

3η ΔΗΜΟΣΙΑ ΔΙΑΒΟΥΛΕΥΣΗ

ΤΕΧΝΙΚΕΣ ΠΡΟΔΙΑΓΡΑΦΕΣ ΕΛΑΣΤΟΜΕΡΙΚΩΝ ΑΝΤΛΙΩΝ ΠΟΛΛΑΠΛΩΝ ΡΟΩΝ ΓΙΑ ΜΤΧ

ΑΝΑΛΓΗΣΙΑ

1. Φορητή αντλία με ελαστομερές μπαλόνι από πολυίσοπρένιο, μιας χρήσης εφοδιασμένη με μηχανισμό ακριβείας, πολλαπλών ταχυτήτων ροής 5-7-12ml/hr που είναι απαραίτητη για την επισκληρίδια οδό χορήγησης, χωρητικότητας 240ml, μέγιστης χωρητικότητας 300ml, κατάλληλη για διάρκεια χορήγησης 20 έως 48 ωρών.
2. Ο αυλός χορήγησης να είναι προσυνδεδεμένος στο σώμα της αντλίας και να είναι απαλλαγμένος από φθαλικά (DEHP-free)».

Η αντλία να διαθέτει ειδικό κλειδί ρύθμισης της ροής για αποφυγή παρέμβασης του ασθενούς στην ταχύτητα ροής. Το περίβλημα της συσκευής να είναι από σκληρό υλικό, ώστε να αποφεύγεται η συμπίεση του θαλάμου υποδοχής του φαρμάκου. Να λειτουργεί με τη διαφορά πίεσης που ασκεί ο θάλαμος υποδοχής του φαρμάκου (το μπαλόνι) στη διάμετρο του ρυθμιστή ροής. Να διαθέτει εσωτερικό φίλτρο σωματιδίων (πλήρως κλειστό κύκλωμα) το οποίο κατακρατεί τις φυσαλίδες και είναι απαραίτητα να μην εισχωρούν στη δεξαμενή υγρού.
3. Η οδός πλήρωσης να φέρει ανεπίστροφη βαλβίδα. Το σύστημα να μην φέρει διακόπτες ή μέσα τα οποία μπορεί να διακόψουν τη ζητούμενη ροή του φαρμάκου. Ο ρυθμιστής ροής να βρίσκεται στο άκρο του αυλού χορήγησης γιατί με αυτόν τον τρόπο διασφαλίζεται η κατακράτηση μεγάλων φυσαλίδων στον αυλό. Να διαθέτει αποστειρωμένη συσκευασία, σήμανση CE, αναγραφή παρτίδας.
4. Να υπάρχει δείκτης διαβάθμισης έγχυσης για την συνεχή παρακολούθηση της έγχυσης. Η αντλία να είναι κατάλληλη για τη χορήγηση φαρμάκων, όπως αντιβιοτικών, αναλγητικών, φαρμάκων αποσιδήρωσης, χημειοθεραπευτικών κ.α. Να διατίθεται η σχετική πιστοποίηση συμβατότητας για τα σκευάσματα των παραπάνω κατηγοριών. Βεβαίωση της κατασκευάστριας εταιρείας που θα δηλώνει ότι το υλικό κατασκευής των αντλιών δεν απορροφά ποσότητα από τα χρησιμοποιούμενα φάρμακα έτσι ώστε να επηρεάζεται η συγκέντρωση του διαλύματος.



ΒΙΟΠΡΟΜΗΘΕΥΤΙΚΗ ΕΠΕ

Η εταιρεία μας θέτει βάσει επιστημονικών άρθρων, κλινικών μελετών και Παγκόσμιων & Ευρωπαϊκών Κατευθυντήριων Οδηγιών τις παρακάτω Παρατηρήσεις –Προβληματισμούς.

Ως προς τις Ειδικές Τεχνικές Προδιαγραφές.

1) Στην προδιαγραφή "Φορητή αντλία με ελαστομερές μπαλόνι από πολυισοπρένιο, μιας χρήσης εφοδιασμένη με μηχανισμό ακριβείας, πολλαπλών ταχυτήτων ροής 5-7-12ml/hr, χωρητικότητας 240ml, μέγιστης χωρητικότητας 300ml, κατάλληλη για διάρκεια χορήγησης 20 έως 48 ωρών".

