Anesthesiology 2001; 95:1371–6 

# *Effect of Clonidine on Lidocaine Clearance* In Vivo

## *A Microdialysis Study in Humans*

*Dan J. Kopacz, M.D.,* Christopher M. Bernards, M.D.†*

***Background:*** **The addition of clonidine to local anesthetics has been shown to prolong both peripheral and central neuraxial local anesthetic blocks. Whether clonidine prolongs local anesthetic block by a pharmacokinetic effect or a pharmacodynamic effect is unclear. By directly measuring lidocaine tissue concentrations at the site of injection in the presence and absence of clonidine, this study was designed to address this question.**

***Methods:*** **Microdialysis probes were placed adjacent to the superficial peroneal nerve in both feet of seven volunteers. Plain lidocaine (1%) was injected along one nerve, and lidocaine with clonidine (10 μg/ml) was injected along the other nerve in a double-blind, randomized manner. The extracellular fluid was then sampled for lidocaine concentration at 5-min intervals using microdialysis, cutaneous blood flow was assessed by laser Doppler at 10-min intervals, and sensory block was assessed every 10 min until resolution.**

***Results:*** **Consistent with previous studies, clonidine prolonged lidocaine sensory block. Blood flow increased in both groups but was significantly lower in the clonidine group, especially during the first 60 min. Consistent with the lower blood flow, the area under the lidocaine concentration-*versus*-time curve was significantly greater in the clonidine group during the first 60 min.**

***Conclusion:*** **When added to lidocaine, clonidine prolonged peripheral nerve block. The pharmacokinetic data suggest that the mechanism of prolongation is at least in part pharmacokinetic.**

TO prolong the duration of peripheral and central neuraxial blocks, clonidine is often added to local anesthetic solutions.[1,2] As an $\alpha_2$-specific adrenergic agonist, it has been presumed that the block-prolonging effect of clonidine results from a pharmacodynamically mediated mechanism. However, the data supporting this assumption are conflicting. For example, consistent with the presumption that clonidine exerts its effects pharmacodynamically, several studies have shown that peak plasma concentrations of local anesthetics are unaltered when clonidine is added.[3,4] However, data from other studies have shown that clonidine does decrease peak local anesthetic plasma concentrations to the same extent as epinephrine, a fact that supports a pharmacokinetic mechanism.[5,6] Other evidence of a pharmacokinetic mechanism comes from studies showing that clonidine itself is incapable of producing nerve block in the absence of coadministered local anesthetics.[7]

We have previously demonstrated that epinephrine slows the elimination of lidocaine from the site of injection and prolongs the duration of blockade, presumably by its ability to concurrently reduce blood flow at the site of injection.[8] Although large doses of clonidine are known to produce significant hemodynamic changes when administered systemically or in the central neuraxis, to our knowledge, its effects on local blood flow have not been directly investigated.

Therefore, this study was designed to determine whether clonidine alters the local clearance of lidocaine after peripheral nerve block in humans and to determine the effects of clonidine on blood flow at the site of injection. To address this issue, we used a previously described human model[8] in which microdialysis probes were placed along the superficial peroneal nerve and *in vivo* lidocaine concentrations were measured continuously after injection of lidocaine with and without clonidine.

## Methods

The Institutional Review Board of the Virginia Mason Medical Center (Seattle, WA) approved our study. We enrolled nine paid volunteers (five men, four women; aged 27–41 yr) after they gave written informed consent.

### *Experimental Preparation*

Microdialysis probe placement and local anesthetic blockade were performed as previously described.[8] Briefly, the right and left intermediate dorsal cutaneous nerves (terminal branch of the superficial peroneal nerve) were identified over the dorsum of the foot by direct visualization, palpation, or both. A 48 mm, 18-gauge intravenous catheter and needle (Insyte; Becton Dickinson, Sandy, UT) was inserted through the skin immediately adjacent to the nerve, threaded through the subcutaneous tissue parallel to the nerve for a distance of approximately 3 cm, and then made to exit through the skin of the dorsum of the foot. The needle was removed, leaving the intravenous catheter tip protruding through the skin. A loop microdialysis probe was inserted through the distal tip of the intravenous catheter, and the catheter was withdrawn 5–10 mm so that its tip rested entirely in the subcutaneous tissue. Microdialysis

* Staff Anesthesiologist, Department of Anesthesiology, Virginia Mason Medical Center. Clinical Associate Professor, Department of Anesthesiology, University of Washington, Seattle, Washington. † Professor of Anesthesiology, Department of Anesthesiology, University of Washington.

