Should clindamycin be used as treatment of patients with infections caused by erythromycin-resistant staphylococci?

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Sir,

Target site modification, i.e. methylation of an adenine residue of bacterial 23S ribosomal RNA, is the most common mechanism of acquired resistance to macrolides, lincosamides and streptogramin-B (MLS) antibiotics and confers cross-resistance to MLS antibiotics (the so-called MLSB phenotype). Expression of MLS resistance in staphylococci is either constitutive or inducible. When it is constitutive, bacteria exhibit resistance to all MLS antibiotics, whereas when inducible, they are resistant to 14-membered (e.g. erythromycin) and 15-membered macrolides only, retaining susceptibility to 16-membered macrolides, lincosamides and streptogramin-B antibiotics. This dissociated resistance arises from differences in the inducing capacities of MLS antibiotics, 14- and 15-membered macrolides being better inducers than the other groups of drugs.1

Staphylococci exhibiting inducible (dissociated) resistance to MLS antibiotics are common in clinical practice.2 When the disc diffusion method is used to determine susceptibility, a distorted ‘D-shaped’ (rather than circular) zone of inhibition is observed around discs impregnated with 16-membered macrolides, lincosamides or streptogramin-B antibiotics if an erythromycin disc is placed nearby. This phenomenon is the result of induction of resistance to non-inducing MLS antibiotics by the erythromycin. Although isolates appear susceptible to lincosamides in the absence of an inducing agent, there is widespread reluctance to prescribe clindamycin as treatment of patients with infections caused by such organisms because of concerns that resistance to them will develop during therapy.3 However, staphylococci that are susceptible to erythromycin have also been shown to become resistant to it or to lincosamides following exposure to these antibiotics both in vitro and in vivo.4

We studied the rate at which staphylococci develop resistance to clindamycin in vitro. The isolates used in the study included six clinical isolates of Staphylococcus aureus that were resistant to erythromycin but susceptible to clindamycin, five of which exhibited inducible resistance, and a further six clinical isolates that were susceptible to both erythromycin and clindamycin; the Oxford S. aureus (NCTC 6571) was used as a control. The MICs of clindamycin for all 12 isolates, which were determined by a standard broth microdilution method, were 0.13 mg/L. The isolates were passaged in the presence of clindamycin. Briefly, 100 μL volumes of two-fold dilutions of clindamycin, ranging from 0.03 mg/L to 16 mg/L, in Brain Heart Infusion broth (Oxoid Ltd, Basingstoke, UK) were added to the wells of microtitre trays. Each well was inoculated with 100 μL of a diluted overnight broth culture (containing 5 × 10⁸ cfu/L) of one of the 13 isolates. After incubation for 48 h, broth from the well containing the highest antibiotic concentration in which there was visible growth was used as the inoculum for the next passage.

All of the five isolates exhibiting inducible resistance became resistant to clindamycin (MICs > 16 mg/L) after only two to four transfers, whereas the isolate that was resistant to erythromycin but did not exhibit inducible resistance remained susceptible to clindamycin. The reference isolate and the six isolates that were susceptible to erythromycin also remained susceptible to clindamycin after four passages, although the MICs for two of these increased from 0.13 mg/L to 0.5 mg/L.

Previous studies have shown that resistance to lincosamides develops rapidly in erythromycin-resistant isolates of S. aureus. Resistance also develops in erythromycin-susceptible isolates, albeit much more slowly and in a stepwise manner, following exposure to these drugs in vitro.5,6 Constitutively resistant mutants can be selected in vitro from isolates exhibiting inducible resistance at frequencies of 10⁻⁷ to 10⁻⁸ after growth in the presence of non-inducing MLS antibiotics.1 Constitutive resistance also develops in vivo, as demonstrated by the recovery of clinical isolates of such mutants.6

These observations suggest that, for the time being, clindamycin should be avoided as treatment of patients with infections caused by staphylococci exhibiting inducible MLSR resistance, even when they appear susceptible on laboratory testing, because the emergence of constitutively resistant mutants is likely to occur during courses of therapy. However, there is a need to evaluate the clinical
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efficacy of clindamycin in patients with infections caused by these organisms, as the patients may be cured and the pathogens eradicated before resistance develops. With regard to erythromycin-susceptible isolates, the potential for the emergence of resistant isolates during treatment exists, although the risk is markedly lower. Susceptibility testing of staphylococci should include the disc diffusion induction test (i.e. erythromycin and clindamycin discs placed 15–20 mm apart), which will facilitate the identification of isolates exhibiting inducible or constitutive resistance to MLS\textsubscript{B} antibiotics. Although the MLS\textsubscript{B} phenotype accounts for the majority of macrolide-resistant clinical isolates, other mechanisms (enzyme inactivation and active efflux) also confer resistance, albeit only to structurally related drugs. Patients with infections caused by such isolates can still be treated with clindamycin without the expectation of resistance developing during therapy.

References