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Short Communication

Stability of adrenaline pH-adjusted solutions of local anaesthetics

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Introduction

Reference books state that increasing the pH of adrenaline (epinephrine) solutions favours their oxidation [1], which becomes significant at pH values above 6 [2]. Thus, during cardiopulmonary resuscitation, bicarbonate and adrenaline are preferably infused in two separate venous lines [3]. Adrenaline is added to local anaesthetics to prolong their duration of action and reduce their systemic toxicity [4]. However, local anaesthetics are weak bases and are prepared commercially in slightly acidic solutions of pH 5–7 [5, 6]. To reduce the rate of oxidation of adrenaline in these solutions, a strongly acidic antioxidant, sodium metabisulphite is added [7].

Recent reports have shown that pH-adjustment of local anaesthetics decreases the time to onset of sensory block [8, 9] and increases the duration of the block [8] by increasing the proportion of the non-ionized lipophilic form of the drug. Surprisingly, preliminary reports suggest that although the pH of the solution is increased to 7, the concentration [10] and biological action [11] of adrenaline remained constant for at least 2 h. The aim of the present study was to determine adrenaline concentrations over 1 week in pH-adjusted solutions of lignocaine (lidocaine) and bupivacaine.

Experimental

Solutions

The solutions studied were commercially prepared solutions (20 ml) of 0.5% w/v bupivacaine with 1:200,000 adrenaline (5 $\mu g\ ml^{-1}$) and of 2% w/v lignocaine with 1:80,000 adrenaline (12.5 $\mu g\ ml^{-1}$) (Lab. R. Bellon, France). The concentration of sodium metabisulphite in these local anaesthetic solutions was 0.03 w/v.

Ten bottles of the same batch were studied for each local anaesthetic. The pH-adjustment was performed with two primary goals: to increase the pH of the solution to that close to physiological pH; and to avoid any macroscopic precipitation. Different volumes and three different concentrations, 1.4, 4.2 and 8.4% w/v of sodium bicarbonate, respectively, were used. The pH-adjusted solutions were exposed to ambient conditions of temperature and light.

Methods

Measurement of pH. Measurements of pH were performed with a pH meter (Radiometer, Copenhagen, pHm 82: sensitivity 0.01 pH unit) calibrated before each measurement with known buffer solutions of pH 4 and 7.

Measurement of adrenaline concentration. Adrenaline concentrations were measured by a

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high-performance liquid chromatographic (HPLC) procedure with electrochemical detection. The diluted samples were analysed with a HPLC system (Waters, Milford, MA, USA) using a CLIN-REP column. Detection was performed by an amperometric system at 0.70 V (Waters, M 460). The mobile phase was methanol–aqueous buffer containing sodium acetate (150 mM), citric acid (20 mM), octane sulphate (3.75 mM), dibutylamine (1 mM) and sodium EDTA (0.135 mM) (5:95, v/v). The assay was linear over the range 1–20 $\mu g\ ml^{-1}$. The RSD was 5% at 5 $\mu g\ ml^{-1}$ ($n = 10$).

Statistical analysis. Values obtained for adrenaline concentrations were analysed statistically using one-way analysis of variance followed by Student's *t*-test when necessary. A probability level of $P < 0.05$ was considered to be statistically significant.

Results

The changes in pH after adjustment with different concentrations and volumes of sodium bicarbonate solution added to solutions of either lignocaine or bupivacaine are shown in Table 1.

Concentrations of adrenaline in solutions of local anaesthetics during the first week after addition of sodium bicarbonate are shown in Table 2. No significant decrease in the concentration of adrenaline could be observed during 1 week in either bupivacaine or lignocaine solutions.

Conclusions

Increases in pH to give values close to physiological pH were obtained by adding sodium bicarbonate solutions of local anaesthetics con-

Table 1
Effect on pH of different concentrations and volumes of sodium bicarbonate solution added to bupivacaine and lignocaine solutions (mean ± SD)

Commercial preparations used (and original pH)	Volume of sodium bicarbonate solution added and resulting pH 1.4% w/v		4.2% w/v		8.4% w/v	
	ml	pH	ml	pH	ml	pH
0.5% Bupivacaine with 1:200,000 adrenaline (pH = 3.66 ± 0.06)	1.5	6.68 ± 0.01	0.7	6.87 ± 0.02	0.2	6.74 ± 0.01
		1.5 ml				1.5 ml
2% Lignocaine with 1:80,000 adrenaline (pH 4.59 ± 0.06)	1.5	6.5 ± 0.02	—	—	1.5	7.05 ± 0.02

Table 2
Concentrations of adrenaline found in solutions of local anaesthetics before and after pH-adjustment and during storage for 1 week

	Concentration of adrenaline ($\mu g\ ml^{-1}$) 0.5% Bupivacaine, 1:200.000			2% lignocaine, 1:80.000	
	Volume sodium bicarbonate solution				
Time	1.4% w/v 1.5 ml	4.2% w/v 0.7 ml	8.4% w/v 0.2 ml	1.4% w/v 1.5 ml	8.4%w/v 1.5 ml
Before addition	6.1	6.1	6.1	12.5	12.5
1 h	5.9	6.4	6.3	11.9	12.4
2 h	6.0	5.7	6.0	13.0	13.3
3 h	6.4	6.0	6.0	11.8	11.5
6 h	6.3	5.7	5.8	—	—
24 h	6.2	5.8	5.9	12.8	12.8
48 h	5.9	5.6	5.6	12.8	12.0
7 days	6.1	5.8	5.7	11.4	11.5

taining adrenaline. The concentration of adrenaline in such pH-adjusted solutions did not decrease significantly after 1 week of storage.

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