Anesthesiology 2000; 93:1045–52

Addition of Sodium Bicarbonate to Lidocaine Decreases the Duration of Peripheral Nerve Block in the Rat

Catherine J. Sinnott, B.A., Joseph M. Garfield, M.D.,* Johannes G. Thalhammer, D.V.M.,† Gary R. Strichartz, Ph.D.*‡*

Background: **Adding sodium bicarbonate to lidocaine to enhance its efficacy during peripheral nerve block is controversial. The authors studied the effect of adding sodium bicarbonate to lidocaine with and without epinephrine *versus* equivalent alkalinization by sodium hydroxide (NaOH) on onset, degree, and duration of peripheral nerve block.**

Methods: **Part I examined alkalinization by sodium bicarbonate *versus* NaOH to pH 7.8 on 0.5% lidocaine, with and without epinephrine (1:100,000), prepared from crystalline salt. Part II examined 0.5% and 1.0% commercial lidocaine solutions, with and without epinephrine, either unalkalinized or alkalinized with sodium bicarbonate or NaOH. With NaOH, pH was adjusted to 7.8, but with sodium bicarbonate, no pH adjustments were made to simulate clinical conditions.**

Results: **In part I, addition of either NaOH or sodium bicarbonate to 0.5% lidocaine without epinephrine produced a faster onset than did unalkalinized lidocaine, without effecting degree or duration of block. In solutions with epinephrine there were no differences in onset, degree, or duration between lidocaine alkalinized with sodium bicarbonate *versus* NaOH. In part II, addition of sodium bicarbonate or NaOH to 1.0% commercial lidocaine without epinephrine did not accelerate onset compared with the unalkalinized solution. However, adding sodium bicarbonate decreased the degree and duration of block by 25% and more than 50%, respectively, compared with lidocaine unalkalinized and alkalinized with NaOH. With epinephrine, sodium bicarbonate hastened onset without effecting degree and duration compared with the unalkalinized solution.**

Conclusions: **With 1% commercial lidocaine without epinephrine, sodium bicarbonate decreases the degree and duration of block. However, in solutions with epinephrine, sodium bicarbonate hastens onset, without effecting degree or duration. (Key words: Adjuvant; epinephrine; local anesthesia.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Pain Research Center, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital; † Klinikvorstand, Medizinische Klinik; ‡ Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School.

Received from the Pain Research Center, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts; the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts; and Klinikvorstand, Medizinische Klinik, Veterinarmedizinische Universitat, Wien, Austria. Submitted for publication January 12, 2000. Accepted for publication May 18, 2000. Supported by grant No. GM 35647 from the US Public Health Service, National Institutes of Health, Bethesda, Maryland (to Dr. Strichartz).

Address correspondence to Dr. Strichartz: Pain Research Center, Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115. Address electronic mail to: gstrichz@zeus.bwh.harvard.edu.

MANY anesthesiologists believe that adding sodium bicarbonate to plain lidocaine hydrochloride can enhance the efficacy of this local anesthetic. This topic has been most widely investigated in epidural anesthesia. Studies have shown that adding sodium bicarbonate to lidocaine hydrochloride without epinephrine improves the quality of epidural block, whereas adding sodium bicarbonate to lidocaine with epinephrine does not. The addition of 8.4% sodium bicarbonate to 2% lidocaine hydrochloride without epinephrine (1:10, vol:vol) was shown to decrease onset time[1,2] and enhance the depth of epidural block at L4–S1.[2] When bicarbonate was added to 2% lidocaine hydrochloride with epinephrine (1:200,000), neither onset time nor depth of epidural block at L4–S1 roots was altered.[3]

Most clinical investigators addressing this question have used epidural anesthesia as their paradigm. Accordingly, the clinical literature remains unclear as to whether adding sodium bicarbonate to either plain lidocaine or lidocaine with epinephrine improves the quality of peripheral nerve block. In addition, the effect of bicarbonate on lidocaine's onset of action in peripheral nerve block remains controversial. For example, Chow *et al.*[4] found that adding 8.4% sodium bicarbonate to 1.5% lidocaine hydrochloride (1:10) with epinephrine (1:200,000) did not speed the onset of analgesia in axillary brachial plexus block. However, adding sodium bicarbonate at the same concentration and volume ratio to 2% lidocaine, with and without epinephrine (1:100,000), did decrease the onset time of peribulbar anesthesia.[5] Apart from effects on onset, the actions of bicarbonate on the depth and duration of peripheral nerve block with lidocaine has not been previously described.

