ILLUMINATIONS

A primer on tissue pH and local anesthetic potency

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Submitted 31 January 2020; accepted in final form 4 May 2020

Pope RL, Brown AM. A primer on tissue pH and local anesthetic potency. Adv Physiol Educ 44: 305–308, 2020; doi:10.1152/advan.00018.2020.—The relationship between pH, pKᵦ, and degree of local anesthetic ionization is quantified by the Henderson-Hasselbalch equation. The degree of ionization of any local anesthetic is not immediately clear due to the x-axis displaying pH - pKᵦ, which requires conversion to pH, based on the pKᵦ for each local anesthetic, a complex process. We present a graphical solution that clarifies the interrelationships between pH, pKᵦ, and degree of ionization by plotting pKᵦ on the x-axis versus the percentage of unionized local anesthetic on the y-axis. The vertical intercept from the x-axis to the pH curves allows rapid and accurate estimation of the degree of ionization of any local anesthetic of known pKᵦ.

INTRODUCTION

The aim of local anesthesia is to rapidly and reversibly block pain, thereby enabling invasive emergency and elective procedures to be safely carried out. Although the molecular target of local anesthetics has been identified as the voltage-gated Na⁺ channel (10, 11), they are not specific for sensory neurons and also block motor fibers, hence the drooping mouth following a visit to the dentist and paralysis that accompanies epidurals. Space limitations preclude a detailed description of the chronological advances in understanding local anesthetic mechanism of action, but the following reviews document this fascinating trajectory (1, 5, 6, 17, 21).

Cocaine was the first compound used as a local anesthetic (6), but its side effects dictated the development of safer structurally related compounds, including novocaine (12), lignocaine (13), mepivacaine, bupivacaine (8), and prilocaine (13). There is still controversy surrounding the mechanism(s) of action of local anesthetics due to the contradictory reports of how they interact with Na⁺ channels at the molecular level. However, a consensus opinion has emerged in which the local anesthetic lodges within the Na⁺ channel, creating an electrostatic barrier that repels Na⁺ from penetrating the channel (14–16).

The local anesthetics share a common structure comprising three elements: 1) a lipophilic aromatic ring, 2) an ester or amide link, and 3) a terminal amine group. The amine group may exist as a tertiary form that is ionized and lipid soluble, or as a quaternary form that is ionized and water soluble. Lipid solubility enhances potency since this facilitates access to peripheral nerves, the target of local anesthetics. Local anesthetics are weak bases with pKᵦ values between 7.6 and 9.2 (7); thus at physiological pH they are mostly in their ionized form (1).

Poor health resulting from asthma, emphysema, diabetes, kidney disease, lung disease, and infection, shock, and hemorrhage can affect blood pH, although acidosis is more common than alkalosis (19). Respiratory acidosis is caused by lung failure, resulting in decreased CO₂ elimination such that the rate of CO₂ production exceeds CO₂ elimination and arterial PCO₂ rises, as does plasma HCO₃⁻ concentration. Metabolic acidosis has multiple causes, including type 1 diabetes, kidney failure, and decreased bicarbonate reabsorption, but the net effect results from the body producing too much, or failing to eliminate sufficient, acid. An extreme example of tissue pH affecting local anesthetic potency is in dental patients with infections, where the inflamed tissue resists the effects of local anesthetics due to the associated acidification (18), which can reach pH 5.0, requiring a course of antibiotics before the tooth can be safely removed using local anesthetics.

The degree of ionization relative to pH can be calculated using the following arrangement of the Henderson-Hasselbalch (3):

\[
\text{pH} - \text{pK} = \log_{10} \left( \frac{[\text{LA}]}{\text{TB} - [\text{LA}]} \right)
\]

where pKᵦ is negative base 10 logarithm of the dissociation constant Kᵦ, and the total buffer (TB), or amount of local anesthetic (LA) is the sum of the ionized LA⁺ concentration ([LA⁺]) and unionized [LA] forms, such that TB = [LA] + [LA⁺]. The ratio depicts [LA]/(TB - [LA]). Derivation and detailed descriptions of this relationship are available in standard medical textbooks (3, 4, 20). The amount of local anesthetic in its unionized form is calculated as:

\[
[\text{LA}] = \frac{\text{TB}}{\text{ratio} + 1} \times \text{ratio}
\]

which can be converted to express the percentage of the unionized LA by dividing by TB and multiplying by 100%