Received from the Department of Anesthesiology, Virginia Mason Medical Center, Seattle, Washington. Submitted for publication March 8, 2001. Accepted for publication August 9, 2001. Supported in part by the Department of Anesthesiology, Virginia Mason Medical Center; the Department of Anesthesiology, University of Washington; and grant No. RO1 DA-07313 from the National Institute on Drug Abuse, Bethesda, Maryland.

Address correspondence to Dr. Kopacz: Department of Anesthesiology, Virginia Mason Medical Center, 1100 Ninth Avenue, Mailstop B2-AN, Seattle, Washington 98111. Address electronic mail to: anedjk@vmmc.org. 

fluid (normal saline) was pumped through the dialysis probe at 10 μl/min using a syringe pump (model PHD 2000; Harvard Instruments, Natick, MA).

Approximately 20 min after the dialysis probe was placed, each volunteer received lidocaine injections in the right and left foot simultaneously. In a double-blind, randomized manner, 2 ml lidocaine, 1%, with or without 10 μg/ml clonidine was injected over 1 min through the intravenous catheter in each foot while the catheters were slowly withdrawn. This process ensured that the local anesthetic was deposited immediately adjacent to the superficial peroneal nerve and that the microdialysis probe rested in the center of the local anesthetic "depot." When the drug injections were complete, dialysate samples were collected continuously every 5 min for the first 40 min, and then every 10 min (*i.e.*, 50 or 100 μl volumes). Collection of dialysate samples was continued from both feet until the return of pin-prick sensation in both feet for two successive testing intervals (20 min).

Pin-prick, light touch, and cold sensitivity (iced test tube) were tested sequentially every 10 min in the area over the third and fourth metatarsal phalangeal joints. The volunteers' reaction to pin prick was assessed using a 27-gauge dental needle. Light touch was assessed using a 3.84-N von Frey hair. Sensations were scored as present or absent; no attempt was made to quantify these sensations. Testing of sensory modes (pin prick, light touch, and cold sensation) were discontinued after return of sensation for two successive testing intervals (20 min).

Hot and warm thermal perception thresholds were determined in the same anatomic area using a custom-built thermode–thermocouple. The temperature was set at 30°C and increased at a rate of 0.5°C/s to a cutoff of 50°C (to prevent thermal injury). The volunteers were asked to tell the investigator when the probe felt noticeably warm and then uncomfortably hot. Thermal thresholds were tested every 10 min.

Cutaneous blood flow velocity at the injection site was tested at baseline before drug injection and then every 10 min after drug injection using a laser Doppler flow probe (MedPacific LD 5000, Seattle, WA). Flow velocity was also measured at an unblocked control site on the anterior leg to verify that there were no spontaneous changes in flow unrelated to local anesthetic administration. Flow velocity was calculated as previously described[9] using the equation:

$$\% \text{ change in blood flow velocity} = (S_x - S_o/S_o) - (C_x - C_o/C_o) \times 100$$

where $S_x$ is the blood flow velocity at the injection site x min after injection, $S_o$ is the baseline blood flow velocity at the injection site, $C_x$ is the blood flow velocity at the control site x min after the injection, and $C_o$ is the baseline blood flow velocity at the control site. Thermal perception thresholds and cutaneous blood flow measurements were continued from both feet until the return of pin-prick sensation in both feet for two successive testing intervals (20 min).