In the present study we used a well-defined laboratory model, *i.e.*, sciatic nerve block in the rat,[6,7] to address the effect of sodium bicarbonate on peripheral nerve block performed with lidocaine. We compared onset time, degree of impairment of nociception, *i.e.*, depth of analgesia, and block duration with different lidocaine solutions in rats receiving percutaneous sciatic nerve blocks. Lidocaine solutions, with and without epinephrine, were prepared from either crystalline salt or from a commercially available source (Abbott Laboratories, North Chicago, IL). These solutions were either not alkalinized (plain lidocaine), alkalinized with sodium bicarbonate, or alkalinized with sodium hydroxide (NaOH).

Table 1. Composition of Solutions Injected for Sciatic Nerve Block

Name	n	Symbol	Description	pH ± 0.05
Part I. 0.5% Solutions prepared from crystalline lidocaine HCl				
L	10	▲	0.5% lidocaine HCl (unalkalinized)	5.13
LOH	10	○	0.5% lidocaine HCl with NaOH	7.85
LBC	10	●	0.5% lidocaine with 8.4% sodium bicarbonate (10:1)	7.85
LE	10	□	0.5% lidocaine with epi. (1:100,000) and NaOH	7.85
LBCE	10	■	0.5% lidocaine HCl epi. (1:100,000) and 8.4% sodium bicarbonate (10:1)	7.85
Part II. 0.5% Commercial lidocaine HCl solutions				
CL	10	▲	0.5% lidocaine HCl (unalkalinized)	6.58
CLOH	10	○	0.5% lidocaine HCl with NaOH	7.85
CLBC	10	●	0.5% lidocaine with 8.4% sodium bicarbonate (10:1)	7.99
CLE	10	□	0.5% lidocaine HCl with epi. (1:100,000) (unalkalinized)	6.46
CLBCE	10	■	0.5% lidocaine HCl with epi. (1:100,000) and 8.4% sodium bicarbonate (10:1)	7.85
1.0% Commercial lidocaine HCl solutions				
*CL	10	▲	1% lidocaine HCl (unalkalinized)	6.64
*CLOH	10	○	1% lidocaine HCl with NaOH	7.85
*CLBC	9	●	1% lidocaine with 8.4% sodium bicarbonate (10:1)	7.75
*CLE	9	□	1% lidocaine HCl with epi. (1:200,000) (unalkalinized)	4.46
*CLBCE	9	■	1% lidocaine HCl with epi. (1:200,000) and 8.4% sodium bicarbonate (10:1)	7.49

Materials and Methods

Animals

Male Sprague-Dawley rats (Taconic Farms, Germantown, NY) weighing 250–350 g were housed in the Brigham and Women's Hospital animal facilities with a 12-h light–dark cycle. All behavioral testing and surgical procedures in this study were approved by the Harvard Medical Area Committee on Animals. All animals used in these experiments were handled for 15 min/day for a 2-week period before the tests to preclude stress-induced analgesia in rats during experimentation. Handling procedures involved persistent tactile contact with one experimenter (C.J.S.) and several applications of a deep pinch with serrated forceps to the fifth metatarsal.[6]

Experimental Design

Percutaneous sciatic nerve blocks were performed with five lidocaine solutions prepared from either crystalline lidocaine hydrochloride at a concentration of 0.5% or commercial lidocaine at a concentration of 0.5% and 1.0% (Abbott Laboratories; table 1).

