT triplett (n1286 to n1288). The length of the inserted cassette was 880 bases ending with the GGT triplett at the terminal. The cassette sequence was followed by a 3'-conserved sequence identical to that of In0, in which ORF4 with another insertion of 1055 bases and the first half of the *sul1* gene were identified.

The bla<sub>ESP</sub> cassette sequence was flanked with direct repeats that formed at the junctions between the cassette and In0 sequences. The seven nucleotide sequences identified were GTTAGAA at the left and GTTAGAT at the right junction; these were consistent with those of the consensus sequence GTTRRRY with the exception of the seventh nucleotide of the left junction. The cassette contained a ribosome binding site AGGA, 741 bases of bla<sub>ESP</sub>, and 127 bases of the 3'-associated sequence in which the termination structure of transcription of bla<sub>ESP</sub> was identified. The bla<sub>ESP</sub> cassette sequence was identical to the bla<sub>IMP</sub> cassette.