*Manufacture of Microdialysis Probes*

Custom loop microdialysis probes were made by one of the authors (C. M. B.) as previously described. Briefly, probes were made from cellulose dialysis fibers (Spectrum Medical Industries, Houston, TX) with a 215-μm ID, a 235-μm OD, and a molecular weight cutoff of 6,000 Da. Epoxy cement was used to coat all but the center 20 mm of the dialysis fiber, thus creating a 20-mm "dialysis window." The epoxy was spread evenly by running a 2-cm length of polyethylene tubing over the fiber while the epoxy was still wet. After the epoxy had cured, a 90-μm-diameter wire was placed in the lumen of the dialysis probe, and the probe was bent in half. The wire allowed the probe to be bent without occluding the lumen. The inflow end of the dialysis probe was connected to a syringe pump, and the outflow end of the dialysis probe was connected to a 40-cm length of polyethylene tubing. The probes were allowed to "cure" for 24 h, after which they were sterilized by exposure to ethylene oxide in the University of Washington gas sterilization facility (Seattle, WA). All probes were used within 72 h of manufacture.

The performance of the probes was corrected for differences in recovery efficiency by placing them in a vial containing a 1% lidocaine solution after being removed from the volunteers. This solution was then dialyzed for 10 min at the same flow rate. The recovery efficiency was calculated as the ratio of the lidocaine concentration in the dialysate divided by the known concentration in the vial. This value was used to correct lidocaine concentrations in all dialysis samples for recovery. We have previously shown that probe recovery efficiency does not deteriorate over time when placed subcutaneously in humans.[8]

*Lidocaine Analysis*

Lidocaine concentration was measured using a modification of a previously described gas chromatography–mass spectrometry method[10] with bupivacaine (250 ng) as the internal standard. The samples were alkalinized with 0.1 M potassium hydroxide and extracted once into 2-ml ethyl acetate–heptane (1:1, vol/vol). The gas chromatograph, a Hewlett-Packard model 5890 II (Mountain View, CA), was equipped with a model 5972A mass selective detector, a model 7673 automatic sampler, a split–splitless capillary inlet system, and an electronic pressure control system (Hewlett Packard Corp.). The capillary column was a J&W Scientific model DB 5 (Folsom, CA). Injections of 1 μl were made in the splitless mode with a helium carrier gas pulse pressure of 40 psi. After 1 min, the head pressure was decreased to 10 psi, and the inlet was purged. The oven temperature was

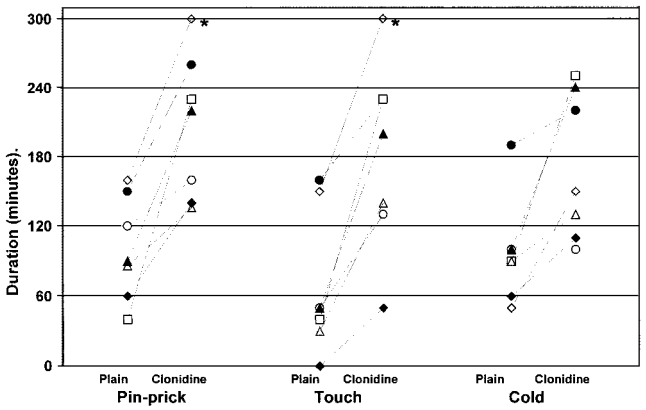


**Fig. 1. The relation of the duration of anesthesia to pin prick, touch, and cold sensation in the feet of each volunteer. Note that the duration of anesthesia is consistently longer in the lidocaine with clonidine foot for all volunteers. One volunteer had a duration of pin-prick and touch anesthesia lasting more than 6 h. These were assigned a value of 300 min (*).**

held at 40°C for 1 min, increased to 220°C at 40°C/min, and then increased again to 300°C at 30°C/min. The injector and transfer line temperatures were 250 and 300°C, respectively. The mass analyzer was set to detect selected ion masses generated by an ionizing current of 70 eV. The intensities of characteristic ions in two groups were monitored for 100 ms dwell times each. Group 1 ions were 86 m/z for lidocaine and 140 m/z for bupivacaine. Lidocaine and bupivacaine eluted at 8.9 and 10.5 min, respectively. The standard curves of peak area ratios (analyte/standard) *versus* analyte concentration were linear ($r^2 > 0.99$) from 0.1 to 50 (g/ml for lidocaine. The interday coefficient of variation was 8% ($\leq$ 2% bias) for six quality control samples containing 2.5 $\mu$g lidocaine.

