

LABORATORY REPORT

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Antimicrobial Activity of Bupivacaine and Morphine

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Antimicrobial activity of bupivacaine and morphine against 10 microbial strains was studied with an agar dilution method. The strains tested were *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), and one of each of the clinical isolates of *Staphylococcus epidermidis* (a multiresistant strain), *Staphylococcus epidermidis* (a sensitive strain), *Streptococcus pneumoniae*, *Streptococcus pyogenes* (A), *Streptococcus faecalis*, *Bacillus cereus*, and *Candida albicans*. The antimicrobial effect of bupivacaine was tested at concentrations of 0.5, 1.25, 2.5, and 5 mg/ml (0.05%, 0.125%, 0.25%, and 0.5%). Bupivacaine at a concentration of 2.5 mg/ml inhibited the growth of the sensitive *S. epidermidis* strain, *S. pyogenes*, and *S. pneumoniae*, and all of the others except *P. aeruginosa* at a concentration of 5 mg/ml. Morphine 0.2 and 2 mg/ml (0.02 and 0.2%) did not inhibit any of the strains. (Key words: Analgesics: morphine. Anesthetics, local: bupivacaine. Bacteria: antibacterial activity; growth rates.)

STRICTLY ASEPTIC TECHNIQUES for introducing and maintaining catheters for regional analgesia and the use of bacterial filters¹ may be the main reason why serious epidural infections²⁻⁴ are so rare. In this respect, less attention has been paid to the potential bacteriostatic and bacteriocidal effect of local anesthetics⁵⁻⁷ in protection against bacterial infections. The increasing popularity of continuous catheter techniques for the treatment of both acute and chronic pain, including home treatment of cancer pain,⁸ has given rise to renewed speculation about infectious complications. We therefore studied the effect of two of the most common drugs used for epidural analgesia, bupivacaine and morphine, on the growth of 10 different microorganisms.

Material and Methods

The microorganisms tested were *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), and one of each of clinical isolates of *Staphylococcus epidermidis* (multi-resistant strain), *Staphylococcus epidermidis* (sensitive strain), *Streptococcus pneumoniae*, *Streptococcus pyogenes* (A), *Streptococcus*

faecalis, *Bacillus cereus*, and *Candida albicans*. The growth medium was Mueller-Hinton agar supplemented with 5% heated horse blood. The inoculum added per plate contained about 10⁵ colony forming units (CFU). The plates were examined after 18 h at 35° C. The result was scored negative if there was no visible growth on agar.

DRUGS

Bupivacaine hydrochloride was donated by Astra Pharmaceutical Company (Sodertalje, Sweden), and the concentrations tested were 0.5, 1.25, 2.5, and 5 mg/ml. Pure morphine hydrochloride was obtained from the pharmacy of the Helsinki University Central Hospital, and the concentrations tested were 0.2 and 2 mg/ml. Neither of the drugs contained any preservatives.

Results

Bupivacaine at 5 mg/ml inhibited the growth of all microorganisms tested, except for that of *P. aeruginosa* (table 1). At 2.5 mg/ml, bupivacaine still was able to inhibit the growth of *S. epidermidis* (sensitive strain), *S. pneumoniae*, and *S. pyogenes* (A), but 1.25 mg/ml had no effect. Morphine hydrochloride was totally ineffective at the concentrations tested. Morphine had no additional effect on the activity of bupivacaine when both drugs were tested in combination at their highest levels, 2 and 5 mg/ml, respectively.

Discussion

Kleinfeld and Ellis⁶ reported that 5 mg/ml tetracaine inhibited the growth of *C. albicans*, *S. epidermidis*, and *P. aeruginosa*. The latter strain of bacteria was, however, resistant to 20 mg/ml lidocaine and procaine,⁷ and to 5 mg/ml bupivacaine in the present study. Abouleish *et al.*,⁹ using 5 mg/ml bupivacaine or 20 mg/ml chloroprocaine for epidural or caudal analgesia, found no bacterial growth in the fluid from inside the catheter. Bupivacaine at 2.5 mg/ml has inhibited the growth of clinical isolates of *S. epidermidis* and *Corynebacterium pyogenes*.¹ In the present study, *S. pneumoniae* and *S. pyogenes* (A) also were inhibited, but at 1.25 mg/ml, a concentration also commonly used for continuous epidural

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TABLE 1. Effect of Bupivacaine Hydrochloride and Morphine Hydrochloride on the Growth of Nine Bacteria and *Candida albicans*. Evaluation after Incubation for 18 h at 35° C.

	Bupivacaine 1.25 mg/ml	Bupivacaine 2.5 mg/ml	Bupivacaine 5.0 mg/ml	Morphine 2.0 mg/ml	Bupivacaine 5.0 mg/ml + Morphine 2.0 mg/ml
<i>Staphylococcus aureus</i> (ATCC 25923)	+	+	-	+	-
<i>Staphylococcus epidermidis</i> (multi-resistant strain)	+	+	-	+	-
<i>Staphylococcus epidermidis</i> (sensitive strain)	+	-	-	+	-
<i>Streptococcus pneumoniae</i>	+	-	-	+	-
<i>Streptococcus pyogenes</i> (A)	+	-	-	+	-
<i>Streptococcus faecalis</i>	+	+	-	+	-
<i>Bacillus cereus</i>	+	+	-	+	-
<i>Escherichia coli</i> (ATCC 25922)	+	+	-	+	-
<i>Pseudomonas aeruginosa</i> (ATCC 27853)	+	+	+	+	+
<i>Candida albicans</i>	+	+	-	+	-

+ = growth; - = no growth.

analgesia, bupivacaine was ineffective. The mechanisms of the antibacterial and antifungal actions of local anesthetics are not known but probably are related to interactions with cell surface macromolecules and cellular membranes.^{10,11} Differences in cell membrane structure between *P. aeruginosa* and other bacteria[‡] may explain the above sensitive differences. Morphine at 2 mg/ml, a concentration regularly used in epidural pain control, did not affect microorganism growth. Drugs of the morphine series, levallorphan in particular, have inhibited the growth of *Escherichia coli*.¹² Morphine at its limit of solubility had no effect on the growth of this strain, however.¹² It is concluded that high clinical concentrations of local anesthetic solutions may provide some protection against bacterial and fungal infections. Any benefit derived from the antimicrobial activity of local anesthetics may be offset by the fact that local anesthetics are potent inhibitors of phagocytosis and leukocyte metabolism.¹³ However, after obtaining the results of the present study, when morphine is used for long-term intermittent epidural analgesia, we have considered it worthwhile filling the catheter with local anesthetic solution after each morphine injection to reduce the risk of intraluminal microorganism invasion.

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