Preparation of 0.5% Solutions from Crystalline Lidocaine Hydrochloride

Five 0.5% lidocaine solutions (all exactly 0.5% with pH = 5.13 or 7.85) were prepared from the crystalline salt: (1) L: 0.5% plain lidocaine hydrochloride (pH = 5.13 ± 0.05)—50 mg lidocaine hydrochloride powder (Sigma Chemical, St. Louis, MO) was dissolved in 10 ml sterile water (Abbott Laboratories); (2) LOH: 0.5% lidocaine hydrochloride alkalinized with NaOH (pH = 7.85)—50 mg lidocaine hydrochloride powder was dissolved in 10 ml sterile water, and the pH was adjusted to 7.85 with 30 μl (1:333) of 2N NaOH (Fisher Scientific, Pittsburgh, PA); (3) LBC: 0.5% lidocaine hydrochloride with 8.4% sodium bicarbonate (10:1; pH = 7.85)—10 ml of 0.55% lidocaine hydrochloride was prepared by dissolving 55 mg lidocaine hydrochloride in 10 ml sterile water; 10 ml of 8.4% sodium bicarbonate was prepared by dissolving 840 mg of sodium bicarbonate powder (Sigma Chemical) in 10 ml sterile water, and 1 ml of this solution was added to the 10-ml lidocaine solution to make a resultant containing 55 mg lidocaine in 11 ml = 0.5%; (4) LE: 0.5% lidocaine with epinephrine (1:100,000) alkalinized with NaOH (pH = 7.85)—100 mg crystalline epinephrine hydrochloride (Sigma Chemical) was dissolved in 10 ml sterile water, and 10 μl of this (1:100) solution was added to 10 ml of 0.5% lidocaine (made as above) to achieve a final epinephrine concentration of 1:100,000; the pH of this solution was adjusted to 7.85 with 40 μl (1:250) of 2N NaOH; and (5) LBCE: 0.5% lidocaine with epinephrine (1:100,000) alkalinized to pH 7.85 with 8.4% sodium bicarbonate (10:1) (pH = 7.85)—this solution was prepared according to the combined regimens 3 and 4, described above. All pHs were measured at room temperature (20–22°C) using a Model 611 pH meter (Orion

Research Inc., Boston, MA) with a combination Ag/AgCl-glass electrode (Corning Inc., Acton, MA) in a slowly stirred solution to minimize vortex-induced dissolution of carbon dioxide.

Preparation of Crystalline Control Solutions

Three control solutions were prepared. The first contained only sterile water, the second contained epinephrine dissolved in sterile water to a concentration of 1:100,000 (according to regimen 4), and the third contained 8.4% sodium bicarbonate dissolved in sterile water (according to regimen 3) and diluted to a ratio of 1:10.

Preparation of Commercial 0.5% Lidocaine Solutions

Five 0.5% lidocaine solutions were prepared from commercially available solutions. The lidocaine concentration in all solutions was exactly 0.5%, and in solutions with NaOH, pH was adjusted to 7.85. In solutions with epinephrine or sodium bicarbonate, there was no intentional adjustment of pH, in order to simulate clinical conditions: (1) CL: 0.5% unalkalinized lidocaine hydrochloride injection (pH = 6.58); (2) CLOH: 0.5% lidocaine hydrochloride alkalinized with NaOH (pH = 7.85)—10 ml of 0.5% lidocaine hydrochloride injection was alkalinized with 10 μl (1:1000) of 2N NaOH; (3) CLBC: 0.5% lidocaine hydrochloride alkalinized with 8.4% sodium bicarbonate (10:1; pH = 7.99)—1% lidocaine hydrochloride injection (Abbott Laboratories) was diluted to 0.55% solution with 0.9% NaCl injection (Abbott Laboratories); 1 ml of 8.4% sodium bicarbonate injection (Abbott Laboratories) was added to 10 ml of the 0.55% lidocaine solution; (4) CLE: 0.5% unalkalinized lidocaine hydrochloride containing epinephrine (1:100,000) injection (Abbott Laboratories; pH = 6.46); and (5) CLBCE: 0.5% lidocaine hydrochloride with 8.4% sodium bicarbonate (10:1) and epinephrine (1:100,000) (pH = 7.85)—1% lidocaine hydrochloride injection was diluted to 0.55% with 0.9% NaCl injection; 1 ml of 8.4% sodium bicarbonate injection was added to 10 ml of the 0.55% lidocaine hydrochloride solution, and 110 μl of epinephrine hydrochloride (1:1000) injection (American Regent Laboratories, Shirley, NY) was added to this solution.

