Plasma levobupivacaine concentrations following scalp block in patients undergoing awake craniotomy

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Background. Levobupivacaine is an effective local anaesthetic agent for nerve blockade with less systemic toxicity than racemic bupivacaine. The safety and efficacy of levobupivacaine for scalp blockade during awake craniotomy have not been addressed previously.

Methods. Serial arterial plasma levobupivacaine concentrations following scalp blockade were measured to 2 h in 10 patients booked for awake craniotomy for epilepsy or tumour surgery. Bilateral scalp blockade providing surgical anaesthesia was achieved with a mean dose of 177 mg (2.5 mg kg⁻¹, range 1.6–3.2 mg kg⁻¹) of levobupivacaine (0.5%, 5 mg ml⁻¹) with epinephrine (5 μg ml⁻¹) added immediately before the block insertion.

Results. The maximum measured plasma levobupivacaine concentration was 1.58 (0.44) μg ml⁻¹ [mean (SD)] with a mean time to peak plasma concentration of 12 (4) min. There were no episodes in any of the 10 patients of symptoms or signs suggestive of either CNS or CVS toxicity.

Conclusions. This study demonstrated a relatively rapid rise of plasma levobupivacaine concentration without evidence of cardiovascular or central nervous system sequelae in a sample population of patients who may be particularly prone to perioperative seizures.

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Patients undergoing anaesthesia for surgical treatment of epilepsy may need to remain awake during the operation to aid with cortical mapping before resection of the seizure focus. The awake patient should be able to perform various tasks including counting, naming objects and moving limbs on command. To undertake an awake procedure safely and painlessly, a scalp block with local anaesthetic injections around the base of the scalp is often performed.

At present, clinical data relating to the use of levobupivacaine for scalp blockade in neuroanaesthesia are lacking. Accordingly, this study was performed to gain experience with this drug in this setting, to determine the time course of plasma levobupivacaine concentration with a given dosage regime and to examine the presence or absence of clinical signs of toxicity. This will allow safe dosage regimens of levobupivacaine to be determined for this setting. The authors have previously completed a similar study using ropivacaine,¹ which has a similar toxicity profile, where no signs of CVS or CNS toxicity were found.

Methods

The protocol was approved by the Ethics Committee responsible for human research at St Vincent’s Hospital, Melbourne. After giving informed consent, 10 patients were recruited subject to the following inclusion/exclusion criteria. Patients who were booked for epilepsy surgery or removal of lesions closely related to the speech or motor areas of the cerebral cortex, aged between 18 and 75 yr, with body weight between 50 and 110 kg, and an ASA status I–III were considered for inclusion. The exclusion criteria were contraindications to the use of local anaesthesia, such as a known allergic reaction.

Patients were pre-medicated with clonidine (3 mg kg⁻¹), 2 h before surgery. A peripheral i.v. line, an antecubital central venous line and an intra-arterial cannula were inserted whilst the patient was in the anaesthetic room before the insertion of the scalp blocks. In addition, ECG and pulse oximetry were monitored. Oxygen was administered via a naso-pharyngeal airway. Propofol (1–5 mg kg⁻¹ h⁻¹) and
Results

Three male and seven female patients, undergoing epilepsy or intracranial tumour surgery were included in the study. Their mean age was 36 (range 23–52) yr and mean weight was 74 (range 56–107) kg. The mean dose of levobupivacaine used was 177 mg (2.5 mg kg\(^{-1}\), range 1.6–3.2 mg kg\(^{-1}\)).

Individual patients’ plasma levobupivacaine concentrations were plotted against time (Fig. 1). The mean \(C_{\text{max}}\) of levobupivacaine was 1.58 (0.44) (range 0.98–2.51) \(\mu\)g ml\(^{-1}\) and the mean \(T_{\text{max}}\) was 12 (4) (range 5–15) min, with the earliest \(T_{\text{max}}\) being found in the first samples drawn at 5 min after insertion of the block in two patients. There was evidence of a secondary rise in plasma levobupivacaine concentration in some patients following injection into the scalp of the remainder of the local anaesthetic solution at 40–60 min. One patient (J) had a detectable level of levobupivacaine at baseline because of a delay in sampling until after commencement of the block.

There were no episodes in any of the 10 patients of symptoms or signs suggestive of either CNS or CVS toxicity as noted by both the nurse dedicated to observations and one of the authors (T.C. or J.C.) who are experienced in neuroanaesthesia and who were present throughout each study period. There were no episodes of intra-operative seizure related to cortical mapping in this group.

