POTENTIATION OF NERVE BLOCK IN VIVO BY PHYSIOLOGICAL ADJUVANTS IN THE SOLUTION

S. KIRCHA, J. BARSA AND B. R. FINK

SUMMARY

One hundred and seventy-four rats received a standardized 0.4-ml injection into the left infraorbital nerve and all solutions contained lignocaine 0.25 g dl⁻¹. In groups 1–4, the solutions were isoosmotic and contained, besides sodium chloride, potassium chloride 0 or 4 mmol litre⁻¹ and glucose 0 or 20 mmol litre⁻¹ (0 or 360 g dl⁻¹). For groups 5–8, the solutions were hypoosmotic, containing sodium chloride to 0.6 of normal tonicity, but were otherwise identical to solutions 1–4. Presence and duration of sensory block were determined from the reflex sublingual electromyographic response to periodic homolateral and contralateral electrical stimulation of the upper lip. In groups 1–4, the presence of potassium chloride 4 mmol litre⁻¹ approximately doubled the duration of blockade (P < 0.001). Groups 5–8 showed that hypoosmolarity also doubled the duration of block (P < 0.001), but hypoosmolarity and potassium chloride did not have additive effects. It is concluded that addition of potassium chloride 4 mmol litre⁻¹ to isotonic solutions of lignocaine is likely to enhance their clinical effectiveness.

Systemic toxic reactions to local anaesthetic agents continue to be an important complication of several techniques of regional anaesthesia. Toxic reactions can occur either as a result of the use of a large dose of local anaesthetic and subsequent systemic absorption, or as a result of intravascular injection. It is known that impulse conduction in peripheral nerves can be reversibly inhibited by modifying extracellular factors such as the potassium concentration (Huxley and Stämpfli, 1951), the glucose concentration (Fink and Calkins, 1981) and ambient osmolarity (Fink, Barsa and Calkins, 1979) in vitro. The present study investigated these factors in an animal model to determine their potential value in clinical practice.

MATERIALS AND METHODS

One hundred and seventy-four Sprague-Dawley male rats, weighing 500–600 g were studied. The animals were fed Purina Rat Chow and tap water ad libitum. They had been lightly anaesthetized with pentobarbitone 30 mg kg⁻¹ i.p. A standardized injection of the maxillary nerve at the left infraorbital foramen was performed (Fink et al., 1975); the contralateral side served as a control. The injections were given double-blind with eight coded solutions (table I), one solution per rat, using a fixed volume of 0.4 ml containing 1 mg of lignocaine hydrochloride (0.25 g dl⁻¹). Solutions 1–4 were isoosmotic (isotonic). They contained sodium chloride and, respectively, potassium chloride 0 or 4 mmol litre⁻¹ and glucose 0 or 20 mmol litre⁻¹. Solutions 5–8 were hypoosmotic, containing sodium chloride sufficient only for 0.6 isotonicity (measured by Wescor osmometer), but otherwise corresponding to solutions 1–4. The final osmolalities of the solutions are listed in table II. Onset and duration of anaesthesia were determined by periodical electrical