- i. Ως προς την προδιαγραφή «ελαστομερές μπαλόνι από πολυισοπρένιο»: Θα θέλαμε να αντικατασταθεί η φράση «από πολυισοπρένιο» με τη φράση από «πολυισοπρένιο ή σιλικόνη» καθώς έτσι επιτυγχάνεται η ανάπτυξη υγιούς ανταγωνισμού από περισσότερες από μία εταιρείες. (έως σήμερα μία μόνο εταιρεία εμφανίζεται με ελαστομερές μπαλόνι από πολυισοπρένιο). Επίσης στην μελέτη την οποία επισυνάπτεται δεν υπάρχει σαφής και ξεκάθαρη αναφορά για σύγκριση στα αποτελέσματα από την χρήση ελαστομερικών αντλιών με μπαλόνι από πολυισοπρένιο σε σχέση με ελαστομερείς με μπαλόνι από σιλικόνη.

ΑΠΑΝΤΗΣΗ ΣΤΟ ΠΑΡΑΠΑΝΩ ΣΧΟΛΙΟ

Ως προς την προδιαγραφή «ελαστομερές μπαλόνι από πολυισοπρένιο»: η φράση «από πολυισοπρένιο» είναι απαραίτητη προκειμένου να αποκλεισθούν οι αντλίες με σιλικόνη. Επιτυγχάνεται η ανάπτυξη υγιούς ανταγωνισμού διότι περισσότερες από μία εταιρείες προσφέρουν αντλίες με ελαστομερές μπαλόνι από πολυισοπρένιο.

Επίσης στην μελέτη την οποία επισυνάπτεται υπάρχει σαφής και ξεκάθαρη αναφορά για τα μειωμένης απόδοσης αποτελέσματα από την χρήση ελαστομερικών αντλιών με μπαλόνι από σιλικόνη.

Local Anesthetics Adsorbed onto Infusion Balloon

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We compared the adsorption of different local anesthetics onto infusion balloons and studied one of the possible mechanisms for adsorption. After injection of lidocaine, bupivacaine, ropivacaine, and mepivacaine solutions (1 mM each, pH 7.4) into balloons of 100-mL volume, their concentrations in effluents flowing out at 4 mL/h were determined over time by high-performance liquid chromatography. All were adsorbed in a structure-dependent manner, and the concentration decreased by 0%–34% within 5 min. Bupivacaine was most strongly adsorbed, followed by lidocaine, ropivacaine, and mepivacaine. QX-314, a quaternary ammonium derivative of lidocaine, was

only weakly adsorbed compared with the parent compound lidocaine. The extent of adsorption of local anesthetics was related to their hydrophobicity (evaluated by reversed-phase chromatography) and was much more at pH 7.4 than at pH 6.0. A hydrophobic interaction with balloon materials appears to be responsible for the adsorption of local anesthetics. When infusion balloons are used for the continuous administration of local anesthetics, attention should be paid to the possibility that their actual concentrations in effluents are smaller than those present when they are initially prepared.

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Many devices, such as IV fluid containers, delivery sets, and syringes, are widely used in medical and surgical practice. However, various drugs, including local anesthetics, are known to interact with device materials (1,2). This may result in patients receiving much smaller concentrations than predicted (3). Infusion balloons have been used to continuously supply local anesthetics systemically or locally for pain control. Lidocaine, frequently administered with this device, can interact with synthetic resins and plastics (4). We reported that lidocaine is adsorbed onto the infusion balloon, thus decreasing the concentration during administration (5). However, we could not find data in the literature on the adsorption of other local anesthetics. The mechanism of adsorption is unclear, although several sorption and binding mechanisms have been suggested (1,2,6).

In this study, we compared the adsorptive characteristics of lidocaine, bupivacaine, ropivacaine, and mepivacaine onto infusion balloons by determining their concentrations in effluents with time. We also performed the adsorption experiments under different

conditions and by using a structural analog of lidocaine to investigate the possible mechanism underlying local anesthetic adsorption.

