pH-Adjustment of 2-chloroprocaine quickens the onset of epidural anaesthesia

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The effect of pH-adjustment of three per cent 2-chloroprocaine (2-CP, Nesacaine MPF®) on the onset, duration, and spread of epidural analgesia and anaesthesia was studied in patients undergoing lower extremity surgery. Forty ASA physical status I and II patients were randomized to two groups. In a double-blinded fashion, patients in both groups received an epidural injection of 15 ml of local anaesthetic (LA) solution via a Tuohy needle at the L₃₋₄ interspace. Local anaesthesia for Group I was prepared by adding 3 mEq NaHCO₃ to 27 ml three per cent 2-CP and for Group II was prepared by adding 3 ml 0.9 per cent NaCl to 27 ml three per cent 2-CP. Both solutions contained epinephrine (1:200,000). The pH of commercially prepared Nesacaine MPF® was 3.19 ± 0.02 . The pH of the solutions used for Group I and Group II patients were 7.32 ± 0.01 and 3.27 ± 0.02 , respectively. Times to analgesia and anaesthesia at the L₂ dermatome were significantly decreased in Group I patients by 2.5 and 6.6 minutes, respectively. Likewise, pH-adjustment accelerated the attainment of maximum level of block by 2.8 min. No statistical differences were found between groups in the maximum level of epidural block, or in time to 2-segment regression. No precipitation of LA was observed in pH-adjusted

solutions of 2-CP after 24 hours. We recommend the use of pH-adjusted three per cent 2-CP (Nesacaine MPF®) to accelerate the onset of epidural block.

Local anaesthetics, being weak bases, exist in two forms in solution: a protonated water soluble form, and an un-ionized free base, which is more lipid soluble. To prevent precipitation and prolong shelf-life, local anaesthetic solutions are commercially marketed with the pH in the acidic range. Increasing the pH of solutions of lidocaine¹ and bupivacaine² has been shown to decrease the latency of epidural anaesthesia (EA). Recently, a study of pH-adjustment of three per cent 2-chloroprocaine (2-CP, Nesacaine CE®) on post-partum patients found no significant change in the onset of EA.³ Since then, a bisulfite-free solution of 2-CP (Nesacaine MPF®) has become available on the US market. Because of concern over possible neurotoxicity of the bisulfite containing preparation of 2-CP, Nesacaine MPF® is replacing Nesacaine CE® for use in EA. We performed this randomized, double-blind study in non-pregnant patients to determine if and to what extent pH adjustment of Nesacaine MPF® affects the onset and duration of EA.

Key words

ANAESTHETICS, LOCAL: chloroprocaine, pH-adjustment;
ANAESTHETIC TECHNIQUES: epidural; SURGERY: lower extremity.

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Methods

With approval of our institutional human subjects committee and after obtaining written informed consent, 40 unpremedicated ASA physical status I and II patients scheduled for lower extremity surgery under EA were assigned randomly in a double-blind fashion to one of two groups. Group I received 15 ml pH-adjusted three per cent 2-CP. Group II received 15 ml unadjusted 2-CP. The solutions were freshly prepared in the following manner: for Group I, a 30 ml vial of Nesacaine MPF® (Astra Pharmaceuticals, Worcester, MA) was opened, 3 ml local anaesthetic was withdrawn and replaced with 3 ml 8.4 per cent solution NaHCO₃ (3mEq). For Group II, the process was the same, except that 3 ml 0.9 per cent NaCl (saline) was added instead of NaHCO₃. Epinephrine (150 µg) was freshly added to both solutions. The final concentration of 2-CP was 2.7 per cent for both groups.

The solutions were prepared by an anaesthetist not involved with data collection. The investigator collecting data was unaware which local anaesthetic (LA) solution had been injected.

The patient was positioned in the lateral decubitus position (operative side dependent), and the epidural space was identified at L₃₋₄ by loss of resistance to air using a Tuohy needle. A 3 ml test dose of the LA solution was injected if no blood or CSF could be aspirated. If no heart rate increase was noted on the ECG monitor after 60 sec, a further 12 ml (total volume 15 ml) were incrementally injected over two minutes. A catheter was then inserted 5 cm into the epidural space, Tuohy needle removed, and the patient turned supine.

Time "zero" was considered to be the end of LA injection. Using a safety pin testing was conducted at one-minute intervals. Times were recorded as follows: (1) analgesia of the anterior thigh (L₂ dermatome): when the patient could no longer discern a difference between sharp and dull ends of the safety pin; (2) anaesthesia over the L₂ dermatome: when the patient felt no sensation when touched by the safety pin; (3) maximum level of hypaesthesia (thoracic dermatome): where the sharpness of the pin felt the same as when tested over a non-anaesthetized area; (4) time to maximum level of hypaesthesia, and (5) time to two-segment regression of maximum hypaesthetic level.