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<th>Group</th>
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<th>6</th>
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<td>23</td>
<td>17</td>
<td>27</td>
<td>20</td>
<td>20</td>
<td>19</td>
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<tr>
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<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Potassium (mmol litre⁻¹)</td>
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<th>Group</th>
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<tr>
<td>Osmolarity (mosmol litre⁻¹)</td>
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<td>306</td>
<td>307</td>
<td>301</td>
<td>170</td>
<td>178</td>
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<td>180</td>
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<tr>
<td>±</td>
<td>8</td>
<td>±4</td>
<td>±7</td>
<td>±5</td>
<td>±7</td>
<td>±5</td>
<td>±8</td>
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stimulation of the upper lip on the injected and control sides and the reflex electromyographic response of the sublingual muscles (fig. 1). The electrical stimulation consisted of 100-mV, 6-ms square-wave pulse trains produced by a Grass S44 stimulator. The stimulation was delivered through bipolar electrodes (two 25-gauge needles, 3 mm apart). The electromyographic response from muscles of the sublingual area was recorded and displayed on a Tektronix 532 cathode-ray oscilloscope and photographed with a Polaroid camera. Absence or depression of electromyographic response by 50% or more unilaterally on the injected side was interpreted as blockade. To verify that the injections were made in the correct position in the infraorbital foramen, all the animals at the end of the experiment received a control injection of a known solution—0.2 ml of 1% lignocaine. This was done to ascertain whether 1% lignocaine, applied at the site of injection, produced a block of standard duration (96 ± 18 min) (Fink et al., 1975). Animals in which the block with 1% lignocaine lasted less than 60 min were excluded from the study. Statistical significance of the group differences was evaluated by Scheffe's test for multiple observations (Brownlee, 1965).

RESULTS

In group 1, regarded as the control group (n = 28), in which the animals received an isoosmotic solution of lignocaine + sodium chloride, with no added potassium or glucose, duration of anaesthesia aver-

![Figure 1](image_url)  
**Fig. 1.** Electromyograms of sublingual muscle responses to electrical stimulation of upper lip in a rat lightly anaesthetized with pentobarbitone, before and after injection of lignocaine hydrochloride 1 mg (0.25 g dl⁻¹) in an isotonic solution containing potassium chloride 4 mmol litre⁻¹, glucose 20 mmol⁻¹ and sodium chloride to a total osmolality of 306 mosmol litre⁻¹. The upper and lower traces in each panel present the response to contralateral and homolateral upper lip stimulation. Stimulation was repeated at intervals of 3–5 min. The response recovered to 50% of control in 80 min, and this was accordingly recorded as the duration of the block in this experiment.
aged 22 ± 11 min (± SD; fig 2). In group 2, in which the isoosmotic solution contained in addition glucose 20 mmol litre⁻¹ (360 mg dl⁻¹), the mean duration of block was 29 ± 14 min. The presence of potassium chloride 4 mmol litre⁻¹ in the isoosmotic solution, without or with glucose (solutions 3 and 4) yielded mean durations of block of 50 ± 22 min and 57 ± 27 min.

The results with hypoosmotic solutions, taken in the same sequence (solutions 5–8), showed mean block durations of 51 ± 17, 52 ± 17, 56 ± 12 and 49 ± 12 min, respectively. The differences between results with solution 1 and each of the other solutions except solution 2 were all significant (P < 0.001); the difference with solution 2 was less significant (P < 0.05).

DISCUSSION

The lignocaine concentration used (0.25 g dl⁻¹) was selected after preliminary experiments demonstrated that this concentration produced a convenient duration of blockade relative to the duration of moderate reflex obtundation obtainable with one i.p. injection of pentobarbitone (30 mg kg⁻¹). In isoosmotic and hypoosmotic solutions, the presence of potassium chloride 4 mmol litre⁻¹ (groups 3, 4, 7, 8) approximately doubled the duration of blockade. The idea of including potassium chloride with local anaesthetic to increase the extracellular potassium concentration and depolarize the membrane has been tried by several authors (Bromage and Burfoot, 1966; Aldrete et al., 1969). Aldrete and colleagues (1969) demonstrated that inclusion of potassium chloride 180 mmol litre⁻¹ prolonged the duration of peripheral nerve block using 2% lignocaine solution. Bromage and Burfoot (1966) used potassium chloride 120 mmol litre⁻¹ in conjunction with 2% lignocaine in clinical extradural anaesthesia and observed a prolongation of block. However, there was an untoward reaction, notably a convulsion, following inadvertent perforation of the spinal dura and injection of a large concentration of potassium.

