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Could alkalinization worsen local anesthetic systemic toxicity?

Local anesthetics (LA) are sodium channel antagonists commonly used for pain control by anesthesiologists, emergency physicians, dentists, and other clinicians [1]. Unintentional intravascular injection or overdose may lead to local anesthetic systemic toxicity (LAST), which is characterized by paresthesias, angor animi, seizures, ventricular dysrhythmias, and cardiac arrest [2]. Treatment guidelines emphasize early administration of intravenous lipid emulsion, low-dose epinephrine, oxygenation, and seizure control [3]. Some sources additionally recommend hypertonic sodium solutions such as sodium chloride or sodium bicarbonate in order to overcome the sodium channel blockade [4,5].

Local anesthetics are weak bases that bind to domain IV loop S6 on the cytoplasmic surface of the sodium channel [6]. In order to reach the target site, the local anesthetic must diffuse across the lipid membrane; to do so, the drug must be in its uncharged (freebase) form [6,7]. Some weak acids, such as salicylic acid, have increased toxicity in the setting of low systemic pH because they become uncharged and lipophilic, cross the cell membrane, and reach their intracellular site of toxicity [8-10]. Most local anesthetics are weak bases, therefore the ratio of freebase to salt is increased by raising pH. Since local anesthetics access their site of action via a pH-modulated pathway, this raises the question: does increased pH increase local anesthetic toxicity? This paper models the toxicokinetics of local anesthetic systemic toxicity in relation to systemic pH.

The model is based on the Henderson-Hasselbach equation, which yields the relative concentrations of a weak base [B] and its conjugate acid [B+] from the pH and the weak base's pKa. Since the sum of [B] and [B+] is equal to 100%, it is possible to manipulate the equation to derive the percentage of total local anesthetic existing as freebase as a function of pH [Fig. 1]. The pKA of various local anesthetics is available in published literature [2,6]. The relative effect of pH on lipophilicity was compared for various local anesthetics. The pH range was selected to reflect the range wherein a patient may be expected to survive, i.e., from 6.8 to 7.6. Special attention was given to pH changes near normal range, i.e., from 7.3 to 7.5.

The results of the model indicate the percentage existing as freebase of all local anesthetics increased with pH except for benzocaine (the only weak acid). The results are summarized in Table 1 and graphically in Fig. 2. Local anesthetics with a low pKa such as lidocaine, prilocaine, mepivacaine, and bupivacaine showed a more dramatic increase in concentration than those with a higher pKa such as procaine, cocaine, and chloroprocaine.

When increasing the pH from 7.3 to 7.5, the percent local anesthetic existing as freebase increased by 9.4% for lidocaine, 10.2% for prilocaine, 10.2% for mepivacaine, and 6.4% for bupivacaine. The same change in pH raised the percentage of freebase by 1.4% for procaine, 2.6% for cocaine, and 0.9% for chloroprocaine. When increasing the pH from 7.3 to 7.5 the percent of benzocaine existing as an uncharged molecule decreased by 9.4%.

This toxicokinetic model is limited because it is based on a mathematical formula, not on clinical data. Limitations include the presumption that the primary site of toxicity for local anesthetics is intracellular, and increased lipophilicity increases toxin entry into the cell. There is no modelling of pH-modulated protein binding, however in toxicity substances may saturate protein binding sites and the free fraction may be greater than in the setting of therapeutic concentrations.

The results of this model indicate that lipophilicity of local anesthetics increases with pH. There are no human clinical data to guide how changing pH affects local anesthetic toxicity, therefore using a toxicokinetic model may help clinical management [11].

When treating LAST some clinicians may administer hypertonic sodium bicarbonate intending to overcome the dangerous sodium channel blockade or to correct metabolic acidosis. The bicarbonate anion transiently raises serum pH, and may allow for more toxin to diffuse into cardiomyocytes and neurons exacerbating toxicity. Additionally, clinicians may hyperventilate a patient in an attempt to compensate for acidosis or to adequately oxygenate the patient. Hyperventilation induces respiratory alkalosis which would also be expected to increase the percentage of local anesthetic freebase.

The concept of pH modulating toxicokinetics in LAST is similar to that in salicylism. In salicylate poisoning low pH exacerbates toxicity because aspirin becomes uncharged and may diffuse across the cell membrane to the mitochondria where it causes toxicity by decoupling oxidative phosphorylation [8,9]. A crucial element of managing aspirin poisoning is pH optimization; physicians alkalinize the serum and urine to prevent aspirin from entering cells [12]. The basic idea is that minimizing lipophilicity prevents aspirin from reaching the site of toxicity. This same principle may apply to LAST; optimizing a patient's pH may diminish the local anesthetic concentration at the site of toxicity.

In the setting of LAST it is unclear whether the risks of alkalinizing a profoundly acidotic patient outweigh the benefits. A canine model examining pH changes in ropivacaine cardiotoxicity found decreased cardiac output with both acidosis and alkalosis, but was not powered to describe clinically meaningful endpoints [13]. Respiratory alkalosis prolongs cardiotoxicity of local anesthetics in a rat model [14]. It is unclear whether hypertonic sodium is effective in the treatment of LAST, however administration of hypertonic sodium chloride rather than sodium bicarbonate provides a sodium load without alkalinization.

