Antimicrobial Effects of Dexmedetomidine and Midazolam in Bicarbonate Buffer: An *in vitro* Study

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Abstract

Objective: Dexmedetomidine and midazolam are commonly used sedatives, administered by infusion. The antibacterial properties of midazolam have been previously described. The aim of this *in vitro* study was to investigate the antimicrobial effects of dexmedetomidine, midazolam, and their solutions buffered with bicarbonate.

Methods: Using the disk diffusion and broth microdilution methods, antimicrobial efficacy was tested against *Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), Enterococcus faecalis (E. faecalis), Klebsiella pneumoniae (K. pneumoniae), Pseudomonas aeruginosa (P. aeruginosa), Staphylococcus epidermidis, Candida albicans*, and *Candida utilis*.

Results: Dexmedetomidine showed an inhibitory effect on *S. aureus, E. coli, E. faecalis*, and *P. aeruginosa* at concentrations of ≥64 µg/mL and above. The antimicrobial effect of midazolam on S. aureus, E. coli, E. faecalis, K. pneumoniae, and P. aeruginosa was observed at concentrations ≥128 mg/mL. We further noted that the antimicrobial potency of dexmedetomidine increased with the addition of bicarbonate; however, this was not observed with midazolam.

Conclusion: We found that adding bicarbonate to dexmedetomidine may be beneficial in preventing bacterial contamination, especially when treating patients in intensive care. Similar to midazolam, dexmedetomidine showed antimicrobial properties against a subset of infectious microorganisms frequently encountered in a hospital environment. Our experiments indicate that the concentration-dependent antimicrobial efficacy of dexmedetomidine can be further enhanced by buffering with bicarbonate.

Keywords: Dexmedetomidine, midazolam, buffering, bicarbonate, antimicrobial effect

Bikarbonat ile Tamponlanan Deksmedetomidin ve Midazolamın Antimikrobiyal Etkinliği: Deneysel Bir Çalışma

Öz

Giriş: Deksmedetomidin ve midazolam, infüzyon yoluyla yaygın olarak kullanılan sedatif ajanlardır. Midazolamın antibakteriyel etkinliği ile ilgili önceki çalışmalarda bilgiler mevcut olmaklabirlikte dexmedetomidinle ilgili bilgiler sınırlıdır. Bu in vitro çalışmanın amacı, deksmedetomidin, midazolam ve bunların bikarbonat ile tamponlanmış çözeltilerinin antimikrobiyal etkilerini araştırmaktır.

Yöntemler: Disk difüzyon yöntemi ve et suyu mikrodilüsyon yöntemi kullanılarak, *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus epidermidis, Candida albicans*, and *Candida utilis*'e karşı antimikrobiyal etkinlik test edildi.

Bulgular: Deksmedetomidin, *S. aureus, E. coli, E. faecalis* ve *P. aeruginosa* üzerinde 64 ug/mL ve üzerindeki konsantrasyonlarda inhibe edici etki göstermiştir. Midazolamın'ın *S. aureus, E. coli, E. faecalis, K. pneumoniae* ve P. *aeruginosa* üzerindeki antimikrobiyal etkisi ise, 128 mg/mL ve üzerindeki konsantrasyonlarda gözlendi. Ayrıca, deksmedetomidinin bikarbonat desteği ile antimikrobiyal potansiyelinin arttığı görülürken; midazolam'da bikarbonat eklenmesinin etkisi gösterilemedi.

Sonuç: Midazolam'a benzer şekilde, deksmedetomidinin, hastane ortamında sıkça karşılaşılan bulaşıcı mikroorganizmalara karşı antimikrobiyal özelliklere sahip olduğu gösterilmiştir. Özellikle yoğun bakım hastalarının tedavisi esnasında sedatif amaçla kullanılan deksmedetomidine bikarbonat eklenerek, bakteriyel kontaminasyondan korunulabilir. Deksmedetomidinin konsantrasyonuna bağlı olan antimikrobiyal etkinliğinin, bikarbonat ile tamponlama yoluyla daha da arttırılabileceği kanaatindeyiz.

Anahtar Sözcükler: Deksmedetomidin, midazolam, tamponlama, bikarbonat, antimikrobiyal etki

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Drugs can be contaminated with various microorganisms during preparation and infusion. In clinical practice, infusion of anesthetic agents is commonly performed in intensive care units (ICUs) for sedation via venous catheters [1]. There are several studies on the clinical significance of bacterial and fungal con-

tamination of anesthetic agents administered by continuous infusion [2, 3].

