Gentamicin-Carbenicillin Synergy Among Gentamicin Resistant *Pseudomonas aeruginosa*

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ABSTRACT

Forty-five isolates of gentamicin resistant *Pseudomonas aeruginosa* were evaluated for gentamicin-carbenicillin synergy. Only 9 percent (4/45) showed synergy. Of nine isolates with demonstrable zones around a gentamicin disc (8 to 12 mm), none showed a synergistic response. Effective treatment of gentamicin resistant *Ps. aeruginosa* with gentamicin and carbenicillin should not be assumed without additional test procedures.

Introduction

The use of synergistic combinations of antibiotics in the treatment of severe infection by *Pseudomonas aeruginosa* is common. Benefits include increased cure rates and a relative decrease in the minimum inhibitory concentration (MIC) of each of the component antibiotics used synergistically compared to their use alone. A decrease in MIC should allow the use of lesser amounts of potentially toxic drugs for *Ps. aeruginosa* isolates synergistically more susceptible to the antibiotic combinations. This brief report examines 45 isolates of gentamicin resistant *Ps. aeruginosa* for gentamicin-carbenicillin synergy. These isolates were collected from multiple hospitals in southern New England and do not reflect the microbial population of a single hospital.

Methods

Gentamicin-resistant isolates of *Ps. aeruginosa* were defined as those with MIC's of ≥ 8 mcg per ml when tested by the microdilution method in Ca++ and Mg++ supplemented Mueller-Hinton broth. Zone sizes around a 10 mcg gentamicin disc were determined by a standardized disc agar diffusion method. Two groups of resistant isolates were defined—one in which no zones of inhibi-
tion could be observed around the disc, and one in which inhibitory zones of 7 to 12 mm were seen. Synergy was assessed for gentamicin and carbenicillin combinations using the microtiter checkerboard technique described by Ryan et al. Synergy was defined as a four fold reduction in the MIC of either antibiotic in the combination compared to the MIC of the single antibiotic. The MIC determination with a control strain (Ps. aeruginosa ATCC 27853) consistently showed values of 2.0 to 4.0 mcg per ml for gentamicin.

Results

Of the 45 isolates tested, two (4.5 percent) had indeterminant susceptibility (13 to 14 mm), both with MIC’s of 32 mcg per ml, nine (20 percent) were resistant but a clear zone was observed around the diffusion disc (8 to 12 mm), and 29 (64 percent) isolates showed no zone of inhibition around the gentamicin disc (MIC, ≥ 32 mcg per ml). Five (11 percent) isolates showed zones of ≥ 15 mm (15 mm to 19 mm), and MIC’s of 16 to 32 mcg per ml. Carbenicillin MIC’s ranged from 32 to > 64 mcg per ml.

Using the stated criterion, synergy could be demonstrated in only 4/45 (9 percent) of the isolates tested. These organisms in which synergy was found had lower MIC’s to gentamicin (two isolates of 16 mcg per ml and two isolates of 32 mcg per ml). Similarly, these organisms showed inhibition zones around the gentamicin disc (one isolate, 14 mm; one isolates, 17 mm; two isolates, 16 mm). In 3/4 instances (75 percent), the gentamicin MIC in the presence of carbenicillin was reduced to 2.0, 4.0, and 8.0 mcg per ml, respectively.

Conversely, of the nine isolates of Ps. aeruginosa with demonstrable zones around the gentamicin disc (8 to 12 mm), none showed synergy when incubated with both gentamicin and carbenicillin.

Discussion

Several studies have suggested that synergistic inactivation of Ps. aeruginosa occurred even when the isolate was resistant to gentamicin alone. Kluge et al in a study of 130 clinical isolates of Ps. aeruginosa concluded that those isolates which are highly resistant to gentamicin will not become significantly more susceptible when carbenicillin is added. They can be identified by the absence of any zone of inhibition around a 10 mcg gentamicin disc. The majority of isolates with zones > 6 mm around the gentamicin disc could be expected to respond synergistically to combination therapy. Keys and Washington reported that gentamicin/carbenicillin therapy was clinically effective in 12/13 cases of infection owing to gentamicin resistant isolates. In 8/9 isolates tested, synergy was observed.

The results of this study are in contrast to these earlier reports. Carbenicillin reduced the gentamicin MIC in only 4/45 (9 percent) instances. Ninety-one percent of these resistant isolates showed no synergy. Even amongst those organisms with inhibitory zones (≥ 7 mm) around the gentamicin disc, 9/16 (56 percent) failed to show synergy. Several explanations are offered. Prior studies of gentamicin resistant Pseudomonads have included strains collected from one or a few closely related hospitals. No attempts were made to distinguish these strains. Accordingly, the actual number of unique strains may have been considerably less than the total number of isolates. Because of the geographic distribution of the strains in this report, they probably do not represent a cluster of strains with similar properties.

Only isolates with MIC’s of ≥ 16 mcg per ml were included in this study. This MIC breakpoint is higher than in the two studies cited (8.0 mcg per ml; ≥ 10 mcg per ml respectively). Isolates with borderline resistance (< 16 mcg per ml) were
discarded. It is precisely this group of bacteria that would be expected to show a synergistic response.

Gentamicin and carbenicillin cannot be relied upon to provide adequate anti-pseudomonal coverage when gentamicin resistant *Ps. aeruginosa* is encountered. In such instances, an alternative aminoglycoside should be considered, but only after “in vitro” testing.

References