Many toxins have intracellular sites of action. Other sodium channel blockers such as flecainide and diphenhydramine are similar to local anesthetics in their chemical structures (terminal amine separated from an aromatic ring by an intermediate group) and clinical toxicity

$$Percent\ freebase\ (B) = \left(\frac{100\%}{1+10^{(pKa-pH)}}\right)$$

Fig. 1. Formula predicting percentage of local anesthetic existing as uncharged molecule at a given pH.

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Table 1
Predicted percentage of local anesthetic existing as uncharged molecule at a given pH.

Drug	Terminal Amine	pKa	pH								
			6.8	6.9	7	7.1	7.2	7.3	7.4	7.5	7.6
Benzocaine	NA	2.6	90.9	88.8	86.3	83.4	79.9	76.0	71.5	66.6	61.3
Mepivacaine	3°	7.7	11.2	13.7	16.6	20.1	24.0	28.5	33.4	38.7	44.3
Prilocaine	2°	7.7	11.2	13.7	16.6	20.1	24.0	28.5	33.4	38.7	44.3
Articaine	2°	7.8	9.1	11.2	13.7	16.6	20.1	24.0	28.5	33.4	38.7
Lidocaine	3°	7.8	9.1	11.2	13.7	16.6	20.1	24.0	28.5	33.4	38.7
Bupivacaine	3°	8.1	4.8	5.9	7.4	9.1	11.2	13.7	16.6	20.1	24.0
Levobupivacaine	3°	8.1	4.8	5.9	7.4	9.1	11.2	13.7	16.6	20.1	24.0
Ropivacaine	3°	8.1	4.8	5.9	7.4	9.1	11.2	13.7	16.6	20.1	24.0
Tetracaine	3°	8.4	2.5	3.1	3.8	4.8	5.9	7.4	9.1	11.2	13.7
Cocaine	3°	8.6	1.6	2.0	2.5	3.1	3.8	4.8	5.9	7.4	9.1
Procaine	3°	8.9	0.8	1.0	1.2	1.6	2.0	2.5	3.1	3.8	4.8
Chloroprocaine	3°	9.1	0.5	0.6	0.8	1.0	1.2	1.6	2.0	2.5	3.1

White: < 10%, Yellow: 10% to <20%, Orange: 20% to <30%, Red: 30% to <40%, Dark red: > 40%.

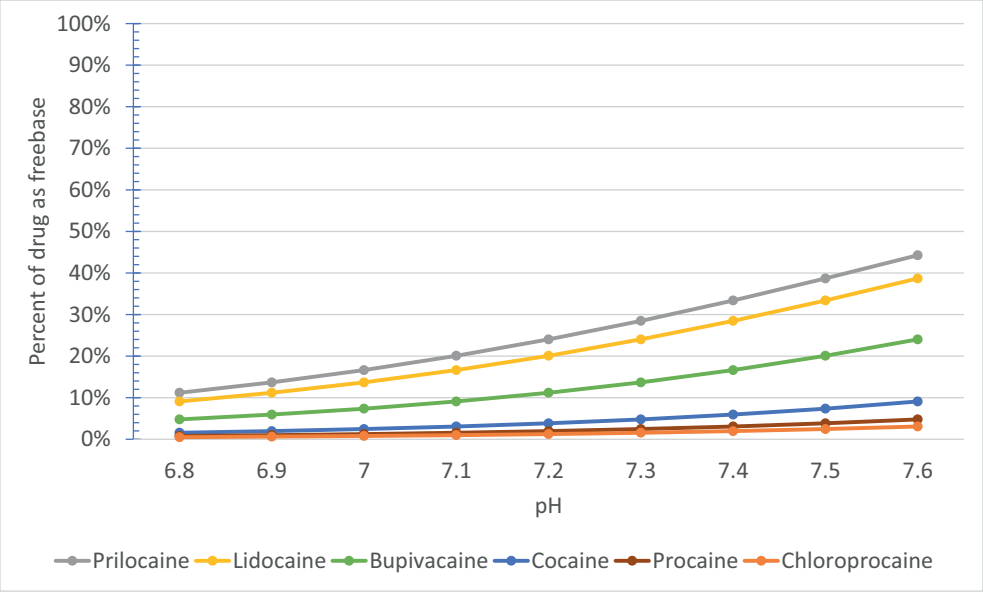

Fig. 2. Graph depicting predicted percentage of local anesthetic existing as uncharged molecule at a given pH.

(e.g., seizures and delayed cardiac conduction). Some of these substances may only be able to reach the toxic site by diffusion across the cell membrane in their de-ionized form. Medical interventions, such as sodium bicarbonate administration or hyperventilation, that raise pH in a patient poisoned with a weak base might worsen toxicity.

Credit authorship contribution statement

Adam Blumenberg: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

None.

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