Midazolam and dexmedetomidine are widely used for anesthesia and/or sedation. While several anesthetic agents may cause systemic bacteremia and wound infections as a result of being contaminated with microorganisms or through immunosuppression [2-4], a few agents have been reported to inhibit microorganisms and their growth [1, 5, 6].

Midazolam is a water soluble benzodiazepine with a pH of 3.0–4.0, and it contains antimicrobial preservative agents [1]. Keles et al. [7] reported that the preservative content and pH value of midazolam add to the antimicrobial properties of midazolam. Dexmedetomidine, a selective alpha 2-receptor agonist, is widely used for sedation by infusion in ICU patients. Dexmedetomidine, which does not contain preservatives, has a pH of 4.5–7.0 and is water soluble [8].

There are several studies hinting at enhanced antibacterial activities of local anesthetics that are buffered with bicarbonate [9, 10]. Thus, we examined if a similar elevated antimicrobial potency could be achieved by buffering midazolam and dexmedetomidine with bicarbonate.

To the best of our knowledge this study is the first to analyze the antibacterial efficacy of buffered midazolam and dexmedetomidine. We aimed to evaluate the antimicrobial efficacy of midazolam, dexmedetomidine, and their solutions buffered with bicarbonate against microorganisms frequently encountered in a hospital environment.

Material and Methods

This study started in the university biology laboratory after informing to the Adnan Menderes University ethic committee about *in vitro* study.

Microbial strains

The antibacterial efficacy and the minimum inhibition concentrations (MICs) of midazolam, dexmedetomidine, and their buffered combinations with bicarbonate were determined using the following standard strains: *Escherichia coli* (*E. Coli*, ATCC 25922); *Staphylococcus aureus* (*S. aureus*, ATCC 25923); *Enterococcus faecalis* (*E. faecalis*, ATCC 29212); *Klebsiella pneumoniae* (*K. pneumoniae*, ATCC 13882); *Pseudomonas aeruginosa* (*P. aeruginosa*, ATCC 27853); *Staphylococcus epidermidis* (*S. epidermis*, ATCC 12228); *Candida albicans* (*C. albicans*, ATCC 10231), *and Candida utilis* (*C. utilis*, ATCC 9950).

Drugs

This study used dexmedetomidine hydrochloride (Precedex, Abbott, Rocky Mount, NC, USA) and midazolam (Demizolam, Aktavis, Levent, Istanbul). Sodium bicarbonate was added to these agents to make up solutions with a final concentration of 25, 50, and 100 mEq/L. The pH values of all formed sedative solutions were measured by a pH meter.

Disk diffusion method

Antibacterial and antifungal susceptibility screening was performed using 6 mm sterile antibiotic disks according to the standard Antimicrobial Disk Susceptibility Tests procedure determined by the National Committee for Clinical Laboratory Standards [11]. The inoculum suspensions of bacteria and yeast tested for susceptibility were prepared from broth cultures (24 h), the turbidity of which was set equivalent to a 0.5 McFarland standard. The 10^{-8}/mL bacterial cells and 10^{-6}/mL yeast cells concentrations were generated. To test the antimicrobial activity of midazolam, dexmedetomidine, and their buffered combinations with bicarbonate, a Mueller–Hinton agar plate was first inoculated with the 0.1 mL broth culture of bacteria or yeast. Thereafter, a hole that was 6 mm wide and deep was made with a sterile swab and filled with 50 µL of the drug solution tested. Plates inoculated with *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), *E. faecalis* (ATCC 29212), *K. pneumoniae* (ATCC 13882), and *P. aeruginosa* (ATCC 27853) were incubated at 37°C for 24 h, while those inoculated with *C. albicans* (ATCC 10231) and *C. utilis* (ATCC 9950) were incubated at 30°C for 24 h. All experiments were performed under aseptic conditions. Six disks containing each drug were used to test each microbe for sensitivity. The diameter of the inhibition zone was measured in millimeters. Disks of gentamycin (CN10, Oxoid) for bacteria and nystatin (NS100) for yeasts were used as positive controls. The inhibition zones were compared with positive and negative reference disks. Negative controls without gentamicin and nystatin in the plates were done at the same time periods and under same incubation conditions.

Dilution method

The broth dilution method was also used to screen for antibacterial and antifungal sensitivity and was carried out through the procedure outlined in the *Manual of Clinical Microbiology*.

