



# Alkalinisation of local anaesthetic solutions

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## Summary

**Commercial local anaesthetic solutions have an acidic pH to maximise their water solubility and chemical stability. This increases their shelf-life. Immediately before injection, alkali can be added to raise the pH towards the physiological pH. This is called 'alkalinisation' or 'buffering' of the solution. Anaesthetic activity is dependent on having both the ionised and non-ionised forms of the drug present after injection. Alkalinisation increases the proportion of non-ionised drug and this could be advantageous. Care must be taken, because if too much alkali is added, the local anaesthetic will precipitate. When used for infiltration anaesthesia or block of small nerves, alkalinised solutions of local anaesthetic are less painful when injected. The onset of local anaesthesia may also be slightly quicker. For epidural anaesthesia or block of large nerves the amount of time saved is minimal and so alkalinisation is not practically useful for these procedures.**

Key words: buffering, lignocaine, pain.

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## Introduction

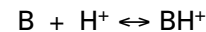
After the injection of a local anaesthetic solution into the tissues there is a delay until the anaesthetic block is working satisfactorily. One technique that may decrease this delay is referred to as 'alkalinisation' of the local anaesthetic solution.<sup>1</sup> This means adding a planned amount of a basic solution (typically sodium bicarbonate) to the local anaesthetic solution before injecting it into the target tissues. This practice may also decrease the pain on injection of the solution.<sup>2</sup> Two key questions to be addressed are:

- What is the basis for this practice?
- Does it make a practically useful difference?

## Local anaesthetic solutions and the pKa-pH relationship

Local anaesthetics are basic drugs which have a pKa (derived from the dissociation constant) close to the normal extracellular pH of 7.4, for example lignocaine has a pKa of 7.9. The drugs

exist in two forms in the solution – the uncharged basic form (B) and the charged form (BH<sup>+</sup>).



The importance of the pKa-pH relationship is that this knowledge allows the calculation of the relative amounts of these two forms. When the pH is equal to the drug's pKa, 50% of the drug is in the uncharged form, and 50% is in the charged form. In acidic solutions most of the drug will be in the charged form. (The exception to this is the topical anaesthetic agent benzocaine which is noncharged and not used for infiltration anaesthesia.) To be useful when injected the local anaesthetic solution must be present in the tissues in both forms. The reason is that the drug has to diffuse to the site of action across several tissue barriers. The uncharged lipid-soluble form will diffuse across lipid barriers, for example, perineural sheath or cell membrane. The charged water soluble form will diffuse across tissue fluid barriers, for example interstitial fluid.

The site of action of the local anaesthetic molecule is the inner (or cytoplasmic) end of the sodium channel in the cell membrane. The final pathway for all injected local anaesthetics is to diffuse to the cell membrane (in the charged form) then re-equilibrate to form both charged and uncharged forms adjacent to the outside of the nerve cell membrane. The molecules diffuse across the nerve cell membrane in the uncharged form then re-equilibrate in the cytoplasm to have both forms present again. Next the charged form diffuses to and binds to its 'receptor' on the inside of the transmembrane sodium channel. This binding results in a conformational change in the channel protein to block the passage of sodium ions into the cell in response to a subsequent action potential. When a sufficient length of an unmyelinated nerve is impaired in this way, a nerve action potential in that nerve axon is blocked. For a myelinated nerve, the sodium channels are located primarily at the nodes of Ranvier. The channels in several adjacent nodes in the axon have to be blocked to prevent transmission of an action potential.

## Commercial local anaesthetic solutions

The pH of a commercially available local anaesthetic solution has to be acidic to maximise stability in solution and shelf-life. The reasons include:

- solubility – local anaesthetic solutions are aqueous solutions and if provided at a pH close to 7.4 the lipid soluble uncharged form could precipitate out due to its lower water solubility

- stability – the uncharged base form is more unstable at physiological pH so degradation is minimised at a low pH where the drug is predominantly in the charged form
- stability of adrenaline – the adrenaline added to some local anaesthetic solutions is unstable at the physiological pH and more stable at an acidic pH.

Commercially available acidic local anaesthetic solutions have a pH of typically 3.5 to 5.5 and have a shelf-life of three to four years. This pH is so far below the drug's pKa that essentially all the drug is present in the more stable, charged, water-soluble form. Hydrochloric acid is added to lignocaine solutions to achieve this low pH.

Local anaesthetic solutions containing adrenaline are generally at a lower pH than the same solution without adrenaline ('plain solution'). The low pH is often said to be the cause of the pain on injection, but the relationship between this pain and pH is not simple.

### Alkalinisation of local anaesthetic solutions

A basic solution can be added to a local anaesthetic solution immediately before injection to raise the pH. Suitable sterile solutions of sodium bicarbonate are readily available and this is the usual basic solution used.

Alkalinisation has potential advantages. Firstly, the higher pH of the solution may result in less stinging pain being experienced by the patient. Secondly, after injection, the pH of the injected solution may more quickly approach that of the normal tissue pH. The faster formation of a mixture with charged and uncharged forms may then result in more rapid drug diffusion and a quicker onset of nerve blocking. This could be particularly useful in body sites with low tissue buffering capacity where there can be a delay in the rise of pH after injection.

