Comparative In Vitro Efficacies of Various Catheter Lock Solutions

Robert J. Sherertz, Michael S. Boger, Casey A. Collins, Lori Mason, and Issam I. Raad

Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; Department of Infection Control, North Carolina Baptist Hospital, Winston-Salem, North Carolina; and Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Received 17 January 2006/Accepted 17 February 2006

MEDTA (minocycline-edetate calcium disodium), taurolidine (2%)–polyvinylpyrolidone (5%) (T/PVP), and ethanol as potential catheter lock solutions have a unique mechanism of action, broad-spectrum activity, and anticoagulant properties. Traditional lock solutions minocycline (M), rifampin (R), ciprofloxacin (C), and vancomycin, except pharmacologic concentrations of C and R and of M and R, were less effective than MEDTA and T/PVP.

Systemic antibiotics alone eradicate only approximately one-third of catheter-related bloodstream infections (20); catheter replacement, often difficult, is usually required (4, 43). Most long-term catheter infections originate in the lumen, where systemic antibiotics do not reach (39). Killing organisms in biofilm requires antibiotic concentrations that systemic therapy cannot deliver (22, 32). A number of studies illustrate that filling a catheter lumen with high concentrations of antibiotics (lock technique) can eradicate bacteria, improving catheter salvage rates.

Minocycline-edetate calcium disodium (MEDTA) (7, 11, 25, 27, 30), taurolidine-polyvinylpyrolidone (T/PVP) (2, 6, 33, 38, 45), and ethanol (E) (14, 21, 23) are promising lock solutions. We examined the relative efficacies of vancomycin (V), ciprofloxacin (C), minocycline (M), minocycline-rifampin (M/R), ciprofloxacin-rifampin (C/R), vancomycin-rifampin (V/R), E, EDTA, MEDTA, and T/PVP at killing Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Candida albicans growing in biofilms.

Silicone Hickman catheter segments (1 cm) were incubated overnight at 37°C in tryptic soy broth (two to four replicates per condition) for growth of each organism. Segments were removed, rinsed thrice in phosphate-buffered saline (PBS), and incubated in various lock solutions for 0, 2, 4, or 24 h at 37°C. Segments were removed, washed 10 times in PBS, placed in tryptic soy broth, sonicated for 3 min, vortexed for 10 s, serially diluted, and plated on blood agar. CFU were counted after 24 h of incubation at 37°C and converted to log 10 values. Each experiment was duplicated. Values were averaged, and the means were graphed. Results at 24 h were compared using analysis of variance and Student’s t test (Minitab, Penn State University, PA).

The most common causative organisms of vascular catheter infections are S. epidermidis, S. aureus, and yeasts, including C. albicans (18). P. aeruginosa causes severe, often difficult-to-eradicate bloodstream infections. We used the P1 S. aureus strain (13, 39), the slime-producing RP62A S. epidermidis strain (12), and P. aeruginosa and C. albicans catheter-related bloodstream infection isolates. MICs (in micrograms per milliliters) were determined for M, R, C, and V: for S. aureus, MICs were ≤0.5, ≤0.12, ≤0.12, and ≤0.5, respectively; for S. epidermidis, MICs were ≤0.5, ≤0.12, 0.25, and 1.0; for P. aeruginosa, MICs were 4.0, >4.0, ≤0.12, and >16.0; and for C. albicans, MICs were 2.0, >8.0, >2.0, and >16.0. The following lock solutions were investigated: the therapeutic concentration (attainable serum concentration) (31, 40, 46, 48) for M was 2

* Corresponding author. Mailing address: Section on Infectious Diseases, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27517. Phone: (336) 716-4584. Fax: (336) 716-3825. E-mail: sherertz@wfubmc.edu.

FIG. 1. Effects of therapeutic concentrations of antibiotic lock solutions on the growth of S. aureus (A) and C. albicans (B). M, minocycline; C, ciprofloxacin; V, vancomycin; R, rifampin; M + R, minocycline plus rifampin; C + R, ciprofloxacin plus rifampin; V + R, vancomycin plus rifampin.
μg/ml, for R was 5 μg/ml, for C was 2 μg/ml, for V was 20 μg/ml (used individually or as M/R, C/R, and V/R); the pharmacologic concentration for M was 3 mg/ml, for C was 3 mg/ml, for R was 3 mg/ml, and for V was 3 mg/ml (used individually or as M/R, C/R, and V/R); and the pharmacologic concentrations for T/PVP were 2% T and 5% PVP, for MEDTA were 3 mg/ml M and 30 mg/ml EDTA, and for ethyl alcohol were 10%, 20%, 30%, 50%, 70%, and 100% (±30 mg/ml EDTA).