*Pharmacokinetic Analysis*

PKAnalyst software (MicroMath Research, Salt Lake City, UT) was used to fit lidocaine concentration-*versus*-time data to either a two- or a three-term exponential equation of the general form:

$$\text{Concentration} = A_1 e^{-k1 \cdot t} + \ldots + A_n e^{-kn \cdot t}$$

The decision to use a two- or a three-term equation was based on both visual inspection of the fit and a variation of the Akaike Information Criterion known as the Model Selection Criteria, which is calculated by PKAnalyst. The area under the concentration-*versus*-time curve (AUC), the area under the moment curve (AUMC), and the mean residence time (MRT) were calculated by PKAnalyst from t = 0 to t = $\infty$. Clearance (CL) was calculated from the equation:

$$CL = \text{Dose}/AUC_{0\text{-}\infty}.$$

*Statistical Analyses*

Differences in the duration of sensory block for each of the sensory modes were assessed for statistical significance using the two-tailed Student paired *t* test (Statview statistical software; SAS Institute Inc., Cary, NC). Differences in pharmacokinetic parameters were assessed using the two-tailed Student *t* test (Microsoft Excel; Microsoft Corp., Seattle, WA). Differences between the groups in lidocaine concentration over time and cutaneous blood flow, and thermal perception thresholds over time were assessed by repeated-measures analysis of variance. All data are reported as average ± SD, with $P < 0.05$ considered significant.

## Results

Pain, touch, and cold sensation were blocked completely in all but one volunteer in whom blockade did not develop in either foot; this volunteer was excluded from sensory testing. One additional volunteer was excluded because of technical difficulties. With the exception of one volunteer who still had block to pain and touch in the foot that had received lidocaine with clonidine, all blocks resolved before the end of the 5-h data collection period. For statistical purposes, this volunteer's time-to-block resolution was assigned a value of 300 min.

For all three sensory modes, the duration of blockade was markedly longer in the clonidine group compared with the plain lidocaine group (fig. 1). The duration of blockade to pin prick, touch, and cold sensation was significantly increased by the addition of clonidine ($P$ = 0.002, 0.001, and 0.017, respectively).

At the time when pin-prick sensation had returned in the foot that had received plain lidocaine (180 min), the threshold temperature for sensing warm and hot stimuli (fig. 2) remained increased in both groups. There was no significant difference between groups in either warm or

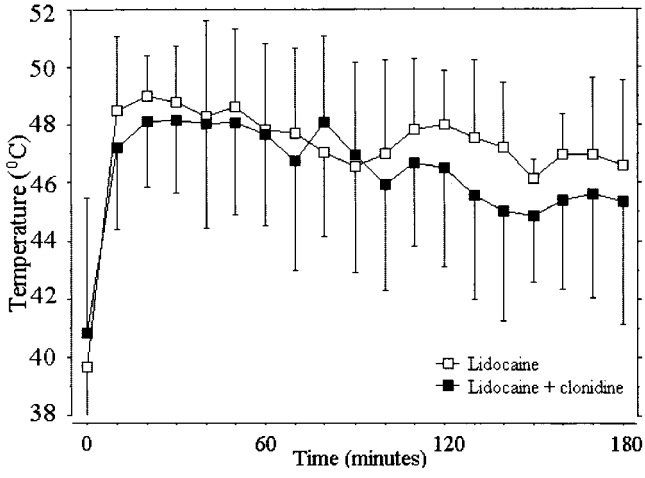


**Fig. 2. The threshold for perceiving the temperature of a thermode as uncomfortably hot. At the time when pin-prick anesthesia had resolved in the foot that had received plain lidocaine, the threshold remained increased in both feet of all volunteers (mean ± SD).**