Preparation of Commercial 1.0% Lidocaine Solutions

Five 1.0% lidocaine solutions were prepared from commercially available solutions. The lidocaine concentration in all solutions was exactly 1.0%, and in solutions with NaOH, pH was adjusted to 7.85. In solutions with epinephrine or sodium bicarbonate there was, again, no intentional adjustment of pH, to simulate clinical conditions: (1) *CL: 1% lidocaine hydrochloride injection (pH = 6.64); (2) *CLOH: 1% lidocaine hydrochloride alkalinized with NaOH (pH = 7.85)—10 ml of 1% lidocaine hydrochloride injection was alkalinized to pH = 7.85 with 15 μl (1:667) of 2N NaOH; (3) *CLBC: 1% lidocaine hydrochloride alkalinized with 8.4% sodium bicarbonate (10:1; pH = 7.75)—a solution of 1.5% lidocaine hydrochloride injection (Abbott Laboratories) was diluted to 1.1% with 0.9% NaCl injection; 1 ml of 8.4% sodium bicarbonate injection was then added to 10 ml of the 1.1% lidocaine solution; (4) *CLE: unalkalinized 1% lidocaine hydrochloride with epinephrine (1:200,000) injection (Abbott Laboratories; pH = 4.46); and (5) *CLBCE: 1% lidocaine hydrochloride with epinephrine (1:200,000) alkalinized with 8.4% sodium bicarbonate (10:1; pH = 7.49)—a solution of 1.5% lidocaine hydrochloride injection was diluted to 1.1% with 0.9% NaCl injection; 1 ml of 8.4% sodium bicarbonate injection was then added to 10 ml of the 1.1% lidocaine solution, and 110 μl of epinephrine hydrochloride injection was then added to this solution.

Preparation of Commercial Control Solutions

Three control solutions were prepared for this component of the study. The first contained only 0.9% NaCl injection, the second contained 1 ml of 8.4% sodium bicarbonate injection combined with 10 ml of 0.9% NaCl injection, and the third contained 100 μl of epinephrine hydrochloride injection (1:1000) combined with 10 ml of 0.9% NaCl injection to make a resultant concentration of 1:100,000.

Injection of Lidocaine Solutions

The injection technique used in this study was the same used by Thalhammer *et al.*[6] and Popitz-Bergez *et al.*[7] to produce a motor and sensory block of the sciatic nerve in a rat. Fifteen groups of rats, each group with n = 9 or 10, received a percutaneous injection with a 27-gauge needle of 100 μl of one of the 15 lidocaine solutions previously described. An additional six groups of rats, each with n = 4, received a percutaneous injection of 100 μl of one of six control solutions.