An epidural block was considered to be present if bilateral sensory and motor block developed. If the operative site was not adequately anaesthetized after 45 min, a supplemental dose of 10 ml of the LA solution was given through the catheter and the patient was excluded from further data analysis. If this failed to provide adequate anaesthesia after ten minutes, general anaesthesia would have been induced. The pH of the LA solutions was measured using a Corning® 125 pH Meter (Corning Scientific Products, Corning Glass Works, Medfield, MA). Ten vials of pH-adjusted 2-CP were set aside and observed for precipitation over 24 hours. The data were tested for statistical significance using a two-tailed unpaired *t* test. Significance was assumed at *P* < 0.05. Data are reported as means ± SD.

Results

There were no significant differences between groups in age, height, or weight (see Table I). All patients developed an epidural block. Anaesthesia of the S₁ dermatome was tested only in patients undergoing ankle procedures. Four patients in Group I and one in Group II who were having ankle surgery did not have adequate anaesthesia over the S₁ dermatome, although anaesthesia was obtained over the L₂ dermatome. Ten ml of LA solution were therefore injected via the epidural catheter produc-

FIGURE 1 Anaesthetic variables in minutes for epidural 2-CP + epi (means ± SD).

ing adequate anaesthesia in all patients. Times to two-segment regression were not obtained on these patients. No patient required general anaesthesia. The pH of commercially prepared 2-CP was 3.19 ± 0.02 . The pH of the LA used in Group I and Group II was 7.32 ± 0.01 and 3.27 ± 0.02 , respectively.

The difference in pH values between the pH-adjusted and the saline adjusted solutions were statistically significant at the *P* < 0.001 level. By applying the Henderson-Hasselbach equation, assuming a pKa of 8.7 for 2-CP,⁴ one can calculate the un-ionized fraction of 2-CP to be 0.00031 per cent for the commercial preparation, 0.00037 per cent for the LA used in the control group, and 4.17 per cent for the LA used in the pH-adjusted group. Thus pH-adjustment produced a ten-thousand-fold increase in the un-ionized fraction of 2-CP present in solution. Times to reach analgesia, anaesthesia, and maximum level of hypaesthesia were significantly shorter in Group I than in Group II patients (see Figure 1 and Table II). Maximum level of hypaesthesia and time to two-segment regression were slightly greater in Group I patients, but this difference did not reach statistical significance (see Figure 2). The pH adjusted solutions of 2-CP showed no evidence of precipitation by visual inspection after 24 hours, although the solution turned yellow in colour.

Discussion

The results of this study demonstrate that increasing the

TABLE I Patient characteristics

	Control group	pH-adjusted group
Age (yrs)	28 ± 9	33 ± 8
Height (cm)	182.2 ± 7.8	180.5 ± 8.2
Weight (kg)	81.0 ± 10.0	82.6 ± 16.2

Values are expressed as mean ± SD. There were no significant differences between groups.

TABLE II Anaesthetic variables (in minutes)

	Control group		pH-Adjusted group		p Value
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range	
Time to analgesia at L ₂	8.8 $\pm$ 2.9	5–14	6.3 $\pm$ 1.8	3–10	0.0025
Time to anaesthesia at L ₂	19.0 $\pm$ 6.1	11–30	12.4 $\pm$ 5.1	6–30	0.0006
Maximum level of hypaesthesia (thoracic dermatome)	8.8 $\pm$ 1.7	T ₁₀ –T ₄	8.0 $\pm$ 1.6	T ₁₀ –T ₅	0.13 (ns)
Time to reach maximum level	10.4 $\pm$ 4.2	4–18	7.6 $\pm$ 2.5	4–14	0.014
Time to 2-segment regression	61.3 $\pm$ 3.1	56–68	65.2 $\pm$ 10.5	55–78	0.124 (ns)

FIGURE 2 Anaesthetic variables for epidural 2-CP + epi (means $\pm$ SD).

pH of three per cent 2-CP (Nesacaine MPF®) from 3.27 to 7.32 accelerates the onset of epidural analgesia and anaesthesia at the L₂ dermatome by an average of 2.5 and 6.6 minutes, respectively. Spread of LA in the epidural space was quicker, but neither the maximum level nor the duration of block were significantly affected by pH-adjustment. Although four patients in Group I and one patient in Group II did not initially reach surgical anaesthesia at the S₁ dermatome, we tested this area only in the few patients undergoing ankle surgery, and therefore feel that no meaningful conclusion can be drawn from this observation.