For S. aureus, therapeutic concentrations of antibiotics (±R), except V/R, significantly reduced CFU (log 10) removed by sonication at 24 h versus PBS results (1 to 2 log units [P < 0.05]) (Fig. 1A). With C. albicans, analysis of variance detected no significant differences compared to PBS results (P > 0.05) (Fig. 1B). For S. aureus, at pharmacologic concentrations, M, R, M/R, C/R, MEDTA, or T/PVP (2.8 to 3.5 log units [P < 0.001]) was significantly more effective than V, V/R, or C (0.7 to 1.2 log units) at reducing 24 h CFU versus the PBS control results (Fig. 2A). V antagonized the effect of R at 2, 4, and 24 h (P < 0.05). The combinations M/R, C/R, MEDTA, or T/PVP at pharmacologic concentrations were superior to all therapeutic concentrations against S. aureus (P < 0.05).

All agents killed S. epidermidis (2.4 to 3.5 log units [P < 0.001]) (Fig. 2B) and P. aeruginosa (2.1 to 4.7 log units [P = 0.007]) (Fig. 2C) at 24 h. With C. albicans, MEDTA, T/PVP, C, C/R, and M/R showed significant killing at 24 h versus PBS results (2.0 to 2.6 log units [P = 0.003]) (Fig. 2D). With C. albicans, M/R, C/R, and MEDTA demonstrated synergy compared to the results seen with each agent individually (P < 0.001). All ethanol concentrations produced 3.6 to 3.9 log units of killing of S. aureus at 2 and 4 h, superior to all other single and combination lock solutions (data not shown). This effect was maintained for 24 h.

Despite being the most extensively studied antibiotic lock solution (9, 10, 19, 35, 37), vancomycin was the least efficacious agent in our study. It lacks significant activity toward organisms in biofilm (30). One concern with vancomycin lock solutions is the risk of resistant organisms. Since other agents were at least as effective, vancomycin does not appear to be an ideal lock solution.

EDTA has broad-spectrum activity; its complex mechanism of action makes resistance doubtful (7, 34). Minocycline and EDTA are synergistic; no toxicities have been reported. MEDTA, when used in concentrations similar to that used in our study, was undetectable in serum (25). Taurolidine has novel activity, making resistance unlikely (5, 8, 16, 17, 45). It is bactericidal with broad-spectrum activity (38). The only significant adverse reactions reported occurred with high intravenous doses, including dose-related, reversible thrombocytopen-
nia and neutropenia (1). It is unlikely that significant toxicities would occur with taurodiline as a lock solution.

Ethanol has broad-spectrum antimicrobial activity based on denaturation rather than a specific molecular target, making resistance unlikely (36). It may reduce the use of broad-spectrum antibiotics and eradicate organisms otherwise difficult to clear. Ethanol combined with antibiotics in lock solutions could be synergistic. Mild side effects—fatigue, headache, dizziness, nausea, and light-headedness—were noted when ethanol was used as a lock solution (14). Theoretical toxicities (central nervous system depression, arrhythmias, flushing, local venous irritation) are unlikely when ethanol is used as a lock solution (3, 15). Ethanol concentrations as low as 30% were effective in our study, although higher concentrations have been thought necessary to inhibit biofilm growth (41).

Thrombosis is a major reason for catheter loss. Ethanol is effective at restoring catheter patency (23, 24, 28, 44, 47). MEDTA, taurolidine, and ethanol lock solutions appear to have intrinsic anticoagulant activity; they may prevent catheter thrombus formation, a potential nidus for infection (24, 26, 33). They could circumvent the need for heparin and its potential complications. Rifampin in combination with other lock solutions is synergistic (29, 42). We found that adding rifampin to minocycline and ciprofloxacin produced broad antimicrobial activity; it was antagonistic with vancomycin.

The results of our in vitro study are promising regarding alternative lock solutions that could overcome some of the pitfalls of current agents. MEDTA, T/PVP, C/R, M/R, and E should be considered as lock solutions in large randomized controlled trials.


REFERENCES