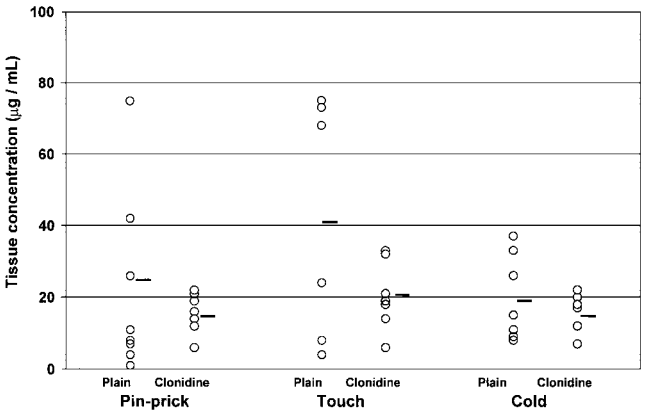


**Fig. 3. Tissue lidocaine concentrations of individual volunteers at the time when anesthesia to pin prick, touch, and cold sensation resolved. Mean concentrations tended to be lower in the feet that had received lidocaine with clonidine, although statistical significance was not reached ($P$ = 0.34, 0.09, and 0.37 for pin prick, touch, and cold sensation, respectively).**

hot thresholds through this time point ($P$ = 0.497 and 0.705, respectively).

The lidocaine concentration in the tissue dialysate when the block resolved tended to be greater in the plain lidocaine group compared with the lidocaine with clonidine group (pin prick: 24.7 ± 25.9 *vs.* 15.7 ± 5.6 μg/ml, $P$ = 0.34; touch: 42.0 ± 33.6 *vs.* 20.4 ± 9.6 μg/ml, $P$ = 0.09; cold: 19.9 ± 12.0 *vs.* 16.3 ± 5.1 μg/ml, $P$ = 0.37; fig. 3). Interestingly, blood flow velocity was increased above baseline values in both groups, but the increase was markedly greater in the plain lidocaine group, especially within the first 60 min (fig. 4; $P$ = 0.01).

Figure 5 shows the data for mean lidocaine concentration *versus* time for both groups and the curve fit by PKAnalyst. However, calculation of pharmacokinetic parameters was performed on data from individual volunteers rather than on averaged group data. $AUC_{0-\infty}$ and MRT were significantly greater for the clonidine group than for the plain lidocaine group, whereas CL was significantly slower for the clonidine group (table 1). AUMC was not different between the two groups.

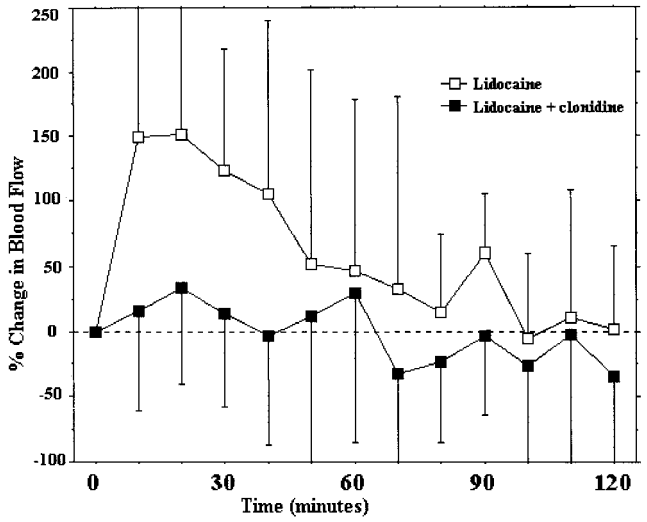


**Fig. 4. The change in cutaneous blood flow after injection of plain lidocaine or lidocaine with clonidine. Flow increased above baseline in both groups but was significantly greater in the plain lidocaine group ($P$ = 0.01). Flows had returned to baseline in the lidocaine with clonidine group within 40–60 min.**