\[
\%\text{unionized} = \frac{100}{\text{ratio} + 1} \times \text{ratio}
\]
The difference between pH and pK_a determines the degree of local anesthetic ionization. A: the sigmoidal relationship between pH and degree of ionization for lidocaine, a local anesthetic with a pK_a of 7.8, is illustrated. The dotted vertical line denotes physiological pH, and the solid vertical line denotes the pH equal to the pK_a of lidocaine, where 50% of the local anesthetic will be in the unionized form. B: the solid vertical lines denote the pK_a values for several common local anesthetics (lignocaine 7.8, bupivacaine 8.1, tetracaine 8.4, procaine 8.9), and the normal physiological pH of 7.4 is denoted by the dotted vertical line. The curves indicate the relationship between the proportion of a local anesthetic present in its unionized form and pK_a at three pH values, upper (7.0), lower (7.8), and normal (7.4) body pH.

The relationship between pH, pK_a, and drug ionization as graphically presented in standard textbooks requires conversion of pH – pK_a to pH based on the pK_a value for a particular drug, as illustrated in Fig. 1A. The difficulty inherent in explaining such transformations to students has been recognized (2). To appreciate the effect of pH across the range of local anesthetic pK_a values, a curve must be generated for each local anesthetic, a laborious process. We have devised a means of presenting the information contained in Eqs. 1 and 3 on a single graph (Fig. 1B), which clarifies the interrelationships between pH, pK_a, and degree of ionization. pK_a is plotted on the x-axis versus the percentage of unionized local anesthetic on the y-axis. Three curves are illustrated: the upper (7.0), lower (7.8), and normal (7.4) limits of the physiological pH range. The pK_a of selected local anesthetics are presented as vertical lines, as is pK_a 7.4.

Workshop. To determine whether our new graphical format facilitated student performance, we delivered a workshop to test student performance in calculations concerning the interrelationships between pH, pK_a, and degree of local anesthetic ionization. We invited 11 students, in the second year of an undergraduate Neuroscience degree, who had performed well in a recent examination of the module, from which the lecture on local anesthetics was drawn, to participate in the workshop. The students were instructed in the relevant content of this paper and then asked to complete questions designed to test their performance (see APPENDIX A). For the first part of the workshop, students were given a conventional graph that displayed pH – pK_a on the x-axis as a visual aid and asked to complete questions in part 1. In the second part of the workshop, the students were given our graph displaying pK_a on the x-axis (Fig. 1B) and asked to complete the questions in part 2. One-half of the students completed part 2 first to counter the practice effect (9).

The mean time taken for students to complete each question is shown (Fig. 2A; data are expressed as means ± SD). In addition, the total time taken for each student to complete the 18 questions was recorded as 846 ± 28 and 518 ± 13 s for parts 1 and 2, respectively. Paired t tests were used to perform comparisons and revealed statistically significant differences, P < 0.0001 and P < 0.0001, respectively, between parts 1 and 2. To test if there was increased accuracy in answering the questions between the two graphical representations, we compared the sum of the squares of the differences between the student estimates and the answer calculated using Eq. 3 for questions 1–9, which revealed a significant difference (P < 0.05; paired t test). Questions 10–18 were not included, as the differences were much smaller and would tend to obscure any effect seen.

DISCUSSION

The objective of the workshop was to determine if our new graphical format improved performance, in terms of time to complete the task and accuracy of the completed task, relating to the interrelationship between pK_a, pH, and degree of local anesthetic ionization. The results suggest that the greatest effect was a reduction in the time taken to complete the tasks, but there was also a significant improvement in accuracy. We split the responses into two sections, since the answers for questions 1–9 were about an order of magnitude larger than for questions 10–18. In addition, the answers to questions 1–9 required the student to interpolate the curve along the y-axis, whose range is 100 units, whereas for questions 10–18 the answer required interpolation of the curve on the x-axis, which extends only 4 units. Figure 2B illustrates this relationship for questions 1–9, which found a significant difference, but for questions 10–18 the P value of 0.12 suggests a trend, which did not reach significance.

In summary, we have developed a graphical format that we consider to facilitate improved performance in quantitative estimates of the interrelationship between pH, pK_a, and degree of local anesthetic ionization, which is supported by statistical analysis of student performance in a dedicated workshop.

APPENDIX A

Students were given a conventional graph that displayed pH – pK_a on the x-axis as a visual aid and asked to complete questions in part 1. The students were given our graph displaying pK_a on the x-axis (Fig. 1B) and asked to complete the questions in part 2.