The practice of adding a basic solution to the local anaesthetic solution is sometimes referred to as buffering. This terminology is wrong. Alkalinisation is a more accurate term. A buffer is a solution that tends to resist a change in its pH whether an acid or a base is added to it. The aim of adding a basic solution to the local anaesthetic solution is to raise the pH, not to resist the change in pH, so this practice is not buffering. In contrast, after injection of the local anaesthetic solution the tissues function as buffers as they tend to minimise the change in tissue pH which occurs when an acidic local anaesthetic solution is injected.

The basic solution that is added has to be carefully specified and mixed (Table 1). If too much is added then the pH rises too far and the non-charged basic form will precipitate out of solution. This will be detected as a white clouding of the solution.

Provided precipitation does not occur, alkalinisation does not adversely affect the efficacy of the local anaesthetic solution.<sup>2</sup> As precipitation increases with time, alkalinised local anaesthetic solutions should generally be freshly prepared and used promptly. They should not be used for infusions.<sup>3</sup>

### Reduction of pain on injection

A literature review on whether adding sodium bicarbonate to a local anaesthetic solution reduced the pain of injection found 22 human randomised controlled trials. The evidence was 'overwhelming' that pain on injection was reduced. The reason for this reduction may be the more rapid onset of action of the alkalinised local anaesthetic, rather than the change in pH.<sup>2</sup>

A systematic review similarly found that the pain of intradermal injection of alkalinised local anaesthetics was decreased as compared to 'unbuffered' local anaesthetics.<sup>4</sup>

Pain reduction is a worthy goal and painless infiltration may be achievable in some cases. The reduction of this stinging pain due to infiltration anaesthesia and the block of small peripheral nerves is the major advantage of alkalinisation of local anaesthetic solutions.

The reduction of pain of infiltration by alkalinisation of the local anaesthetic solution is significant and so is likely to be useful in general practices and emergency departments where many such blocks are done, and particularly in children. Alternative methods may be a better approach in some situations, for example the use of local anaesthetic cream before intravenous cannulation in children.

### Alkalinisation to reduce onset time

For epidural anaesthesia, pain on injection of the local anaesthetic is not a major issue, but time to achieve surgical anaesthesia is important. Onset of epidural anaesthesia is quicker with alkalinised local anaesthetic solutions, but only by a few minutes.<sup>5</sup> More time is taken up in preparing the modified solution than is gained by using it. Onset time can be

*Table 1*  
**Alkalinisation of local anaesthetic solutions<sup>2</sup>**

Anaesthetic solution	Volume of 8.4% sodium bicarbonate to be added to 20 mL
Lignocaine 1% or 2%	2 mL
Bupivacaine 0.25% or 0.5%	0.1 mL*
Ropivacaine 0.2% <sup>†</sup>	0.1 mL* (must be used within 5–10 minutes)

\* The small volume of 8.4% sodium bicarbonate to be added requires great care as adding too much will cause precipitation

<sup>†</sup> Higher concentrations of ropivacaine (for example 0.75%) precipitate at a pH greater than 6 so are not suitable for alkalinisation<sup>6</sup>

decreased by using a faster acting drug, such as lignocaine, in a suitable concentration rather than a slower onset drug such as bupivacaine.

The onset of spinal anaesthesia is rapid. There is no advantage in using alkalinised solutions.

Alkalinisation of the solution does not provide any practical advantage in plexus blocks,<sup>1,7</sup> or intravenous regional anaesthesia.<sup>8</sup> With blocks of larger peripheral nerves, onset time is decreased and the quality of the block improved by minimising the diffusion distance by injecting the local anaesthetic solution close to the nerve. This can be achieved by using peripheral nerve stimulation, ultrasound guidance or other techniques to accurately position the needle tip.

In infiltration anaesthesia, the onset of the block is generally rapid so there is minimal time to be gained.

Alkalinisation of local anaesthetics to reduce the onset time of regional anaesthesia or major nerve blocks is not useful.

## Conclusion

Alkalinisation of local anaesthetic solutions reduces the pain of infiltration. It also reduces the onset of anaesthesia, but the time saved is small.

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*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page 195)*

3. Injections of lignocaine with adrenaline are less painful if sodium bicarbonate is added to the local anaesthetic solution.
4. Alkalinisation of the solution delays the onset of action of local anaesthetics.

## Dental notes

*Prepared by Michael McCullough, Chair, Therapeutics Committee, Australian Dental Association*

### Local anaesthetic solutions

Dental local anaesthetic solutions are usually contained in premade cartridges, designed for injection without any further mixing or addition. The only exception is 0.5% bupivacaine, with or without adrenaline. It is supplied in vials and so requires the use of a separate syringe. This type of anaesthetic is used by

oral and maxillofacial surgeons for pain control after removal of impacted teeth.

There has been at least one incident where a dentist used an injection of local anaesthetic from a cartridge and then separately injected sodium bicarbonate in an effort to counteract the acidic pH in an area of acute inflammation. This resulted in a permanent nerve injury with adverse medico-legal consequences for the dentist.

It is therefore recommended that dentists do not inject other solutions when using local anaesthetic cartridges.