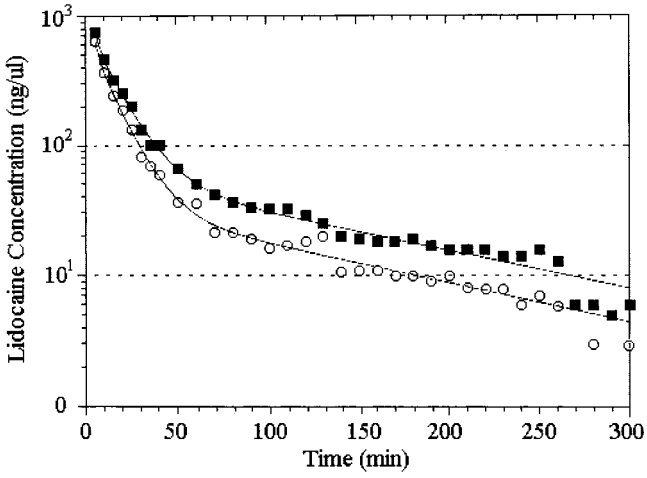


**Fig. 5. The tissue lidocaine concentration over time in the plain lidocaine group (*open circles*) and the lidocaine with clonidine group (*closed squares*).**

## Discussion

The purpose of this study was to determine whether clonidine alters the clearance of lidocaine from tissue. Consistent with our expectations, the addition of clonidine significantly prolonged the duration of anesthesia to pin prick, touch, and cold sensation. The fact that local cutaneous blood flow velocity and CL were significantly lower in the clonidine group suggests that the prolongation is, at least in part, pharmacokinetically mediated. The greater AUC and MRT in the clonidine group are also consistent with a pharmacokinetically mediated effect of clonidine.

Interestingly, it seems that the pharmacokinetic effect of clonidine is exerted only early after lidocaine injection. This supposition is consistent with the time course

**Table 1. Pharmacokinetic Parameters**

| Parameter | Plain Lidocaine | Lidocaine + Clonidine |
|---|---|---|
| $AUC_{0-\infty}$ ($\mu g \cdot min \cdot ml^{-1}$) | 16,678 ± 3,190 | 22,824 ± 8,578* |
| $AUMC_{0-\infty}$ ($\mu g \cdot min^2 \cdot ml^{-1}$) | $2.0 \times 10^6 \pm 3.5 \times 10^6$ | $1.8 \times 10^6 \pm 1 \times 10^6$ |
| Mean residence time (min) | 48 ± 17 | 74 ± 24* |
| Cl (ml/min) | 1.2 ± 0.3 | 0.94 ± 0.3* |

Mean ± SD.

* $P < 0.05$.

AUC = area under the concentration-*versus*-time curve; AUMC = area under the moment curve.

of blood flow effects and tissue concentrations of lidocaine in the clonidine group. Specifically, inspection of the mean tissue concentration data (fig. 5) clearly shows that the terminal elimination phases are exactly parallel, but the initial rate of drug clearance is greater for the plain lidocaine injection during the first hour than it is for the lidocaine plus clonidine injection. This slower rate of elimination during the first hour presumably results from clonidine's ability to attenuate the lidocaine-induced increase in local blood flow.

Clonidine's ability to prevent the lidocaine-induced increase in blood flow likely results from the fact that although clonidine is highly selective for $\alpha_2$ adrenoreceptors, it does retain some $\alpha_1$ activity.[11] $\alpha_1$-Mediated vasoconstriction by clonidine would be expected to oppose lidocaine-induced vasodilation just as does epinephrine.[8]

However, it is unlikely that the prolongation of lidocaine blockade is entirely due to a pharmacokinetic mechanism. The tissue concentration of lidocaine at the time when pin-prick, touch, and cold sensation returned tended to be lower with the lidocaine plus clonidine injection, which suggests a pharmacodynamic mechanism. Furthermore, when tissue lidocaine concentrations from this study are compared with those of our previous study, which used the same methodology to evaluate the effect of epinephrine on lidocaine pharmacokinetics, it is clear that the magnitude of the pharmacokinetic effect exerted by epinephrine is greater than that exerted by clonidine (fig. 6). In addition, when the results of these two studies are compared, the prolongation of lidocaine blockade seems to be greater with epinephrine than with clonidine.

Other studies also suggest that a pharmacodynamic mechanism has a role in clonidine's prolongation of local anesthetic blockade. For example, Butterworth and Strichartz used an *in vitro* rat sciatic nerve model to demonstrate that clonidine produces dose-dependent inhibition of the compound action potential of A$\alpha$ and C fibers.[12] Similarly, Gaumann showed that clonidine also enhances the ability of lidocaine to inhibit C-fiber action potentials *in vitro*.[13] Nakamura and Ferreira[14] have demonstrated another pharmacodynamic mechanism that may have a role in clonidine's prolongation of local anesthetic nerve block, namely locally mediated $\alpha_2$-adrenergic effects in the peripheral nervous system, which are naloxone sensitive.