Methods

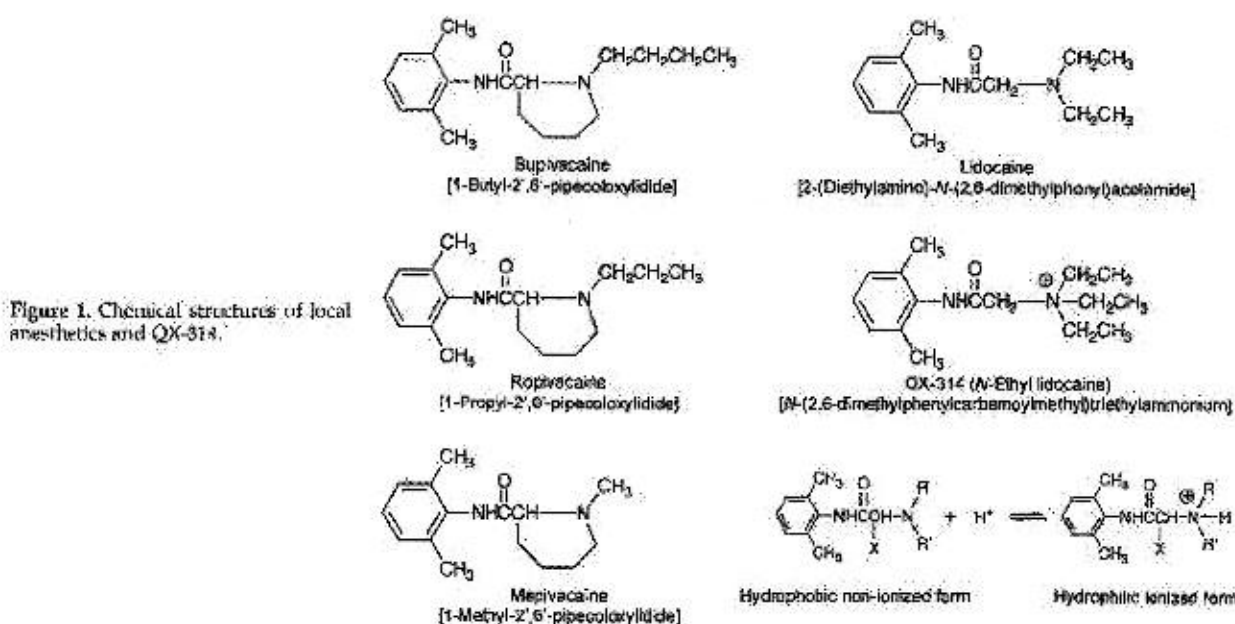
Lidocaine hydrochloride, bupivacaine hydrochloride, ropivacaine hydrochloride, and mepivacaine hydrochloride (Fig. 1) were supplied by AstraZeneca (Södertälje, Sweden). QX-314, N-ethyl lidocaine [N-(2,6-dimethylphenyl)carbamoylmethyl]triethylammonium bromide; see Fig. 1 for the structure], and prilocaine hydrochloride were purchased from Sigma (St. Louis, MO). These chemicals were dissolved in water of a liquid chromatographic grade (Kishida, Osaka, Japan), and the pH was adjusted to 7.4 or 6.0 with 0.01–0.1 M NaOH. To compare the adsorption of structurally different local anesthetics, their solutions were prepared to be an equimolar concentration: 1.0 mM each. The solutions of lidocaine, bupivacaine, ropivacaine, mepivacaine, and QX-314 were injected into infusion balloons made from silicone of either 100- or 50-mL volume (B-100 International, Tokyo, Japan) and were then allowed to flow out at 4 mL/h at room temperature (25°C). Effluents were collected at 5, 15, 30, and 60 min after injection because the adsorption of local anesthetics reached a plateau within 60 min in a preliminary experiment, as reported previously (5). For determining the concentrations in original and effluent solutions, 20 μ L of each sample was mixed with 80 μ L

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of 0.2 mM prilocaine in 0.0125 M HCl, and an aliquot of the mixture was subjected to quantitative analysis by high-performance liquid chromatography (HPLC). All procedures were performed with glassware to prevent concentration changes of chemicals during analysis except for adsorption onto balloons.

Chromatography was performed by using a Shimadzu HPLC system (Kyoto, Japan) that consisted of an LC-10ADVP liquid chromatograph connected to an SH-10ADVP autosampler (sample volume of 20 μ L), a Shim-pack CLC-C₁₈(M) column (4.6 mm inner diameter $\times$ 25 cm; particle size of 5 μ m) placed in a thermostatic controller, and an SPD-M10AVP diode array detector. Either 40% (vol/vol) methanol in 0.01M HCl for concentration analysis or 60% (vol/vol) methanol in 0.07 M phosphate buffer (pH 7.4) for capacity factor analysis was delivered to the column at a flow rate of 1.0 mL/min and at 50°C. Column eluates were detected at absorption wavelength of 220 nm. The concentrations in original and effluent solutions were determined on the basis of calibration graphs, which were prepared by plotting the peak area ratios to prilocaine against the known concentrations of analytes. A capacity factor, defined as the ratio of the concentration of an analyte in the stationary phase to that in the mobile phase, was calculated by the formula $(t_R - t_0)/t_0$, in which t_R is the retention time of a local anesthetic retained on the column and t_0 is the mobile phase holdup time (7).

