EDITORIAL VIEW

The changing world of local anesthetics

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ABSTRACT

With the renewed interest in multimodal postoperative analgesia and the rapidly evolving medical specialty of interventional pain management, the concerns about the toxicity and the undesirable short duration of local anesthetic agents has lead the researchers to explore different options. These include modification of drug molecule with the discovery of new molecules, e.g. levobupivacaine, as well as drug molecule binding with liposomes. Various studies are being carried out to document comparative biophysical parameters of these drugs. This editorial compliments a similar research study by Narayanappa AB, et al, being published in this issue.

Key words: Pain, Postoperative; Pain, Management; Anesthetics, Local; Levobupivacaine; Bupivacaine

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Local anesthetics are being increasingly used in the practice of anesthesia, and intraoperative and postoperative pain management. However, there have been concerns about their toxicity, and the short duration of action is often outlasted by the pain. Efforts are being made to reduce toxicity and prolong the duration of action of the local anesthetic drugs. In early nineties, a working party of both the Royal Colleges, in their statement wished and recommended that only a safe local anesthetic, with duration of action in days, could help in managing postoperative pain.[1]

Various methods, tried so far to prolong the effect and reduce toxicity of the drugs, include manipulation of molecular structure, covering with liposomes, addition of adrenaline and combining two or more agents with different modes of action. Manipulation of the structure is an effective method to achieve the desired goals but it is limited by the fact that the altered structures thus produced may also develop irritant and neurotoxic properties.[2,3]

Addition of adrenaline can extend the short duration of action by delaying the absorption by vasoconstriction, but have little effect on prolonging the duration of action of longer acting agents.[4] Low molecular dextran mixed to lignocaine was used in early 1960s to extend its duration of action but later studies did not prove this .[5,6]

Some researchers tried to cover the drug molecules to slow their release so as to prolong the duration and to reduce toxicity. This was done by incorporating the molecule in to a liposome. These are small vesicles ranging from 0.03 -10 μm and consist of two layers of phospholipids around an aqueous phase. The drug molecule can be placed in either the lipid phase or the aqueous phase, depending on the physicochemical characteristics of the drug and the type of the lipid forming the outer layer of the liposome.[7] The phospholipid shell acts as a barrier to the drug diffusion from the unit. It acts as a slow release preparation which prolongs the duration of action and avoids toxicity as it allows the serum levels to rise very slowly.[8] The liposome formulations of both lignocaine and bupivacaine have been studied by various groups. A recent study by Umbrain V, et al, done on rodents has shown that multilamellar vesicles remain localized in the extradural space after injection with little absorption, whereas, unilamellar vesicles do not.[9] The study also showed that the preparation of liposomes did not produce any known cytotoxin or neurotoxin. The equilibrium dialysis carried out during these studies showed that liposomal preparations of both lignocaine and bupivacaine do release the active agents slowly from the extradural space.[10,11].

Nerve blocking activity of such preparations was also studied on animals and found that after infiltration of liposomal bupivacaine in rodents' tail, the onset time of the paralysis was the same with liposomal and plain solution, but duration was significantly longer with liposomal solutions. A complete recovery also occurred suggesting that there was no local toxicity.[11] With nerve blocks a theoretical concern does arise that if drug is

released slowly from the liposome ,onset of the block may be very slow or even inadequate as the removal by capillary circulation may prevent establishment of tissue concentration sufficient to achieve nerve penetration , but this was not observed in these studies and probably the initial block was caused by the anesthetics dissolved in the liposome suspension fluid . This was speculated that the slow release could be compensated by manipulating the free concentration of drug or to include two agents, with only one agent bound to liposome for a phased effect.

Perhaps such an approach could be used to combine agents with different mode of actions such as adding opioids to local anesthetics.

None of the above mentioned methods to modify the effects of the local anesthetics was adopted widely. Bupivacaine, the market leader and time tested product, is widely used in spite of some cardiotoxic properties associated with it. It is a racemic mixture (50-50) of S & R enantiomers. The R–somer is mainly responsible for the unwanted cardiotoxicity because of its avid and prolonged binding to inactivated cardiac sodium (Na+) channels.[10,11]

Ropivacaine, the s-isomer s enantiomer was found in 1996. It is selective on the sensory fibers, is less cardiotoxic and has less effect on the motor fibers as compared to bupivacaine. Another s-isomer of bupivacaine, levobupivacaine, was introduced in year 2000. It has a much lower cardiotoxicity and neurotoxicity due to its decreased potency at the sodium channels and faster protein binding rate.[12] Toxic symptoms of the drug are usually self-limiting and easily treatable.

A study published in this issue 'Levobupivacaine vs bupivacaine in cesarean patients' has compared these two drugs. It shows an edge of levobupivacaine over bupivacaine in the hemodynamic parameters: SBP, HR, nausea, vomiting and shivering. Possible reasons for this could be the difference in the baricity of the drugs and limitations of the study due to the small sample size and it's retrospective design. Reliance on the results can be guarded and farther double blind prospective and multicentre studies have to be conducted to ascertain superiority of any preparation in the practical field.

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