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Development of Local Drug Delivery System : Prolonged Sciatic Nerve Blockade From Biodegradable Microspheres

Jeong-ok Lim

Department of Anesthesia, Harvard Medical School

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Microspheres containing tetracaine or bupivacaine with poly-lactic-glycolic acid were prepared with a range of compositions. Using the rat scicatic nerve model in vivo it was found that prolonged blockade for periods of 2-7 days, depending on composition variables.Polymer-local anesthetics microspheres are feasible delivery vehicle for prolonged regional nerve blockade.

Long acting anesthetic agents are particularly desirable in the management of postoperative pain, in the relief of severe pain associated with terminal states of patients suffering from cancer, and for various nerve blocks carried out in pain clinics. Approaches so far taken for prolonging the duration of local anesthesia has been primarily confined to the area of chemical modification of a compound known to have local anesthetic action. The problems of currently available local anesthetics are their limitations in acting duration. The longest acting agents at present are bupivacaine and tetracaine. Depending on the site of administration, the duration may be as short as 3 hours, or as long as 8 to 12 hours.

There is no reliable means at present to provide analgesia for longer than 6 to 8 hours by single injection. One of the attempts to sustain analgesia for several days involved the application of polymers. An implantable pellet device using bupivacaine in a polyanhydride matrix gave degrees of sensory and motor blockade of the rat sciatic nerve in vivo for 3 to 5 days.[1),2)] Biochemical, histologic and behavioral studies shown that this material was well tolerated and that recovery from blockade was completed.

As one of the means to prolong the duration of action of presently available generic local anesthetics and improve the way of administration to patients, novel type of local anesthetics by forming into microspheres may be of clinical value. Microspheres are small particles that range in size from a few tenths of a μm up to several hundred μm in diameter. They may be prepared in different ways, including various polymerization processes and encapsulation. Microspheres have various applications in biology and medicine as they are of growing importance as carriers for drugs. An essential requirement of modern drug therapy is the controlled delivery of the pharmacological agent to its site of action in the body in the correct concentration-time profile. The combination of drugs and microspheres allows the possibility of more selective administration. It would be more useful in many clinical situations to deliver local anesthetics by injection rather than by surgical implantation of a pellet. Suspensions of microspheres can be injected through standard needles and may be used for drug incorporation and controlled release. Preliminary reports by other groups using local anesthetic microspheres have not produced blockade for

more than 8 hours.[3),4)] We report on the incorporation of the local anesthetics, tetracaine and bupivacaine, into microspheres, on the kinetics of drug release *in vitro*, and on the use of microspheres in rats in vivo for sciatic nerve blockade for the period of 2~6 days.

Materials and Methods

Microspheres containing tetracaine (T) or bupivacaine (B) with poly (lactic-co-glycolic acid) (PLGA) (70:30) were synthesized by a solvent evaporation method using emulsion polymerization in drug loadings ranging from 50~75% w/w.[5)] *In vitro* release of drug was assayed by absorption spectra as described.[1)] Microsphere morphology was evaluated by ESEM (Environmental Scanning Electron Microscopy).[6)] Animal experiments were approved by the Animal Care Committee. Microspheres were either implanted surgically along the sciatic nerve in the upper thigh or injected percutaneously in suspension. In order to test *in vivo* blockade, the rat sciatic nerve systems was chosen because examination for sensory, motor and proprioceptive effects is feasible, the dissection is easy, contralateral sciatic nerves can be used as a within-animal control, and there is a long track-record of its use in behavioral studies.

For behavioral testing of the rats which received microspheres, hot plate testing was performed. A hot plate assay for sensory blockade of the sole of the paw is humane and ethically permissible, since it is not injurious to tissue, and the animal can escape the stimulus as soon as it is perceived as bothersome. Withdrawal depends on hip flexors and knee extensors, not under sciatic control, so that even if an animal had sciatic weakness, they could still withdraw. To better assess intensity of sensory block, hot plate latencies were subdivided into 4 classes: maximum block density (12 seconds), dense block (7-11 seconds), partial block (4-seconds) and no block (less than 4 seconds).