Results are expressed as mean $\pm$ SE ($n = 4-8$). Statistical analysis was performed with StatView 5.0 (SAS Institute, Cary, NC). To evaluate differences over time within each group, a repeated-measures analysis of variance was used. When significant differences

were detected by analysis of variance, a *post hoc* Scheffé F test was used. The data on pH difference were analyzed with Student's *t*-test. A *P* value < 0.05 was considered significant.

Results

After the solutions (pH 7.4) were injected into the balloons of 100-mL volume, the concentrations of lidocaine, bupivacaine, ropivacaine, and mepivacaine in effluents decreased to $< 86\%$ – 94% of the initial concentrations within 5 min (Fig. 2). Bupivacaine was most strongly adsorbed after 60 min, followed by lidocaine, ropivacaine, and mepivacaine. The relative adsorption to lidocaine (1.00) was as follows: bupivacaine, 1.12 ± 0.02 ; ropivacaine, 0.89 ± 0.04 ; and mepivacaine, 0.58 ± 0.04 . Concerning the pH of local anesthetic solutions, the original value of 7.4 decreased to 7.21 ± 0.01 for lidocaine, 7.09 ± 0.00 for bupivacaine, 7.17 ± 0.01 for ropivacaine, and 7.34 ± 0.01 for mepivacaine in effluents after flowing out for 60 min.

Reversed-phase HPLC analysis showed a capacity factor of 2.31 ± 0.03 for mepivacaine, 2.81 ± 0.03 for lidocaine, 3.97 ± 0.09 for ropivacaine, and 5.22 ± 0.15 for bupivacaine. When these were plotted against the concentration decreases indicating adsorption (Fig. 3), a linear regression analysis provided $y = 0.422x - 0.288$ ($R^2 = 0.909$). Although a correlation was found between chromatographic retention and balloon adsorption of bupivacaine, ropivacaine, and mepivacaine ($r = 0.953$; $P < 0.0001$), lidocaine tended to deviate from the relation, showing more intensive adsorption than assumed from its capacity factor.

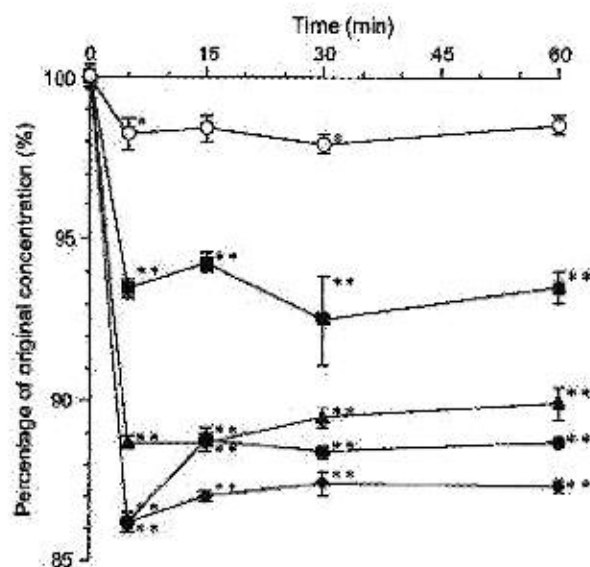


Figure 2. Concentration changes of local anesthetics flowing out of infusion balloons injected with solutions of pH 7.4. The sample solutions (1.0 mM each) were injected into the balloons of 100-mL volume, and the effluents were analyzed over time by high-performance liquid chromatography: lidocaine (●), bupivacaine (◆), ropivacaine (▲), mepivacaine (■), and QX-314 (○). Data are mean $\pm$ SE ($n = 4$). * $P < 0.05$ and ** $P < 0.01$; significantly different from initial concentration (0 min).

Compared with local anesthetics, QX-314 showed exceptionally weak adsorption at pH 7.4 (Fig. 2). Its relative adsorption to lidocaine (1.00) was 0.13 ± 0.03 after flowing out for 60 min.

When the solutions of pH 6.0 were injected, lidocaine, bupivacaine, ropivacaine, and mepivacaine were adsorbed onto the balloons of 100-mL volume (Fig. 4). Decreases of their concentrations in effluents were, however, much less than those at pH 7.4.