The risk of convulsion and cardiac arrhythmia prevented further clinical trials of local anaesthetic solutions containing a high concentration of potassium. In the present study on animals, we used a safe, physiological concentration of potassium chloride tested successfully in vitro on a previous occasion (Fink and Calkins, 1981). The effectiveness of the physiological concentration can be understood in the light of the Nernst equation, according to which successive equal increments in the extracellular potassium concentration will have a geometrically decreasing effect on the membrane potential.

The presence or absence of glucose 20 mmol litre⁻¹ in the anaesthetic solution did not seem to influence the duration of block. Hypoosmolarity of the solution in the absence of potassium chloride also prolonged the period of block (groups 5 and 6); however, there was no additional prolongation with the inclusion of potassium chloride (groups 7 and 8). Presumably, absorption or equilibration of the injected solution prevented

![Graph](image-url)

**Fig. 2.** Duration (min) of infraorbital nerve block following injection of various solutions containing lignocaine 0.25 g dl⁻¹. mM = mmol litre⁻¹.
cumulative prolongation of the adjuvant effects.

Previous experiments have shown that ambient hypoosmolarity depresses nerve excitability, even in the absence of local anaesthetic (Fink, Barsa and Calkins, 1979) and it has been suggested that this effect may contribute to the effectiveness of hypobaric spinal anaesthesia (Barsa et al., 1979). Peripheral nerves are known to withstand this treatment in vivo without harm (Barsa et al., 1982).

CONCLUSIONS

The presence of a physiological concentration of potassium doubled the duration of blockade produced by a solution of lignocaine in plain isotonic sodium chloride. Hypoosmolarity of the solution conferred no additional advantage. One may suggest that inclusion of potassium chloride 4 mmol litre\(^{-1}\) in isotonic commercial solutions of local anaesthetic might decrease the amount of lignocaine required for a nerve block and constitute a safety measure that deserves a clinical trial.

ACKNOWLEDGEMENTS

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REFERENCES


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POTENTIALISATION DU BLOC NERVEUX IN VIVO PAR DES ADJUVANTS PHYSIOLOGIQUES DANS LA SOLUTION

RESUME

Cent soixante-quatorze rats ont reçu une injection standardisée de 0,4 ml dans le nerf sous-orbitaire gauche et toutes les solutions contenaient 0,25 g dl\(^{-1}\) de lignocaine. Dans les groupes 1-4, les solutions étaient iso-osmotiques et contenaient, outre du chlorure de sodium, du KCl 0 ou 4 mmol litre\(^{-1}\) et du glucose 0 ou 20 mmol litre\(^{-1}\) (0 ou 360 g dl\(^{-1}\)). Dans les groupes 5-8, les solutions étaient hypo-osmotiques, contenant du chlorure de sodium à 0,6 fois la tonicité normale, mais étaient par ailleurs semblables aux solutions 1-4. L'existence et la durée du bloc sensitif étaient déterminées par la réponse électromyographique du réflexe sublingual à la stimulation électrique périodique homolatérale et contralatérale de la lèvre supérieure. Dans les groupes 1-4, la présence de KCl 4 mmol litre\(^{-1}\) doublait approximativement la durée du bloc (P < 0,001). Les groupes 5-8 permirent de montrer que l'hypo-osmolarité doublait également la durée du bloc (P < 0,001) mais que l'hypo-osmolarité et le KCl n'avaient pas d'effets additifs. Nous en concluons que l'adjonction de KCl 4 mmol litre\(^{-1}\) à des solutions isotoniques de lignocaine, peut sûrement augmenter leur efficacité clinique.

