TÜBİTAK

ORIGINAL ARTICLE

Turk J Med Sci
2007; 37 (1): 7-10
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E-mail: medsci@tubitak.gov.tr

Comparison of the Antibacterial Effects of Two Local Anesthetics: Lidocaine and Articaine*

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Aim: The antibacterial effect of lidocaine has been studied widely, but the effect of articaine has not yet been evaluated. We aimed to investigate whether commercially available articaine possesses bactericidal or bacteriostatic effect in comparison with lidocaine in a prospective laboratory setting.

Materials and Methods: The antibacterial effects of articaine and lidocaine were studied on *Pseudomonas aeruginosa* ATCC27853, *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC35218, and *Proteus mirabilis* ATCC7002 strains and a patient isolate of *Serratia marcescens*. For this study, 2% lidocaine HCl and articaine HCl were diluted to 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156, and 0.078 mg ml^{-1} concentrations to determine the antibacterial effect. All bacterial strains were inoculated to 2 ml antibiotic broth at a concentration of $5X10^5$ m^{-1} for each well. For each bacterial strain, minimal bactericidal concentration (MBC) was evaluated by inoculating the content of wells onto blood agar plates and incubating for 24 hours.

Results: MBC was detected for both of the local anesthetics. Although articaine showed bacteriostatic effect on all bacterial strains, two of five strains were resistant to lidocaine.

Conclusions: The finding of articaine's bacteriostatic effect against all bacterial strains might be an evidence for its antibacterial use.

Key Words: Local anesthetics, articaine, lidocaine, infection, bactericidal

İki Lokal Anesteziğin Antibakteriyal Etkilerinin Karşılaştırılması: Lidokain ve Artikain

Amaç: Lidoakainin antibakteriyal etkisi çok iyi araştırılmıştır, fakat artikainin etkisi henüz değerlendirilmemiştir. Biz artikainin ticari formunun lidokainle kıyaslandığında bakterisit ya da bakteriostatik etkisini prospektif olarak araştırmayı amaçladık.

Materyal ve Metot: Lidokain ve artikainin antibakteriyal etkisi *Pseudomonas aeruginosa* ATCC27853, *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC35218, *Proteus mirabilis* ATCC7002 suşları ve hastadan izole edilen *Serratia marcescens* üzerinde araştırıldı. Bu çalışma için %2 lidokain HCl ve artikain HCl antibakteriyal etkiyi belirlemek için 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156 ve 0.078 mg ml^{-1} konsantrasyonlarına dilüe edildi. Tüm bakteri suşları her kuyucuk için $5X10^5$ ml^{-1} konsantrasyon içeren 2 ml antibiyotik broth ile inoküle edildi. Herbir bakteri için minimum bakterisit konsantrasyon (MBK) kuyucuk içerikleri kanlı agarda 24 saat inkübe edilerek saptandı.

Bulgular: Her iki lokal anestezik için de MBK belirlendi. Artikain bu araştırmadaki tüm bakteri suşlarına karşı bakteriostatik etki göstermesine rağmen, beş suştan ikisi lidokaine karşı dirençli bulundu.

Sonuç: Artikainin tüm bakteri suşlarına karşı baktriostatik olması bulgusu antibakteriyal kullanımı için bir ipucu olabilir

Anahtar Sözcükler: Lokal anestezikler; artikain, lidokain, enfeksiyon; bakterisit

Received: August 23, 2005
Accepted: March 13, 2006

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Introduction

Local anesthetics occupy an important place in anesthesiology and dentistry (1-3). Articaine, one of the most widely used local anesthetic, especially in dentistry, has been occasionally preferred in regional anesthesia (4,5). However, it has recently been shown that hyperbaric articaine hydrochloride was suitable for day-case spinal anesthesia (6).

Some of the drugs used in anesthesiology practice might exhibit potential for unusual clinical uses apart from their known mechanism of action. In this respect, ketamine's

* Presented at the XXIIIth European Society of Regional Anaesthesia and Pain Therapy Congress, Greece, 2004. Reg Anesth Pain Med 2004; 29(5) (Suppl 2): 102.

antibacterial effect was determined (7). The underlying mechanism is still unknown but it could be explained by ketamine's local anesthetic activity in animals (8). Beyond their anesthetic and analgesic properties, an antibacterial effect has been demonstrated for local anesthetics like lidocaine, bupivacaine and ropivacaine (9-13). To our knowledge, there has been no study demonstrating the antibacterial effect of articaine. Therefore, we aimed to investigate the antibacterial effect of articaine on some of the bacteria that may cause nosocomial infections, and we compare the results with those of lidocaine.