The influence of balloon size on adsorption was studied by injecting lidocaine solutions of pH 7.4 into balloons of a smaller volume. After flowing out for 60 min, the concentration-decreasing degree in effluents was 0.57 for a 50-mL volume, compared with 1.00 for a 100-mL volume, indicating that lidocaine was adsorbed more by an increase of balloon size. Neither flowing out with shaking the balloon nor the increasing flow rate (from 4 to 8 mL/h) showed an influence on the adsorption of lidocaine.

Discussion

Lidocaine was previously reported to adsorb onto infusion balloons (5). To investigate whether other local anesthetics are similarly adsorbed and, if so, whether they show adsorption profiles associated with structural differences, we used a chromatographic technique to selectively analyze anesthetics flowing out of the balloons. Because all analytes are stable under the

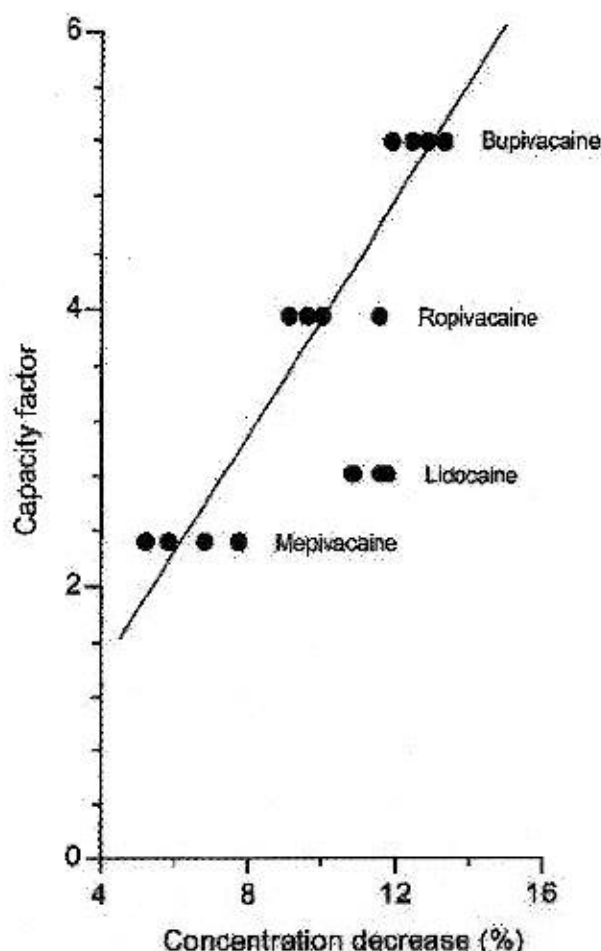


Figure 3. Relation between capacity factor and adsorption. The capacity factors of local anesthetics determined by reversed-phase high-performance liquid chromatography were plotted against their concentration decreases indicating adsorption at pH 7.4.

present experimental conditions (pH, temperature, and during flowing out), a decrease of their concentrations in effluents is conclusively referred to as adsorption of local anesthetics. Bupivacaine, ropivacaine, and mepivacaine are adsorbed, as is lidocaine, resulting in a loss of nearly 6%–15% of the original contents within 5–60 min after injection of their solutions at pH 7.4. When infusion balloons are used to administer local anesthetics, e.g., for continuous epidurals, attention should be paid to the possibility that their actually infused concentrations may be smaller than the initially prepared ones. Alkalinization of lidocaine (8), bupivacaine (9), ropivacaine (10), and mepivacaine solutions (11) increases the anesthetic activity by promoting the penetration and uptake to nerve cell membranes (12). However, such a pH strategy is discouraged for application of local anesthetics by infusion balloons because their adsorption is enhanced with increasing pH.

