Bactericidal Activities of Five Antibiotics During Short-Term Exposure to Coagulase-Negative Staphylococci

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After a 1-h exposure to concentrations used for topical prophylaxis in neurosurgical procedures, bacitracin, vancomycin, and oxacillin were bactericidal against more than 90% of 48 body fluid isolates of coagulase-negative staphylococci. More than 10% of isolates survived despite exposure for 4 h to concentrations of gentamicin and streptomycin greater than those employed for topical prophylaxis.

Even though the incidence of infection after cerebrospinal fluid shunt placement has decreased over recent decades (1), a recent report places the expected postoperative infection rate in clean neurosurgical procedures at 3 to 4% (6). Coagulase-negative staphylococci are responsible for more than half of reported infections, and clustering of infections in the 2 months after surgery suggests that the infective organisms are usually introduced in the perioperative period (8). Some studies of systemic perioperative antibiotic prophylaxis have shown it to be beneficial (6); others have not (1). Topical antibiotic prophylaxis, however, is used by many neurosurgeons but has not been well studied (2). Since brief contact occurs between microorganisms and antibiotic during topical prophylaxis, bacterial killing in vitro after brief periods of contact between representative antibiotics and coagulase-negative staphylococci was studied.

Powdered reagent standards of bacitracin (The Upjohn Co., Kalamazoo, Mich.), vancomycin (Eli Lilly & Co., Indianapolis, Ind.), oxacillin (Bristol Laboratories, Syracuse, N.Y.), gentamicin (Schering Corp., Kenilworth, N.J.), and streptomycin (Pfizer Inc., New York, N.Y.) were used. Doubling dilutions of each drug were prepared in Mueller-Hinton broth, and 200 µl of each dilution was placed in successive wells of microtiter trays (Dynatech Laboratories, Inc., Alexandria, Va.). Concentrations of drugs ranged from 6.25 to 400 U/ml for bacitracin, 6.25 to 400 µg/ml for streptomycin, 12.5 to 800 µg/ml for gentamicin and vancomycin, and 500 to 32,000 µg/ml for oxacillin. These ranges of dilutions encompass the concentrations of drugs which are currently used in neurosurgical centers to wash the shunt tubing and to irrigate the operative field (3, 4; personal survey of five neurosurgical centers).

A total of 48 strains of coagulase-negative staphylococci stored in skim milk at −70°C after culture from human cerebrospinal fluid, blood, and intravascular catheters were passed through at least three successive daily subcultures. The strains were then grown to log phase in Mueller-Hinton broth. Duplicate wells of the microtiter trays were inoculated with samples of this broth to achieve a final inoculum density of 5 × 106 CFU/ml. Growth-control and sterility wells were included with each series of antimicrobial dilution and each strain of microorganism. Quality control strains were Staphylococcus aureus (ATCC 29213) and Escherichia coli (ATCC 25922). Trays were incubated at 35°C for 1 h, after which 10 µl was carefully removed without agitation from each well and placed on Mueller-Hinton agar without drug. The microtiter plate was then incubated for an additional 3 h, after which 10 µl was transferred from each well to drug-free agar. The agar plates were incubated for 16 to 18 h, and bactericidal concentration was the concentration of drug in the microtiter well that prevented subsequent growth of more than one colony on drug-free agar after each incubation period in broth. MIC was the concentration of drug which prevented visible bacterial growth in the microtiter well after 16 to 18 h of incubation.

Growth of 90% of isolates was inhibited by the lowest test concentration of bacitracin, vancomycin, oxacillin, and gentamicin (Table 1). Although some isolates were able to grow in solutions containing streptomycin, more than 90% were inhibited by 100 µg/ml. Bacitracin killed 90% of bacterial isolates at a concentration of 200 U/ml with 1 h of exposure. There was improved killing with extension of exposure to 4 h (Table 1). After 1 h of exposure, 90% of isolates were killed by 100 µg of vancomycin per ml and by 1,000 µg of oxacillin per ml. The bactericidal effect of these drugs was not improved significantly by increasing the duration of exposure to 4 h.

The aminoglycosides gentamicin and streptomycin were markedly less effective as bactericidal agents against coagulase-negative staphylococci with short-term incubation than were the other antimicrobial agents with the concentrations tested. Whereas more than half of the isolates were killed by 1- and 4-h exposures to 12.5 µg of gentamicin per ml and 100 µg of streptomycin per ml, more than 10% of the isolates survived despite exposure for 4 h to 800 µg of gentamicin per ml or to 400 µg of streptomycin per ml.

These results indicate that short exposure, such as 1 h, of coagulase-negative staphylococci to the tested concentrations of bacitracin, oxacillin, and vancomycin is sufficient for killing of the bacteria. In a previous study, Scherr et al. (7) showed that a 60-s exposure to 50 U of bacitracin per ml was adequate to achieve killing of 50% of the organisms from a single coagulase-negative staphylococcal isolate. They observed 90% killing when a combination of bacitracin and polymyxin B was used. To our knowledge, no other studies of short-term bactericidal activity against coagulase-negative staphylococci have been performed. McDonald et al. (5) demonstrated that S. aureus was significantly inhibited by exposure to penicillin and gentamicin for 2 h. However, although there was dose-related persistence of the inhibitory effect with penicillin in their study after removal of the

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antibiotic, no persistence of inhibition was observed with gentamicin.

There is considerable interest among neurosurgeons concerning the use of prophylactic intraoperative antibiotics because of the relatively high incidence of infections after procedures such as shunt placements and because of the potentially devastating consequences of central nervous system inflammation as well as compromise of the shunt (4, 6). In a recent review of topical antibiotic prophylaxis in neurosurgery, Haines (2) noted that reports of the use of topical antibiotics in clean neurosurgical procedures are either uncontrolled or are so fragmentary that no useful judgements can be made concerning their utility. Our informal survey of five neurosurgical centers revealed no consistent choice of antimicrobial agent, concentration, or duration of application.

The in vitro data obtained in this study provide guidelines for the design of clinical studies of the effectiveness of topical antibiotic prophylaxis during surgical procedures. Streptomycin, which is commonly used for topical application at a concentration of 50 μg/ml (3, 4), required greater than 400 μg/ml to kill 90% of potentially pathogenic coagulase-negative staphylococci after 1 h of exposure, whereas gentamicin required greater than 800 μg/ml. Oxacillin required 1,000 μg/ml. In contrast, since 200 U of bacitracin per ml and 100 μg of vancomycin per ml were sufficient to kill these organisms, these concentrations might be useful for short-term, intraoperative application to shunts and tissues.

LITERATURE CITED