Initially, the bacterial and yeast strains were grown in nutrient broth (30–37°C for 24 h) and malt extract broth (30°C for 48 h), respectively. Midazolam and its buffered combinations with bicarbonate (25, 50, and 100 mEq/L) were diluted with cation-adjusted Mueller–Hinton broth (CAMHB) to the final concentrations of 512 $\mu g \cdot mL^{-1}$, 256 $\mu g \cdot mL^{-1}$, 128 $\mu g \cdot mL^{-1}$, 64 $\mu g \cdot mL^{-1}$, 32 $\mu g \cdot mL^{-1}$, 16 $\mu g \cdot mL^{-1}$, 8 $\mu g \cdot mL^{-1}$, 4 $\mu g \cdot mL^{-1}$, 2 $\mu g \cdot mL^{-1}$, and 1 $\mu g \cdot mL^{-1}$. Similarly, dexmedetomidine hydrochloride

and its buffered combinations with bicarbonate (25, 50, and 100 mEq/L) were diluted with CAMHB to final concentrations of 128 μg·mL^{-1}, 64 μg·mL^{-1}, 32 μg·mL^{-1}, 16 μg·mL^{-1}, 8 μg·mL^{-1}, 4 μg·mL^{-1}, 2 μg·mL^{-1}, and 1 μg·mL^{-1}.

To prepare the broth microdilution panels, 0.1 ml of microbial broth containing each anesthetic concentration mentioned above was dispensed into the sterile wells of microdilution trays. Further, 0.1 ml of each microbial broth without anesthetics was used as a negative control, while bacterial broth treated with streptomycin and yeast broth treated with fluconazole were used as a positive control. Test cultures were incubated at 37°C (24 h). The lowest concentration of antimicrobial agent that resulted in complete inhibition of the microorganisms was represented as MIC (μg·mL^{-1}). In each case, the test was performed 10 times, and the results were expressed as means.

Statistical Analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences version 20 (IBM Corp., Armonk, NY, USA). Results are expressed as the mean and standard deviation. For each microorganism, the Kruskal–Wallis test was applied as a non-parametric test to evaluate the effect of inhibition of drug concentrations. Tamhane's post-hoc analyzes were used as post-hoc test to find out the concentration that caused the difference. A p value<0.05 was considered statistically significant.

Table 1. Diameters of inhibition zones of dexmedetomidine, its buffered combinations with bicarbonate on bacterial plates (mm).

	Dex 100μg.ml^{-1}	Dex 100μg.mL^{-1} +$NaHCO_3$ 25mEq/L	Dex 100μg.mL^{-1} +$NaHCO_3$ 50mEq/L	Dex 100μg. mL^{-1} +$NaHCO_3$ 100mEq/L	CN10	NS100	p
E. coli	12±1.6	14 ±1.3	11±1.5	11±1.3	21	NA	0.013*
S. aureus	12±1.8	13±2.4	12±1.6	12±1.7	20	NA	0.022*
E. feacalis	13±1.7	15±2.5	15±2.1	0	11	NA	0.021*
K. pneumonia	0	0	0	0	19	NA	-
P. aeruginosa	10±1.5	10±1.8	0	0	20	NA	0.035*
S. epidermidis	0	0	0	0	17	NA	-
C. albicans	0	0	0	0	NA	22	-
C. utilis	0	0	0	0	NA	21	-

MIC: Minimal Inhibitory Concentration; Dex: Dexmedetomidine: CN10: Gentamycin; NS100: Nystatin; $NaHCO_3$: Bicarbonate; NA: Non-assessed
*:p<0.05

Table 2. The MIC values of dexmedetomidine and its buffered combinations with bicarbonate on microorganisms

	Dex 100μg. mL^{-1}	Dex 100μg.mL^{-1} +$NaHCO_3$ 25mEq/L	Dex 100μg.mL^{-1} +$NaHCO_3$ 50mEq/L	Dex 100μg.mL^{-1} +$NaHCO_3$ 100mEq/L	CN10	NS100
E. coli	64	32	32	32	64	NA
S. aureus	64	32	32	32	32	NA
E. feacalis	128	32	64	-	64	NA
K. pneumonia	-	-	-	-	64	NA
P. aeruginosa	64	32	-	-	64	NA
S. epidermidis	-	-	-	-	64	NA
C. albicans	-	-	-	-	NA	64
C. utilis	-	-	-	-	NA	64

MIC: Minimal Inhibitory Concentration; Dex: Dexmedetomidine: CN10: Gentamycin; NS100: Nystatin; $NaHCO_3$: Bicarbonate; NA: Non-assessed
*:p<0.05

Results

The diameters of the inhibition zones and MIC values of test solutions containing dexmedetomidine are presented in Tables 1 and 2, respectively. In this study, dexmedetomidine has shown an inhibitory effect on *S. aureus, E. coli, E. faecalis, and P. aeruginosa* at concentrations ≥64 µg/mL. The contribution of bicarbonate to the inhibitory effect of dexmedetomidine on microorganisms was also determined. We also noted that *K. pneumoniae, S. epidermidis, C. albicans,* and *C. utilis* were not inhibited by dexmedetomidine and its solutions buffered with bicarbonate.