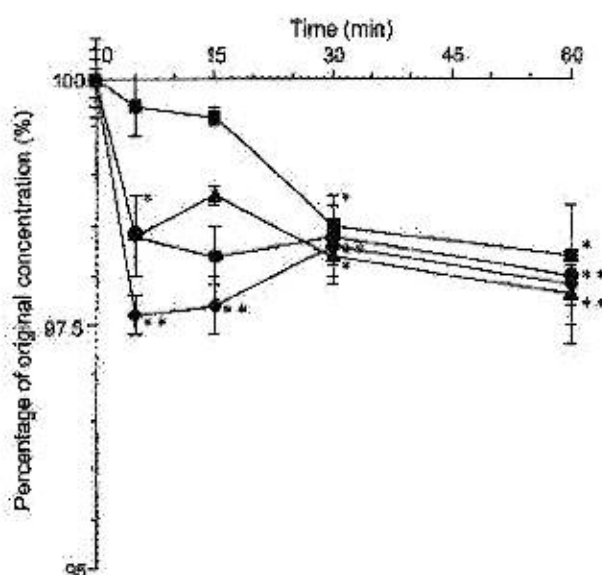


Figure 4. Concentration changes of local anesthetics flowing out of infusion balloons injected with their solutions of pH 6.0. The sample solutions (1.0 mL each) were injected into the balloons of 100-mL volume, and the effluents were analyzed over time by high-performance liquid chromatography: lidocaine (●), bupivacaine (◆), ropivacaine (▲), and mepivacaine (■). Data are mean $\pm$ se ($n = 8$). * $P < 0.05$ and ** $P < 0.01$; significantly different from initial concentration (0 min).

Bupivacaine, ropivacaine, lidocaine, and mepivacaine have pK_a values of 8.1, 8.1, 7.9, and 7.6, respectively (13). As represented by the Henderson-Hasselbalch equation ($pH = pK_a - \log [\text{nonionized anesthetic}]/[\text{ionized anesthetic}]$), these local anesthetics with pK_a ranging 7.6 to 8.1 are present in hydrophobic nonionized forms under alkaline conditions, whereas their hydrophilic ionized forms become predominant at acidic pH (12). All the tested anesthetics were adsorbed at pH 7.4 more strongly than at pH 6.0, suggesting that a hydrophobic interaction with balloon materials is the possible underlying mechanism for adsorption. Local anesthetics are at equilibrium between nonionized and ionized forms. If hydrophobic nonionized anesthetics are lost by the adsorption, the concentrations of hydrogen ions should be increased. In fact, the pH of effluents of local anesthetics was decreased in association with the extent of their adsorption. The adsorption was greatest in the order of bupivacaine, ropivacaine, and mepivacaine. The HPLC-determined capacity factors of bupivacaine, ropivacaine, and mepivacaine showed the same increasing order as in their adsorption degree. Because a reversed-phase column was used in this chromatographic study, a capacity factor (defined as the concentration ratio of solutes in the stationary phase to the mobile phase) indicates the hydrophobic degree of local anesthetics. Hydrophobicity of local anesthetics is proportional to their retention in reversed-phase

chromatography (14,15). QX-314 is a quaternary ammonium that is always present as a positively charged form (Fig. 1). This *N*-ethyl lidocaine derivative was much less adsorbed than the parent molecule lidocaine. These results also support the suggestion that hydrophobicity is responsible for the adsorption of local anesthetics onto infusion balloons.

Concerning the structure/adsorption relation, bupivacaine, ropivacaine, and mepivacaine were adsorbed in increasing order of intensity. One explanation for this structure dependence of adsorption is that a hydrophobic interaction is enhanced with increasing the chain length of alkyl substituents: a methyl group in mepivacaine, a propyl group in ropivacaine, and a butyl group in bupivacaine. Similar effects have been reported for the action of local anesthetics on lipid bilayers (15). Bupivacaine, ropivacaine, and mepivacaine belonging to 1-alkyl-2',6'-pipecoloxylidide compounds showed a good correlation between the extent of adsorption and the hydrophobicity evaluated by capacity factors. However, lidocaine was adsorbed more than expected from its hydrophobic property despite having a 2,6-dimethylphenylcarbamoyl structure common to the tested local anesthetics. In addition to the hydrophobic interaction, the adsorption onto infusion balloons appears to be determined by the structure-specific mechanism in which an *N,N*-diethylaminomethyl moiety is more suitable for adsorption than an *N*-alkylpiperidine moiety.

Different factors have been assumed to influence the adsorption of local anesthetics, as reported previously for other drugs (1,6). Although neither shaking the balloons nor varying the flow rate was critical, an increase of balloon volume resulted in increased adsorption of lidocaine. The balloon surface area is likely to determine the number of active sites (the adsorptive capacity) for local anesthetics.

In conclusion, local anesthetics are often adsorbed onto infusion balloons, and such adsorption is considered to occur by a possible hydrophobic and structure-dependent interaction when local anesthetics are continuously administered with the balloons. Therefore, the concentrations actually supplied to patients may be smaller than predicted.

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