It is noteworthy that clonidine alone has been shown to be incapable of producing analgesia when administered as the sole agent onto human peripheral nerves.[15] This observation suggests that the pharmacodynamic effects of clonidine observed *in vitro* are too weak to explain the prolongation of local anesthetic block observed *in vivo*. Therefore, it is perhaps likely that prolongation of local anesthetic block occurs because of a combination of pharmacokinetic and pharmacodynamic effects on local anesthetic actions.

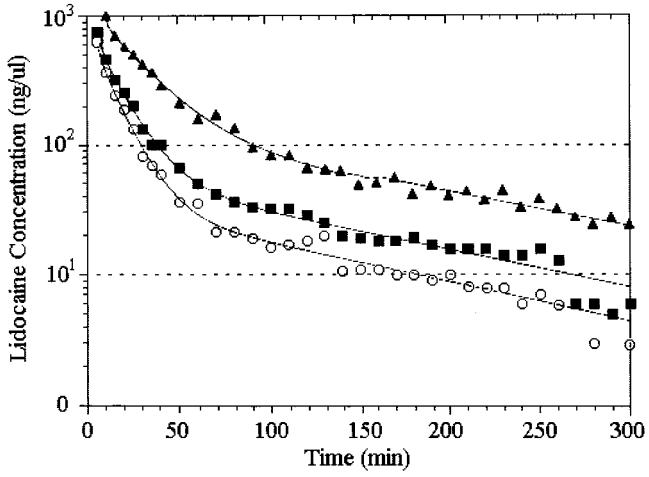


**Fig. 6. The tissue lidocaine concentration over time of the plain lidocaine (*open circles*) and lidocaine with clonidine groups (*closed squares*) compared with previously published data for lidocaine with epinephrine (*closed triangles*) using identical sampling methodology.[8] The effect of the addition of epinephrine (2.5 $\mu$g) on lidocaine clearance is much greater than the effect of adding clonidine (10 $\mu$g) within the first 60 min. The rate of decrease in plasma lidocaine concentration after 60 min is remarkably consistent for all three groups.**

The mechanism by which clonidine prolongs local anesthetic nerve block in the central neuroaxis differs from peripheral nerve sites. When injected into the central neuraxis, clonidine is thought to activate $\alpha_2$-adrenorecetors located on spinal nerve terminals and neurons in the spinal cord. Importantly, when administered centrally, clonidine can produce analgesia when administered as the sole agent.[2] Analgesia can also be attained with intravenous, intramuscular, oral, or transdermal administration of clonidine,[16–18] where it most likely acts at sites within the brainstem to produce analgesia and possibly also sedation, hypotension, and bradycardia.

For peripheral nerve blockade, clonidine has been added to local anesthetic solutions in a concentration range from 0.5 to 20 $\mu$g/ml, and when the total dose surpasses 100–150 $\mu$g, side effects from systemic absorption (hypotension, sedation) can develop.[19–22] Consequently, in this study, we chose a dose of clonidine (10 $\mu$g) that is in the clinically used dose range and has been shown to produce maximal local effects without confounding effects attributable to systemic absorption.

In conclusion, we report the effect of the addition of clonidine on *in vivo* tissue lidocaine concentration and corresponding nerve function in humans. We found that clonidine prolongs local anesthetic block partly by a pharmacokinetic mechanism. This slowing of lidocaine elimination from the injection site is most pronounced in the first 60 min after injection, is simultaneous with a decrease in local blood flow relative to plain lidocaine, and is much smaller in magnitude compared with the effect that we have previously reported for the addition of epinephrine.