Materials and Methods

Bacterial Strains

Five bacterial strains (*Pseudomonas aeruginosa* ATCC27853, *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC35218, *Proteus mirabilis* ATCC7002 and *Serratia marcescens* patient isolate) were included in this study. The strains were grown on blood agar plates for 24 hours (h) at 35 °C prior to the antibacterial assay.

Antibacterial Assay

The effect of the drugs on bacterial growth was determined by broth microdilution method. The test medium used was antibiotic broth (Merck-Germany) for all bacteria. In this study 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156 and 0.078 mg ml^{-1} concentrations of local anesthetics were tested. Aliquots (100 µl) of inoculated double strength test media were added into micro plate wells that already contained increasing concentrations of drug preparations in 100 µl sterile distilled water. All bacterial strains were inoculated to 2 ml antibiotic broth. After a 2 h incubation at 35 °C, growth was measured by spectrophotometer (Shimadzu-UV1201, Japan). The densities of microorganisms were prepared according to 0.5 Mc Farland. Uninoculated test medium was used to blank the spectrophotometer. Final bacterial concentrations were adjusted to $5x10^5$ ml^{-1} for each well. Positive control (bacteria and growth media) and negative control (growth media) were used for each test. For each organism, bacteriostatic effect was defined by minimum inhibitory concentration (MIC) and bactericidal effect was defined as minimum bactericidal concentration (MBC). After an incubation of 18 h at 35 °C, MIC values of local anesthetics were noted. To determine the MBC, each well exhibiting no visible growth (viability) after 18 h was tested for viable organisms by subculturing 10 µl samples of each well onto blood agar. The plates were incubated at 35 °C to observe the growth of any colony after 24 h (14).

Drugs

Commercially available solutions of lidocaine hydrochloride (Jetokain Simplex 2%, Adeka, Turkey) and articaine hydrochloride (Ultracain 2% ampul, Aventis, Turkey) without preservative were diluted with sterile distilled water to produce study concentrations. The pH values of lidocaine and articaine at 10^{-3} M concentration were 7.34.

Results were expressed as visible bacterial growth observed or not.

Results and Discussion

The antibacterial effects of the local anesthetics are shown in Table.

Regarding all studied concentrations, articaine inhibited growth of all bacteria included in this study (*P. aeruginosa*, *S. marcescens*, *P. mirabilis*, *S. aureus* and *E. coli*). No visible growth was observed (Table).

P. aeruginosa and *S. aureus* were found to be resistant to lidocaine. *E. coli* had an MIC value of 5 mg ml^{-1}. *E. coli*, *S. marcescens* and *P. mirabilis* were shown to be equally sensitive to lidocaine and articaine (Table).

MBC values were not detected with either of the local anesthetic agents in any of the bacterial strains at the concentrations studied.

In the present study, the bacteriostatic effects of commercially available articaine and lidocaine have been shown. We observed that articaine was shown to have bacteriostatic effect against all bacteria included in this study, whereas lidocaine was found to be bacteriostatic against all except *P. aeruginosa* and *S. aureus* at all concentrations studied. The bacteriostatic effects of lidocaine and articaine were equal for *E. coli*, *S. marcescens* and *P. mirabilis*, but bacteriostatic effect appeared at 5 mg ml^{-1} for *E. coli*.

The antibacterial effect of lidocaine was well established when combined with propofol and bicarbonate buffer (9,15). It has also been shown that antibacterial effect was

Table. The effect of different concentrations of lidocaine and articaine on five bacterial strains (MIC values).

Bacterial Strains	Lidocaine HCl Concentration (mg ml^{-1})								Articaine HCl Concentration (mg ml^{-1})							
	0.078	0.156	0.312	0.625	1.25	2.5	5	10	0.078	0.156	0.312	0.625	1.25	2.5	5	10
P. Aeruginosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-*
E. Coli	+	+	+	+	+	+	-*	-	+	+	+	+	+	+	-*	-
P. Mirabilis	+	+	+	+	+	+	+	-*	+	+	+	+	+	+	+	-*
S. Aureus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-*
S. Marcescens	+	+	+	+	+	+	+	-*	+	+	+	+	+	+	+	-*