Evaluation of Sensory Functional Deficit

Analgesia was measured in the ipsilateral limb every 2 min after injection for up to 40 min, and every 10 min thereafter. The neurologic evaluation was a modification of the protocol described by Thalhammer *et al.*[6] Nociception was quantified by evaluating the rat's withdrawal response to a deep pinch (forceful enough to reach bone) by serrated forceps at the fifth metatarsal. The withdrawal response was graded on an ordinal scale of 0 (no withdrawal response) to 4 (a normal, brisk withdrawal response). A score of 4 meant a normal reaction characterized by a brisk, strong paw withdrawal, vocalization, and an attempt to bite the forceps. A score of 3 was characterized by a slower, weaker withdrawal response, vocalization, and no attempt to bite the forceps. A score of 2 corresponded to an even

slower withdrawal response, no vocalization, and no biting of the forceps. A score of 1 was characterized by a very weak attempt to withdraw. And a score of 0 was given when the rat showed none of these responses. Previous reports showed that motor block of the sciatic nerve could not account for withdrawal response deficits, proving that true sensory loss was being tested.[6]

Analgesia was reported as the mean withdrawal response to deep pinch ± SD. The duration of block was defined as the time until the response returned to a value of 3 (75% of normal) after injection. The time of onset was the time it took for the response to reach a value of 2 (50% of normal), from a normal response of 4, after injection. The maximum degree of impairment was considered the lowest withdrawal response score achieved after injection of local anesthetic.

Statistical Analysis

The duration of onset, the degree of block, and the duration of block achieved with lidocaine solutions were compared using the Mann–Whitney U rank sum test (SPSS Software, Chicago, IL). Only groups of rats receiving injection of lidocaine solutions at the same concentration (either 0.5% or 1.0%) and prepared from the same materials (crystalline or commercial lidocaine) were compared against each other. Furthermore, only pairwise comparisons were made between either two groups (those receiving injections of lidocaine solutions without epinephrine) or three groups (those receiving injections of lidocaine solutions with epinephrine). Therefore, the criterion for significance was adjusted, using a Bonferroni approximation, to $P = 0.025$ for pairwise comparison between two groups and $P = 0.017$ for pairwise comparison between three groups.

Results

Analgesia with 0.5% Crystalline Lidocaine Solutions

None of the three control solutions (sterile water, 8.4% sodium bicarbonate (1:10), or epinephrine (1:100,000) produced any impairment of nocifensive function, *i.e.*, a normal withdrawal response of 4 was present for 60 min after injection. Furthermore, there were no indications of motor deficits, such as foot pronation, toe curling, or dragging of the limb.

Considering onset time, alkalinization of 0.5% lidocaine without epinephrine by either NaOH (LOH) or sodium bicarbonate (LBC) produced a faster onset than did unalkalinized lidocaine (L): 3.2 ± 1.3 ($P = 0.006$) and 2.9 ± 1.0 min ($P = 0.0024$) *versus* 6.0 ± 2.1 min (± SD), respectively (fig. 1). Furthermore, onset times with either alkalinizing agent did not differ significantly from each other ($P = 0.678$). Considering degree of block and duration of block, these parameters did not differ significantly among the three solutions. Mean values (± SD) of the lowest withdrawal response score achieved with the L, LBC, and LOH solutions were 1.2 ± 1.0, 1.0 ± 0.8, and 0.4 ± 0.7, respectively ($P \geq 0.059$), and those for duration of block were 15.0 ± 6.2 min, 11.4 ± 3.0 min, and 17.8 ± 7.8 min. Duration of block achieved with the LBC solution was less, but insignificantly so, than that with both L ($P = 0.054$) and LOH ($P = 0.085$).

When 0.5% crystalline lidocaine with epinephrine (1:100,000) was alkalinized to pH 7.85 with either sodium bicarbonate or sodium hydroxide, there were no significant differences ($P \geq 0.1$) between the two in onset, degree, or duration of block (fig. 2). Mean onset times were 2.8 ± 1.0 min for both, mean withdrawal response scores were 0.0 ± 0.0 for LE and 0.2 ± 0.3 for