Part 1. The correct answers are in parentheses after the question.
1. For a local anesthetic (LA) of pK_a 8.7, what is the percentage of the LA in the unionized state at pH 7.0? (1.9%)
2. For a LA of pK_a 6.7, what is the percentage of the LA in the unionized state at pH 7.4? (83.4%)
3. For a LA of $pK_a$ 8.4, what is the percentage of the LA in the unionized state at pH 7.8? (20.1%)

4. For a LA of $pK_a$ 9.0, what is the percentage of the LA in the unionized state at pH 7.0? (1.0%)

5. For a LA of $pK_a$ 8.0, what is the percentage of the LA in the unionized state at pH 7.4? (20.1%)

6. For a LA of $pK_a$ 6.0, what is the percentage of the LA in the unionized state at pH 7.8? (98.4%)

7. For a LA of $pK_a$ 7.8, what is the percentage of the LA in the unionized state at pH 7.0? (13.7%)

8. For a LA of $pK_a$ 6.2, what is the percentage of the LA in the unionized state at pH 7.4? (94.1%)

9. For a LA of $pK_a$ 9.4, what is the percentage of the LA in the unionized state at pH 7.8? (2.4%)

10. What $pK_a$ of LA is required for the drug to be 20% unionized at pH 7.0? (7.6)

11. What $pK_a$ of LA is required for the drug to be 25% unionized at pH 7.4? (7.9)

12. What $pK_a$ of LA is required for the drug to be 15% unionized at pH 7.8? (8.6)

13. What $pK_a$ of LA is required for the drug to be 10% unionized at pH 7.0? (7.9)

14. What $pK_a$ of LA is required for the drug to be 10% unionized at pH 7.4? (8.4)

15. What $pK_a$ of LA is required for the drug to be 40% unionized at pH 7.8? (8.0)

16. What change in pH will be required to increase the percentage of drug in the unionized state from 10 to 20% for $pK_a$ of 8.0? (+0.35 pH units)

17. What change in pH will be required to increase the percentage of drug in the unionized state from 30 to 20% for $pK_a$ of 8.0? (−0.23 pH units)

18. What change in pH will be required to increase the percentage of drug in the unionized state from 40 to 20% for $pK_a$ of 8.0? (−0.43 pH units)

**Part 2.** The correct answers are in parentheses after the question.

1. For a LA of $pK_a$ 8.3, what is the percentage of the LA in the unionized state at pH 7.0? (4.8%)

2. For a LA of $pK_a$ 8.4, what is the percentage of the LA in the unionized state at pH 7.4? (9.1%)

3. For a LA of $pK_a$ 8.5, what is the percentage of the LA in the unionized state at pH 7.8? (16.6%)

4. For a LA of $pK_a$ 9.2, what is the percentage of the LA in the unionized state at pH 7.0? (0.6%)

5. For a LA of $pK_a$ 9.3, what is the percentage of the LA in the unionized state at pH 7.4? (1.2%)

6. For a LA of $pK_a$ 9.4, what is the percentage of the LA in the unionized state at pH 7.8? (2.4%)

7. For a LA of $pK_a$ 7.6, what is the percentage of the LA in the unionized state at pH 7.0? (20.1%)

8. For a LA of $pK_a$ 7.7, what is the percentage of the LA in the unionized state at pH 7.4? (33.4%)
9. For a LA of $pK_a$ 7.8, what is the percentage of the LA in the unionized state at pH 7.8? (50%)

10. What $pK_a$ of LA is required for the drug to be 25% unionized at pH 7.0? (7.5)

11. What $pK_a$ of LA is required for the drug to be 25% unionized at pH 7.4? (7.9)

12. What $pK_a$ of LA is required for the drug to be 25% unionized at pH 7.8? (8.3)

13. What $pK_a$ of LA is required for the drug to be 15% unionized at pH 7.0? (7.8)

14. What $pK_a$ of LA is required for the drug to be 15% unionized at pH 7.4? (8.2)

15. What $pK_a$ of LA is required for the drug to be 15% unionized at pH 7.8? (8.6)

16. What change in pH will be required to increase the percentage of drug in the unionized state from 9 to 20% for $pK_a$ of 8.0? (+0.40 pH units)

17. What change in pH will be required to increase the percentage of drug in the unionized state from 50 to 28% for $pK_a$ of 8.0? (−0.41 pH units)

18. What change in pH will be required to increase the percentage of drug in the unionized state from 20 to 38% for $pK_a$ of 8.0? (+0.39 pH units)

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.M.B. conceived and designed research; R.L.E.P. and A.M.B. analyzed data; A.M.B. prepared figures; R.L.E.P. and A.M.B. drafted manuscript; R.L.E.P. and A.M.B. approved final version of manuscript.

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