The diameters of the inhibition zones and MIC values of test solutions containing midazolam are presented in Tables 3 and 4, respectively. The inhibitory effect of midazolam on *S. aureus, E. coli, E. faecalis, K. pneumoniae*, and *P. aeruginosa* was observed at concentrations ≥128 µg/mL. Contrary to this finding, midazolam had no antimicrobial effect on *S. epidermidis, C. albicans,* and *C. utilis*. Further, it was observed that the antimicrobial potency of midazolam was not enhanced by the addition of bicarbonate, as the MIC values showed no change in favor of the antimicrobial effect.

The mean pH values of midazolam and dexmedetomidine were 3.98 and 6.63, respectively. The mean pH values of buffered midazolam and dexmedetomidine solutions with bicarbonate (25, 50, and 100 mEq/L) were 7.33 and 8.68, respectively.

Table 3. Diameters of inhibition zones of midazolam, its buffered combinations with bicarbonate on bacterial plates (mm).

	Mid 1mg.mL^{-1}	Mid1mg.mL^{-1} +$NaHCO_3$ 25 mEq/L	Mid1mg.mL^{-1} +$NaHCO_3$ 50 mEq/L	Mid1mg.mL^{-1} +$NaHCO_3$ 100 mEq/L	CN 10	NS100	p
E. coli	0	10 ±1.3	0	0	21	NA	0.021*
S. aureus	14±1.2	14±1.4	13±1.5	14±1.4	20	NA	0.003*
E. feacalis	17±1.6	12±2.4	10±1.9	0	11	NA	0.018*
K. pneumonia	12±1.8	13±2.1	13±1.7	13±2.0	19	NA	0.025*
P. aeruginosa	14±2.2	11±1.6	1±0.4	1±0.3	20	NA	0.032*
S. epidermidis	0	0	1±0.3	1±0.4	17	NA	0.684
C. albicans	0	0	0	0	NA	22	-
C. utilis	0	0	0	0	NA	21	-

Data are presented as mean±SD. Mid: Midazolam; CN10: Gentamycin; NS100: Nystatin; $NaHCO_3$: Bicarbonate . NA: Non-assessed
*:p<0.05

Table 4. The MIC values of midazolam and its buffered combinations with bicarbonate on microorganisms

	Mid 1mg.mL^{-1}	Mid1mg.mL^{-1} +$NaHCO_3$ 25 mEq/L	Mid1mg.mL^{-1} +$NaHCO_3$ 50 mEq/L	Mid1mg.mL^{-1} +$NaHCO_3$ 100 mEq/L	CN10	NS100
E. coli	256	-	-	-	64	NA
S. aureus	128	256	512	512	32	NA
E. feacalis	128	128	128	-	64	NA
K. pneumonia	256	512	512	-	64	NA
P. aeruginosa	512	512	-	-	64	NA
S. epidermidis	-	-	-	-	32	NA
C. albicans	-	-	-	-	NA	64
C. utilis	-	-	-	-	NA	64

MIC: Minimal Inhibitory Concentration; Mid: Midazolam: CN10: Gentamycin; NS100: Nystatin; NaHCO3: Bicarbonate; NA: Non-assessed
*:p<0.05

Discussion

Dexmedetomidine and midazolam are effective sedating agents used for long-term sedation in ICUs. Recently, the use of both drugs has increased in anesthesia practice [12, 13]. However, the caveat of using these drugs is that they are susceptible to contamination by microorganisms during preparation and dilution for infusion [2, 3]. In the present study, we found that diluted midazolam solutions without bicarbonate had an inhibitory effect on *S. aureus, E. coli, E. faecalis, K. pneumoniae, and P. aeruginosa.* At a concentration of 512 µg/ml, midazolam effectively inhibited all microorganisms except *S. epidermidis, C. albicans,* and *C. utilis*. Buffering midazolam with bicarbonate was shown not to contribute its antimicrobial efficacy. The other agent, dexmedetomidine, was found to inhibit *S. aureus, E. coli, E. faecalis*, and *P. aeruginosa* at a concentration of 128 µg/mL. However, a similar antimicrobial sensitivity was not detected when they were tested against *K. pneumoniae, S. epidermidis, C. albicans, and C. utilis*. Finally, unlike our observation with midazolam, solutions of dexmedetomidine buffered with bicarbonate showed improved potency and antimicrobial efficacy.