Discussion

This study examined a scalp blockade technique using levobupivacaine as the study drug and was undertaken following a similar protocol to a previous study examining the pharmacokinetic profile of ropivacaine in scalp blockade for awake craniotomy.\(^1\) Comparing these two studies is somewhat tenuous as different concentrations and total doses of local anaesthetic were used (7.5 mg ml\(^{-1}\), 260 mg = 3.6 mg kg\(^{-1}\) for ropivacaine; 5 mg ml\(^{-1}\), 177 mg = 2.5 mg kg\(^{-1}\) for levobupivacaine) and, particularly, as the timing of blood sampling in the ropivacaine study (first post-block sample taken at 15 min) may have missed an early peak as found in this study. Nevertheless, the results were remarkably similar with \(C_{\text{max}}\) of ropivacaine of 1.5 \(\mu\)g ml\(^{-1}\) compared with 1.58 \(\mu\)g ml\(^{-1}\) for levobupivacaine and \(T_{\text{max}}\) of ropivacaine 15 min compared with 12 min for levobupivacaine. There is a similar rapid rise of drug blood concentrations in each study despite the addition of epinephrine in each case. The decision to add epinephrine to the local anaesthetic agent was made as it was assumed that the absorption of local anaesthetic would be rapid from this highly vascular area. A further study could delineate whether this addition of epinephrine is necessary, particularly as hypertension, probably caused by the epinephrine, was present during the blocks in several patients both during and after injection.

Levobupivacaine has now been used in a wide variety of clinical areas for the provision of intra-operative anaesthesia and postoperative analgesia. A recent study of interscalene...
brachial plexus blockade for shoulder surgery showed levobupivacaine 0.5% (30 ml) produced a blockade of similar onset and quality as that produced by a similar volume of ropivacaine 0.5%.4

There are other studies demonstrating an acceptable safety profile of levobupivacaine when used for a wide range of different blocks5–10 and as with ropivacaine it has produced uniformly satisfactory blockade for all these forms of surgery. Unfortunately, there is still a paucity of human studies directly comparing the toxicity of these long-acting agents. Studies have demonstrated larger tolerated doses of i.v. ropivacaine or levobupivacaine compared with bupivacaine before the onset of CNS symptoms in humans.11–13 In the study of Bardsley and colleagues, levobupivacaine was infused intravenously in volunteers until the onset of CNS symptoms. Mean peak plasma concentrations

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**Fig 1** Concentration–time curves for levobupivacaine.
in that study were 2.62 μg ml⁻¹ and cardiovascular parameters were considered superior to bupivacaine, which was infused in the same regimen. This would imply that the concentrations reached in our study (1.58 μg ml⁻¹) are relatively safe with the understanding that the patient population being studied were having surgery for epilepsy or for tumours which may be associated with seizures, they were sedated during the blocks and were on anticonvulsant medication all of which may raise the threshold for CNS signs. More recently Stewart and colleagues examining CNS and CVS effects of levobupivacaine and ropivacaine, found a similar onset of effects between the two drugs at equal dose regimens. At present there are no definitive data for the effects of epinephrine on peripheral nerve blockade with levobupivacaine; however, data for epidural neuraxial blockade with levobupivacaine do not demonstrate a material advantage on either block characteristics or plasma drug concentration profiles when epinephrine was added.15

Despite the lack of human data there is now general agreement in the anaesthetic community that the wide therapeutic window between clinical efficacy and adverse side-effects seen with both levobupivacaine and ropivacaine suggests the need for these two agents to be used preferentially over bupivacaine in clinical practice. This attitude stems from an increasing volume of laboratory animal evidence pointing to the greater potential for lethal toxic effects of racemic bupivacaine compared with similar doses of levobupivacaine and ropivacaine.14–18 Further, lethal dose (LD₅₀) values obtained in rats, mice, and rabbits indicate that the margin of safety regarding lethality is such that 32–57% more levobupivacaine is required to produce death when compared with bupivacaine.19 The volume of evidence for the CNS and or CVS toxicity of the longer-acting local anaesthetics has necessarily been smaller in the human model because of the obvious ethical difficulty in infusing these drugs in healthy volunteers.

This study addressed the efficacy and safety of levobupivacaine in the clinical setting of awake craniotomy. The drug was demonstrated to be a useful addition to the armamentarium of the clinical neuroanaesthetist by showing a similar plasma concentration profile to ropivacaine in the same clinical area without evidence of CNS or CVS toxic side-effects. The finding of peak plasma concentrations earlier than 15 min post-block further raises the need for heightened awareness by anaesthetic staff where there is potential for adverse CNS or CVS symptoms to occur as early as 5 min post-block insertion.

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