pH adjustment of 1.5 per cent lidocaine¹ has been shown to shorten the time of onset of epidural anaesthesia. The mechanism by which this occurs presumably results from the increased fraction of local anesthetic found in the uncharged, un-ionized, and thus more lipid soluble form,⁵ and has been extensively discussed elsewhere.^{1,2}

Interestingly, a recent study of pH adjustment of three per cent 2-CP for EA in patients undergoing post-partum tubal ligation found no significant alteration in the latency of epidural blockade.³ Several explanations may account for our different results. Firstly, our method of testing may have been different. In our study analgesia was not

considered to be present until the patient could detect no difference between the sharp and dull ends of a safety pin. We feel our definition is more rigorous than defining analgesia as the time when the safety pin no longer feels sharp, as this sensation could vary from one patient to another. Anaesthesia was not considered to be present until absolutely no sensation was felt by the patient when touched by a safety pin over the L₂ dermatome. We feel this criterion corresponds to adequate surgical anaesthesia. Secondly, Glosten *et al.* used post-partum patients, who may be more sensitive to local anaesthetics than our non-pregnant subjects.⁶ Thirdly, we used Nesacaine MPF®, which has a lower pH than the Nesacaine CE® (3.19 vs. 3.82), and contains ethylenediaminetetraacetic acid (EDTA) as a preservative instead of sodium bisulfite. We did not study the effect of the preservative *per se* on onset of nerve block, but the lower pH of the MPF® preparation could conceivably make a difference in onset time. As Nesacaine MPF® is gradually replacing Nesacaine CE® in the US due to concern about the role of sodium bisulfite in chloroprocaine related neurotoxicity,⁷ it will be frequently encountered in clinical practice.

Most important, we added a larger volume of NaHCO₃ (3 mEq per 27 ml 2-CP) resulting in a higher pH than the LA solution used by Glosten (7.32 vs 7.08), effectively increasing the fraction at LA found in the un-ionized form. We believe that it is important to consider the pKa of the LA and the final pH when deciding how much NaHCO₃ to add. For example, adjusting solutions of lidocaine (pKa 7.8) and 2-chloroprocaine (pKa 8.7) to the same pH produces a greater proportion of un-ionized local anaesthetic in the lidocaine solution. It may be that raising the pH more than we did would produce an even faster onset of 2-CP EA than we saw.

In summary, pH adjustment of three per cent 2-CP (Nesacaine MPF®) using 3 mEq NaHCO₃ (3 ml of an 8.4 per cent solution) added to 27 ml LA results in a decreased latency of EA. The onset of surgical anaesthesia at the L₂ dermatome was reached 6.6 min and the maximum level of block 2.8 min sooner. Depending upon the clinical situation, this may be important. There appears to be no

danger of immediate or delayed precipitation of 2-CP. Alkalinizing 2-CP (Nesacaine MPF®) for EA decreases time to reach surgical anaesthesia and may therefore quicken detection of failed blocks and decrease operating room turn over time.

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Résumé

L'effet de l'ajustement du pH du 2-chloroprocaine à trois pour cent (2-CP, Nésacaine MPF®) sur le début d'installation, la durée, et l'étendue de l'analgesie et l'anesthésie épidurale a été étudié chez les patients subissant une chirurgie des membres inférieurs. Quarante patients ASA I et II ont été randomisés en deux groupes dans une étude à double insu. Les patients ont reçu une injection épidurale de 15 ml d'un anesthésique local à travers une aiguille Tuohy au niveau L₃₋₄. Un anesthésique local pour le groupe I fut préparé par l'addition de 3 mEq de NaHCO₃ à 27 ml de trois pour cent de 2-CP. L'anesthésique local pour le groupe II fut préparé par l'addition de 3 ml de 0.9 pour cent de NaCl à 27 ml de trois pour cent de 2-CP. Les deux solutions contenaient de l'épinéphrine (1:200,000). Le pH de la solution commerciale préparée de Nésacaine MPF® était de 3.19 ± 0.02 . Le pH des solutions utilisées pour le groupe I et le groupe II était de 7.32 ± 0.01 et 3.27 ± 0.02 , respectivement. Les temps de l'analgesie et de l'anesthésie au dermatome L₂ étaient significativement diminués dans le groupe I de 2.5 ± 6.6 minutes, respectivement. De même, l'ajustement du pH a accéléré l'atteinte d'un niveau maximal du bloc à 2.8 minutes. Aucune différence statistique ne fut trouvée entre les groupes dans le niveau maximal du bloc épidural ou dans le temps de régression. Aucune précipitation du LA ne fut observée dans les solutions où le pH fut ajusté après 24 heures. On recommande l'utilisation d'un ajustement du pH afin d'accélérer le débit d'installation du bloc épidural.