Several previous studies have investigated the antimicrobial effects of prevalent anesthetic agents; however, there is a lack of clarity and understanding of their mode of action. Antimicrobial effects of some anesthetics have been shown to be dependent on pH, molecular weight, thermodynamic activity, and interaction between the cytoplasmic membrane and macromolecule [14-17].

Gudmundsson et al. [11] reported that an acidic pH has an overall deleterious effect on the activity of antibiotics against *P. aeruginosa* and *E. coli*. The study demonstrated that MIC was higher and the bactericidal rate was lower at the pH 5 than at a more alkaline pH value. The bactericidal properties of thiopentone are thought to be associated with a pH as high as 10.53 [15]. The pH value of midazolam was reported 3.0–4.0 and that of dexmedetomidine 4.5–7.0 [1, 6]. In this study, the mean pH value of dexmedetomidine was found to be 6.63, while the mean pH value of the midazolam was found to be 3.98. As a result of the buffering of both anesthetic drugs, the mean pH values increased to 7.33 for midazolam and to 8.68 for dexmedetomidine. Pathogenic bacteria generally colonize at pH values ranging from 6 to 8 [6, 7, 16]. Therefore, strong bases and acids may prevent microbial growth [7, 15]. Keles et al. [7] reported that the antimicrobial effect of midazolam resulted from HCl, which was used as a preservative. The reduction of acidic properties by buffering midazolam could perhaps cause the pH value to become suitable for microbial growth. As for dexmedetomidine, buffering may have contributed to an improved antimicrobial activity since the pH value becomes more alkaline than the average pH.

There are very few studies related to the antimicrobial effect of dexmedetomidine [6, 7]. Ayoglu et al. [6] demonstrated that *in vitro*, dexmedetomidine has antibacterial effects on *E. coli, P. aeruginosa, S. aureus,* and *E. faecalis.* On the contrary, Keles et al. [7] suggested that dexmedetomidine had no antimicrobial effect on *A. baumanni, P. aeruginosa, E. coli,* and *E. coli ESBL*. Our study has shown that dexmedetomidine has an antimicrobial effect on *S. aureus, E. faecalis, E. coli,* and *P. aeruginosa,* which are frequently found in ICU environment. We also noted that despite its antimicrobial role, dexmedetomidine did not have an inhibitory effect on *K. pneumoniae, S. epidermidis, C. albicans,* and *C. utilis*. Together, our findings highlight the significance and importance of the addition of bicarbonate to dexmedetomidine toward improving its antimicrobial potency.

Durak et al. [18] reported that the inhibitory effect of midazolam on *S. aureus* and *E. faecalis* was only at a concentration of 0.225 mg/mL. In the ICU setting, midazolam is usually used in highly diluted forms for infusion, and thus, more dramatic results are expected when tested at higher concentrations [6]. However, the midazolam and dexmedetomidine concentrations we used in our study were based on clinical application. Dexmedetomidine and midazolam were found to have concentration-dependent antimicrobial effects. These drugs in clinical usage may not produce a systemic antibacterial effect, but their antibacterial effects may be useful in terms of preventing microbial contamination during the preparation of infusion solutions.

Dexmedetomidine is usually initiated by loading infusion for 10 minutes (1 µg/kg), followed by maintenance with low-dose infusion (0.2 to 0.7 µg/kg/h). To prepare an infusion solution at a low infusion rate and low concentration, this drug is diluted in a certain proportion (4 µg/mL) [19]. According to our results, this final concentration has no *in vitro* antibacterial properties. Therefore, it can be said that preparing the solution at a concentration ≥64 µg/mL is more effective in terms of antibacterial activity.

To the best of our knowledge, this is the first study to investigate the antibacterial effect of buffered dexmedetomidine and midazolam. Dexmedetomidine does not include any preservatives, and its pH may permit microbial growth [20]. In our opinion, adding bicarbonate to dexmedetomidine may be beneficial in preventing microbial contamination, especially when treating patients in ICUs.

In conclusion, we demonstrated that dexmedetomidine has antimicrobial properties similar to midazolam on some microorganisms frequently encountered in a

hospital environment. Our study also shows that the concentration-dependent antimicrobial efficacy can be further enhanced by buffering with bicarbonate.

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