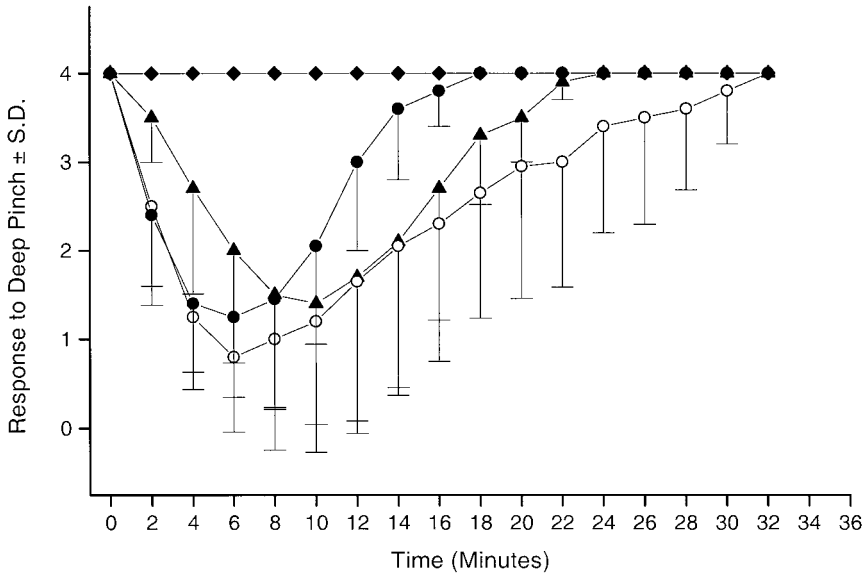

Fig. 1. Time course of analgesia (inhibition of the response to an intense pinch) after injection of 0.5% lidocaine hydrochloride solutions prepared from crystalline lidocaine hydrochloride: plain lidocaine hydrochloride (▲ L; pH = 5.1; n = 10); lidocaine hydrochloride alkalinized with NaOH (○ LOH; pH = 7.8; n = 10); lidocaine hydrochloride alkalinized with sodium bicarbonate (● LBC; pH = 7.8; n = 10); control (◆ n = 4).

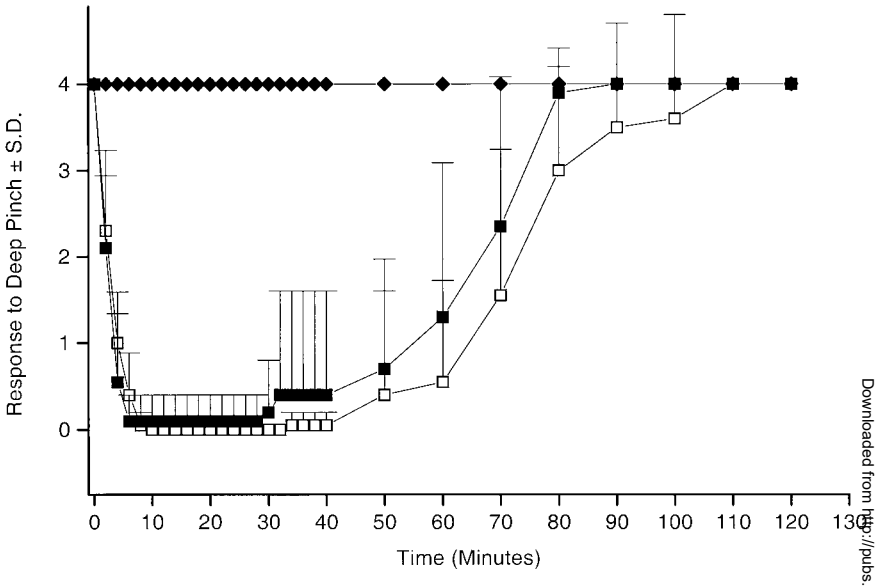

Fig. 2. Time course of analgesia after injection of 0.5% lidocaine solutions with epinephrine prepared from crystalline lidocaine hydrochloride: lidocaine hydrochloride with epinephrine (1:100,000) and neutralized with NaOH (□ LE; pH = 7.9; n = 10); lidocaine hydrochloride with 8.4% sodium bicarbonate (10:1) and epinephrine (1:100,000; ■ LBCE; pH = 7.8; n = 10); control (◆ n = 4).