+: Visible growth was observed
-: No visible growth was observed
*: MIC values

observed when lidocaine was used in bronchoalveolar lavage fluid and tumescent liposuction (16,17). With respect to the bacterial strains we studied, it has been reported that lidocaine 2% had both bacteriostatic and bactericidal effect against *S. marcescens*. However, lidocaine 1% and 0.6% were found to be bactericidal and bacteriostatic for *E. coli*, respectively. As for *S. aureus*, lidocaine 2% and 0.2% were bactericidal and bacteriostatic, respectively (9). Although we used lidocaine 2% corresponding to 20 mg ml^{-1} in our study, it became diluted in the media and resulted in a concentration of 10 mg ml^{-1} corresponding to 1% at the final concentration. Therefore, we observed only bacteriostatic effect with lidocaine 1% against *S. marcescens*, which was half of the effect demonstrated by Gajraj et al. (9). Similarly, we observed bacteriostatic effect at 10 mg ml^{-1} for *S. marcescens*. Our finding for *E. coli* was similar regarding the bacteriostatic effect with lidocaine 0.5%, which was observed at the half concentration.

Olsen et al. (16) demonstrated that lidocaine decreased the viable S. pneumoniae but not *P. aeruginosa* in bronchoalveolar lavage fluid, which simulates clinical conditions better than laboratory studies. In contrast to that study, we used bacterial growth media. The measured pH of the growth media was between 7.2-7.4 and the two local anesthetics had the same pH value of 7.34. Therefore, the discrepancy in the lidocaine results between the studies could be due to the different study protocols.

The therapeutic plasma concentration of lidocaine has been reported to be 1-5.6 µg ml^{-1} (18), and the mean maximum plasma concentration of articaine after submucosal injection in dentistry is 580 µg l^{-1} (5). With respect to plasma concentrations, the present bacteriostatic effects of lidocaine and articaine were much higher than clinical plasma concentrations.

Mullin and Rubinfeld (19) demonstrated that commercially available preserved topical local anesthetics (proparacaine, tetracaine and cocaine) used commonly in ophthalmology exhibited antibacterial effect in vitro on *S. aureus* and *P. aeruginosa*, which are commonly isolated from ophthalmic cultures. Since higher plasma concentrations can be achieved generally at or near the site of injection, lidocaine and articaine should be used as a local anesthetic in case of anticipated antibacterial effect. In contrast to plasma concentrations of the two local anesthetics, when the commercially available concentrations (2% for both drugs in the present study) were taken into account, the results of this study might provide evidence for the antibacterial effect observed in clinical conditions.

We preferred to study these bacterial strains because they have been the most commonly encountered pathogens in the setting of nosocomial infections. It also allowed for a comparison with the results reported by Gajraj et al. (9). In the current study, we did not observe any bactericidal effect in any of the bacterial strains. Regarding the bacteriostatic and bactericidal effects of lidocaine in Gajraj et al.'s (9) study, bacteriostatic and bactericidal concentrations of lidocaine against *S. marcescens* were the same (20 mg ml^{-1}), and the concentration difference between bacteriostatic (0.2%, 2 mg ml^{-1}) and bactericidal (2%, 20 mg ml^{-1}) effect was 1/10, but for *E. coli* this was 1/2. Though the highest concentration we studied was 10 mg ml^{-1}, bactericidal effect was not observed against *E. coli* with either of the local anesthetics.

After lidocaine's inhibitory and bactericidal activity against a variety of organisms responsible for nosocomial infections had been confirmed, potential application of lidocaine in the treatment of open wounds colonized or infected with antibiotic-resistant bacteria was recommended by Parr et al. (20). In this respect, further studies confirming articaine's antibacterial activity against different organisms might open a new window for unusual clinical uses.

Although the underlying mechanism of the antibacterial effect of local anesthetics is not yet clearly understood, we assume that it might be mediated via inhibition of cell wall synthesis or distortion of function of cytoplasmic membrane by the local anesthetics. Additionally, lidocaine's membrane-stabilizing property was known to have potent antimicrobial activity that might compromise the growth of bacterial microorganisms (21).

Our study involved only aerobic bacterial strains. Therefore, further studies might be done with anaerobic strains for comparison. We used commercial forms of local anesthetics without preservatives for this study because of the necessity of investigating their possible antibacterial effect if used in clinical practice.

Consequently, bacteriostatic effect was shown for both lidocaine and articaine. Since this is the first study in which articaine showed a more favorable bacteriostatic effect than lidocaine, our results might provide experimental support for investigating the potential benefit of using articaine beyond its conventional anesthetic and analgesic role in different indications, particularly where antibacterial effect is anticipated.

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