SUMMARY

Hundred and seventy-four rats received a standardized injection of 0.4 ml in the infraorbital nerve, with each solution containing 0.25 g dl\(^{-1}\) lignocaine. In groups 1-4, solutions were iso-osmotic and contained, apart from sodium chloride, KCl 0 or 4 mmol litre\(^{-1}\) and glucose 0 or 20 mmol litre\(^{-1}\) (0 or 360 g dl\(^{-1}\)). In groups 5-8, solutions were hypo-osmotic, containing sodium chloride at 0.6 times normal tonicity and were otherwise similar to solutions 1-4. The existence and duration of sensory block were determined by the electrophysiological reaction on periodical homolateral and contralateral evoked sublingual reflex. In groups 1-4, the presence of KCl 4 mmol litre\(^{-1}\) doubled approximately the duration of the block (P < 0.001). Groups 5-8 permitted to show that hypo-osmolarity doubled also the duration of the block (P < 0.001), but that hypo-osmolarity and KCl did not have additive effects. We conclude that the addition of KCl 4 mmol litre\(^{-1}\) to isotonical lignocaine-solutions, can certainly increase their clinical efficiency.

ZUSAMMENFASSUNG

Hundert vierundsechzig Ratten erhielten eine standardisierte Injektion von 0,4 ml in den Nervus infraorbitalis, wobei jede Lösung Lignocain 0,25 g dl\(^{-1}\) enthielt. Bei den Gruppen 1–4 waren die Lösungen isosmotisch und enthielten, neben NaCl, KCl 0 oder 4 mmol litre\(^{-1}\) und Glucose 0 oder 20 mmol litre\(^{-1}\) (0 oder 360 g dl\(^{-1}\)). Bei den Gruppen 5–8 waren die Lösungen hypoosmotisch und außer einem NaCl von 60% normaler Tonicität mit den Lösungen der Gruppen 1–4 identisch. Vorhandensein und Dauer des sensorischen Blocks wurden aus der reflektoriengeschen sublingualen elektromyographischen Reaktion auf periodische homolaterale und kontralaterale Elektrostimulation der Oberlippe bestimmt. Bei den Gruppen 1–4 verdoppelte die K\(^+\)-Konzentration von 4 mmol litre\(^{-1}\) anhaltend die Dauer der Blockade (P < 0,001). Bei den Gruppen 5–8 zeigte sich, daß Hypoosmolarität ebenfalls die Dauer der Blockade verdoppelte (P < 0,001), zusätzlichlicher K\(^+\)-Gehalt jedoch keinen zusätzlichen Einfluß hatte. Der Zusatz von KCl 4 mmol litre\(^{-1}\) zu isotonischer Lignocain-Lösung verstärkt also ihre klinische Wirksamkeit.

POTENZIERUNG VON IN-VIVO-NERVENBLOCKADEN DURCH PHYSIOLOGISCHE ADJUVANTIEN DER LÖSUNG

SUMARIO

Aciento setenta y cuatro ratas se les administró una inyección normalizada de 0,4 ml en el nervio infraorbital izquierdo, conteniendo todas las soluciones 0,25 g dl\(^{-1}\) de lignocaina. Para los grupos 1 a 4, las soluciones fueron isosmóticas y contenían,
además de cloruro sódico, cloruro potásico 0,64 mmol litro$^{-1}$ y glucosa 0,620 mmol litro$^{-1}$ (0,6360 g dl$^{-1}$). Para los grupos 5 a 8, las soluciones fueron hipoosmóticas, conteniendo cloruro sódico con una toxicidad del 0,6 de lo normal, pero fueron idénticas a las soluciones de los grupos 1 a 4 en todo lo demás. La presencia y duración del bloqueo sensorial se determinaron de la respuesta electromigrática del reflejo sublingual ante la estimulación eléctrica y periódica contralateral y homolateral del labio superior. La presencia de 4 mmol litro$^{-1}$, aproximadamente, de cloruro potásico prolongó al doble la duración del bloqueo ($P < 0,001$). Los grupos 5 a 8 mostraron también que la hipoosmolarity también dobló el periodo de duración del bloqueo ($P < 0,001$), pero la hipoosmolarity y el cloruro potásico no presentaron efectos aditivos. Se concluye que la incorporación de 4 mmol litro$^{-1}$ de cloruro potásico a las soluciones isotónicas de lignocaina posiblemente realzará su efectividad clínica.