LBCE, and the mean durations of block were 72.0 ± 16.0 min for LE and 61.0 ± 13.8 min for LBCE.

Analgesia with 0.5% Commercial Lidocaine Solutions

Sciatic nerve injections with the three control solutions for this component of the study (see Methods) produced no analgesia or motor block indications for 60 min after injection.

Regarding onset time, with 0.5% commercial lidocaine without epinephrine, *i.e.*, CL, CLBC, and CLOH, it was not possible to compare this parameter among the solutions because several animals never achieved a withdrawal response score of 2, which was the criterion for onset. Assessment of degree of block showed that alkalinization with sodium bicarbonate (CLBC) produced no significant difference in degree of analgesia (mean withdrawal response score was 3.0 ± 0.6) compared with unalkalinized lidocaine (CL, 2.8 ± 1.1; fig. 3). However, alkalinization with sodium hydroxide CLOH resulted in a significantly greater degree of impairment (1.1 ± 1.2) than that with CL ($P = 0.017$) and CLBC ($P = 0.004$). With regard to block duration, there were no significant differences between unalkalinized lidocaine (13.2 ± 8.3 min) *versus* that alkalinized with sodium bicarbonate (4.6 ± 4.6, $P = 0.021$) or NaOH (12.8 ± 5.5). However, block duration with CLBC was significantly less than that with CLOH ($P = 0.006$).

Compared with unalkalinized solutions of 0.5% commercial lidocaine with epinephrine (1:100,000; CLE), solutions alkalinized with sodium bicarbonate (CLBCE) produced no significant differences relative to onset (4.0 ± 1.3 min for CLE and 3.8 ± 1.1 min for CLBCE; $P = 0.72$), degree (a score of 0.0 ± 0.0 for both), or duration

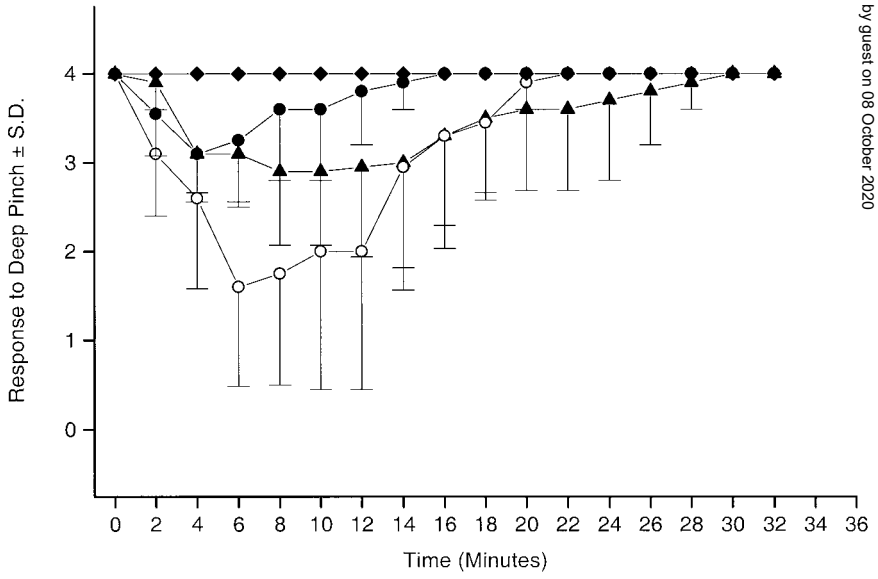

Fig. 3. Time course of analgesia after injection of commercial 0.5% lidocaine solutions: plain lidocaine hydrochloride (▲ CL; pH = 6.6; n = 10); lidocaine hydrochloride alkalinized with NaOH (○ CLOH; pH = 7.8; n = 10); lidocaine hydrochloride alkalinized with 8.4% sodium bicarbonate (10:1; ● CLBC; pH = 8.0; n = 10); control (◆ n = 4).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.