Liposomes are vesicles ranging in size from 0.03 to 10 μm and consist of bilayers of phospholipid surrounding an aqueous phase. Drug molecules can be incorporated into the lipid or aqueous phases, the site depending on the physicochemical characteristics of the drug and the type of lipid forming the bilayer [8]. This phospholipid can act as a barrier to drug diffusion from the liposome, effectively providing a slow release preparation with prolonged duration. This method of drug formulation has been used to treat lysosomal enzyme deficiencies and to reduce the systemic toxicity of several drugs [9, 10, 11]. These features suggest that liposomal formulations of local anaesthetics could have advantages and their performance has been studied by several groups over the past decade. A number of local anaesthetics (usually lignocaine or bupivacaine) have been studied in various ways, but each group has had to produce its own preparation and until now there has been little assessment of the influence of formulation on drug release. A recent study of the effect of formulation on the biodistribution of liposomes has shown that multilamellar vesicles remain localised in the extradural space after injection with little absorption, whereas unilamellar vesicles do not [12]. This study also showed that no known cytotoxins or neurotoxins were produced during the manufacture of liposomes. However, variations in the composition of liposomes makes direct comparisons of different investigators results difficult, as does the use of different animal species. However, a fairly consistent pattern of performance exists and equilibrium distribution has shown that liposomal preparations of both lignocaine and bupivacaine do release the active agent slowly [13, 14].

Unfortunately, little of the research has been on the nerve blocking activity of these preparations. In two studies abolition of reflex tail withdrawal from heat by rodents was used as an indicator of the effect of infiltration with liposomal bupivacaine [14, 15]. Onset time was the same with liposomal and plain solutions, but duration was significantly longer with the former. Complete recovery occurred, suggesting that there was no local toxicity. More definitively, somatosensory evoked potentials (SSEP) were used to compare plain and liposomal preparations of lignocaine after extradural injection in the dog [13]. Onset time was not significantly different, but a further increase in SSEP latency occurred 2 h after the liposomal drug and, overall, the changes suggested more complete and prolonged nerve block. One theoretical concern is that the onset of block may be very slow, or even inadequate, if the liposomes only release the active agent slowly, because removal by the capillary circulation may prevent the establishment of a tissue concentration sufficient to achieve nerve penetration. However, a conclusion of the three studies noted above was that the initial block was caused by local anaesthetic dissolved in the liposome suspension fluid. Thus it might be possible to manipulate free concentration to compensate for slow release when rapid onset is required, or even to compound two different agents, with only one bound to liposomes for a phased effect. Perhaps such an approach could also be used to combine agents with different actions, such as a local anaesthetic with an opioid.

In spite of these potential applications, most animal studies have examined pharmacokinetics, distribution or toxicity. After brachial plexus injection, peak systemic concentrations were the same after liposomal compared with conventional bupivacaine, but the time to peak was significantly delayed after the former [16]. This confirms that slow release occurs, but was not the pattern after extradural injection of lignocaine in dogs, possibly reflecting physicochemical differences between the agents [13]. In addition, a study of extradural injection of radiolabelled bupivacaine in the rabbit found that peak plasma concentration was lower, and time to peak longer, after liposomal bupivacaine compared with a plain solution [17]. Concentrations in heart and liver tissue followed the same pattern, suggesting that liposomal encapsulation may also reduce systemic toxicity. This is supported by the finding that the LD₅₀ of liposomal bupivacaine after i.p. injection in the mouse was nearly five times that of the plain solution [14]. The results of a study of i.v. infusion
of 0.25 % bupivacaine in liposomal and conventional solutions (with and without adrenaline) in the rabbit further support reduced toxicity, significantly more liposomal bupivacaine being required to produce convulsions, ventricular arrhythmia and asystole [18]. However, the rate of bupivacaine injection was very slow and the study did not simulate accidental i.v. injection.

These results provide some evidence for a prolonged effect of liposomal local anaesthetics and one study also found that the concentration of bupivacaine in the lumbosacral nerves after extradural injection was greater than after a conventional preparation [17]. However, studies in humans are few and far from convincing. Liposomal amethocaine was found to have a long duration after dermal application, but a slow onset time that limited clinical usefulness and supports the theoretical concerns about slow release noted above [19]. A recent study of postoperative extradural injection found that liposomal bupivacaine had the same onset time, but a significantly prolonged duration (6.25 vs 3.2 h) compared with bupivacaine combined with adrenaline [20]. Unfortunately no data on sensory block were presented, although it was noted that this would have been inadequate for surgery after the liposomal preparation. The patients did not develop motor block in the lower limbs whereas there was some block (Bromage grade 1–2) in patients who received bupivacaine with adrenaline. This suggests that a prolonged, low intensity block may result from extradural injection of liposomal bupivacaine in humans, as does the report of administration of liposomal bupivacaine to a patient with a chronic pain problem [21]. However, the finding needs confirmation in randomized, double-blind studies. First though, more basic information is needed. The lack of studies on the basic performance characteristics has been mentioned and little, if any, work has been done to ensure that these formulations are without neurotoxicity. Liposomal bupivacaine may have many desirable features (longer duration, less motor block and less systemic toxicity than conventional preparations), but so far the evidence is weak and more systematic studies are required.

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References