## References


1. Murphy D, McCartney C, Chan V: Novel analgesic adjuncts for brachial plexus block: A systematic review. Anesth Analg 2000; 90:1122–8
2. Eisenach J, De Kock M, Klimsha W: $\alpha_2$-Adrenergic agonists for regional anesthesia: A clinical review of clonidine. ANESTHESIOLOGY 1996; 85:655–74
3. Molnar R, Davies M, Scott D, Silbert B, Mooney P: Comparison of clonidine and epinephrine in lidocaine for cervical plexus block. Reg Anesth Pain Med 1997; 22:137–42
4. Gaumann D, Forster A, Griessen M, Habre W, Poinsot O, Della Santa D: Comparison between clonidine and epinephrine admixture to lidocaine in brachial plexus block. Anesth Analg 1992; 75:69–74
5. Boico O, Bonnet F, Mazoit J: Effects of epinephrine and clonidine on plasma concentrations of spinal bupivacaine. Acta Anaesthesiol Scand 1992; 36:684–8
6. Mazoit J, Benhamou D, Veillette Y, Samii K: Clonidine and or adrenaline decrease lignocaine plasma peak concentration after epidural injection. Br J Clin Pharmacol 1996; 42:242–5
7. Sia S, Lepri A: Clonidine administered as an axillary block does not affect postoperative pain when given as a sole analgesic. Anesth Analg 1999; 88: 1109–12
8. Bernards C, Kopacz D: Effect of epinephrine on lidocaine clearance *in vivo*: A microdialysis study in humans. ANESTHESIOLOGY 1999; 91:962–8
9. Liu S, Carpenter R, Chiu A, McGill T, Mantell S: Epinephrine prolongs duration of subcutaneous infiltration local anesthesia in a dose-related manner: Correlation with magnitude of vasoconstriction. Reg Anesth 1995; 20:378–84
10. Rosseel M, Bogaert M: Determination of lidocaine and its desethylated metabolites in plasma by capillary column gas-liquid chromatography. J Chromatogr 1978; 154:99–102
11. Maze M, Tranquilli W: $\alpha_2$ Adrenoreceptor agonists: Defining the role in clinical anesthesia. ANESTHESIOLOGY 1991; 74:581–605
12. Butterworth J, Strichartz G: The $\alpha$2-adrenergic agonists clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibers. Anesth Analg 1993; 76:295–301
13. Gaumann D, Brunet P, Jirounek P: Clonidine enhances the effects of lidocaine on C-fiber action potential. Anesth Analg 1992; 74:719–25
14. Nakamura M, Ferreira S: Peripheral analgesic action of clonidine: Mediation by release of endogenous enkephalin-like substances. Eur J Pharmacol 1988; 146:223–8
15. Sia S, Lepri A: Clonidine administered as an axillary block does not affect postoperative pain when given as the sole analgesic. Anesth Analg 1999; 88: 1109–12
16. Bernard J, Kick O, Bonnet F: Comparison of intravenous and epidural clonidine for postoperative patient-controlled analgesia. Anesth Analg 1995; 81:706–12
17. Bonnet F, Boico O, Rostaing S, Loriferne J, Saada M: Clonidine-induced analgesia in postoperative patients: Epidural *versus* intramuscular administration. ANESTHESIOLOGY 1990; 72:423–7
18. Segal I, Jarvis D, Duncan S, White P, Maze M: Clinical efficacy of oral-transdermal combinations during the perioperative period. ANESTHESIOLOGY 1991; 74:220–5
19. Singelyn F, Gouverneur J, Robert A: A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Anesth Analg 1996; 83:1046–50
20. Reinhart D, Wang W, Stagg K, Walker K, Bailey P, Walker E, Zaugg S: Postoperative analgesia after peripheral nerve block for podiatric surgery: Clinical efficacy and chemical stability of lidocaine alone versus lidocaine plus clonidine. Anesth Analg 1996; 83:760–5
21. Casati A, Magistris L, Fanelli G, Beccaria P, Cappelleri G, Aldegheri G, Torri G: Small-dose clonidine prolongs postoperative analgesia after sciatic-femoral nerve block with 0.75% ropivacaine for foot surgery. Anesth Analg 2000; 91: 388–92
22. Bernard J, Macaire P: Dose-range effects of clonidine added to lidocaine for brachial plexus block. ANESTHESIOLOGY 1997; 87:277–84