Male sprague-Dowley rats were tested to a hot plate of 56℃. Held in the experiment's hand, the animal's hindpaw was placed on the hot plate and latencies recorded, starting as contact and ceasing with withdrawal from hot plate. If latencies exceed 12 seconds, the rat's hindpaw was removed for preventing injury.

Results

Microspheres were prepared and sieved with diameters ranging from 20~120 μm. *In vitro* release kinetics profile of tetracaine and bupivacaine displayed different. Tetracaine showed fairly abrupt release for the first 2~3 days and remained steady afterwards. Approximately 60~80% of the loaded tetracaine were released within 3~4 days. Meanwhile bupivacaine showed slow and sustained release for 2 weeks (Fig. 1).

Rats implanted with tetracaine-microspheres and bupivacaine-microspheres along the sciatic nerve showed sensory and motor blockade for 2 to 10 days for doses ranging from 50~400 mg/400 kg of drug, no systemic toxicity at doses < 300 mg/kg, and full recovery of strength and se-

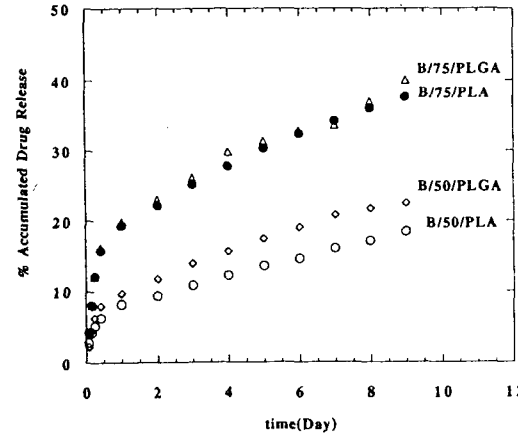

Figure 1—*In-Vitro* release of bupivacaine.

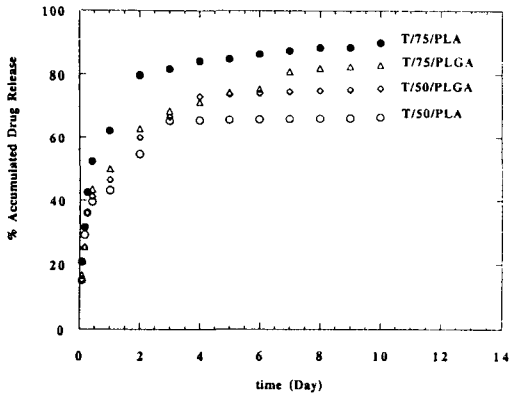

Figure 2—*In-Vitro* release of tetracaine.

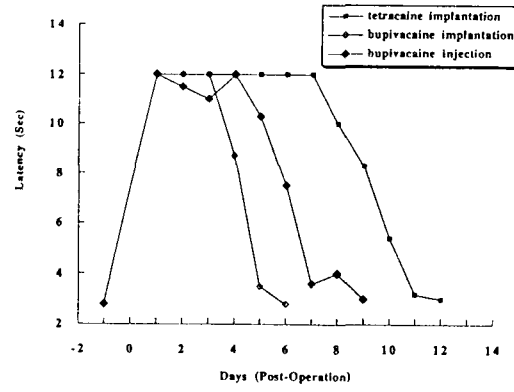

Figure 3—*In-Vivo* data for microspheres injection and implantation.

nsation to baseline function (Fig. 2). Inflammation and encapsulation were minimal.

Rats injected with bupivacaine-microspheres showed sensory and motor blockade for 4 to 5 days on average.

Microspheres before release were spheres and round and smooth surface with diameters of 20 ~120 μm for the low loading of drugs, but microspheres for the higher loading of local anesthetics, surface became irregular, rough and invaginated. This indicates that polymer forms a thin coating over the aggregated local anesthetic particles during the process of microsphere formation. All the microspheres became mixture of porous and disintegrated forms after release for 2 weeks. In the case of tetracaine 75% loading, they were totally disintegrated after 2 weeks release with total weight loss approximately 90%. The other electron micrographs demonstrated the process of degradation or disintegration of microspheres as losing their round contour.

Discussion

Prolonged regional anesthesia appears feasible with controllable duration using implantable and injectable local anesthetic microspheres. Further studies are in progress to optimize the safety and effi-cacy of these preparations.

References

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