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BRIEF COMMUNICATION

Simple Catheter Preparation for Permitting Bolus Intrathecal Administration During Chronic Intrathecal Infusion

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YAKSH, T. L. AND C. W. STEVENS. *Simple catheter preparation for permitting bolus intrathecal administration during chronic intrathecal infusion.* PHARMACOL BIOCHEM BEHAV 25(2) 483–485, 1986.—This paper briefly describes a simple method for preparing a polyethylene "Y" catheter in which the stem of the "Y" is inserted into the intrathecal space, one arm of the "Y" is externalized for intrathecal injection and the other arm of the "Y" connected to an osmotic infusion pump. This simple preparation permits the chronic infusion of drug into the spinal space and without further surgical preparation, permits bolus injection of drugs through the same catheter.

Intrathecal injection Chronic infusion Tolerance

WITH the description of the simple methodology for placing catheters into the rodent's spinal space [12], there has been increasing interest in defining the pharmacology of spinal function insofar as a variety of endpoints are concerned including those related to analgesia, cardiovascular and motility of the gastrointestinal tract and bladder (see [8,11] for references). An important methodology in examining the characteristics of the receptors acted upon by drugs given spinally is the phenomenon of tolerance and cross-tolerance. Previous studies have, for example, demonstrated that morphine given chronically either by repeated bolus intrathecal or systemic administration, or by the implantation of pellets [1, 3, 5, 9, 10], will produce significant shifts in the dose response curve for intrathecal opioids.

The use of implantable infusion pumps (e.g., osmotic minipump; Alza Corporation, Palo Alto, CA; gas driven [2]), has facilitated the study of tolerance in the spinal cord as they permit the achievement of chronic and stable levels of infused agents for extended periods of time [4, 6, 7]. Once tolerance to a particular agent has been developed, the degree of cross-tolerance to another drug ("probe" agent) is assessed by bolus injection. This administration of the probe drug at the end of a chronic infusion period has previously been done by anesthetizing the animal, making an incision, disconnecting the catheter from the minipump and externalizing it for bolus injection when the animal recovers. Though feasible, the stress of the surgery and the anesthetic within a short period of time preceding the probe agent clearly prevents a straightforward assessment of the results. The straightforward alternative to this problem is the preparation of an easily made "Y" catheter that can be constructed with a great deal of certainty and is durable enough to withstand the implantation procedures and the manipulations after its placement.

PREPARATION OF CATHETER

To prepare the "Y" catheter for intrathecal infusion, three pieces of polyethylene tubing are cut: a 10-cm length of PE-10 tubing (Clay Adams, Parsippany, NJ; 0.28 mm i.d., which forms the stem of the "Y" to be threaded into the intrathecal space), a 6-cm length of PE-10 (the external arm of the "Y" for intrathecal bolus injection), and a 4-cm length of PE-60 (0.76 mm i.d., the arm of the "Y" connected to the Alza minipump), as shown schematically in Fig. 1. To construct the "Y" joint, two pieces of stylette wire (0.12 mm dia., pen cleaning wires supplied with the Grass polygraph) are placed through the three pieces of tubing as shown in Fig. 1. The ends of the three pieces of the PE tubing are then butted as close together as possible and placed in the stream of a hot air jet. The hot air jet is provided by passing wall air through a brass tube fitted with a 20-ga needle tip and heated by a Bunsen burner. As the tubing begins to soften, a small amount of compression is placed so that the tips remain in close contact with one another. With limited experience, one will then recognize that the tubing has softened to a somewhat fluid glob. At this time, the fluid glob is pressed be-

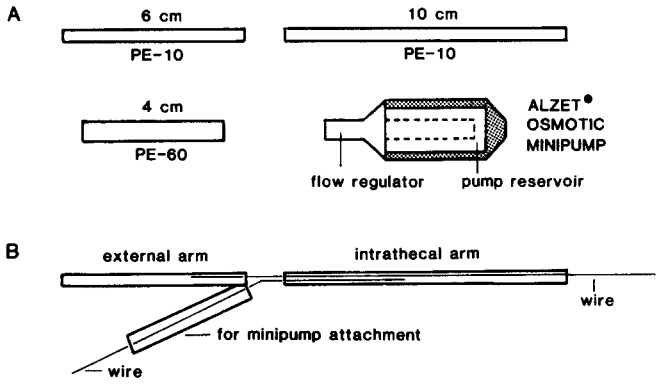

FIG. 1. A: Schematic of the catheters and their lengths for preparing the "Y" arm of the chronic infusion system. B: Schematic shows the orientation of the three catheter tips and the placement of the two 0.12 mm wires which are used to maintain the patency of the "Y" joint during heating.

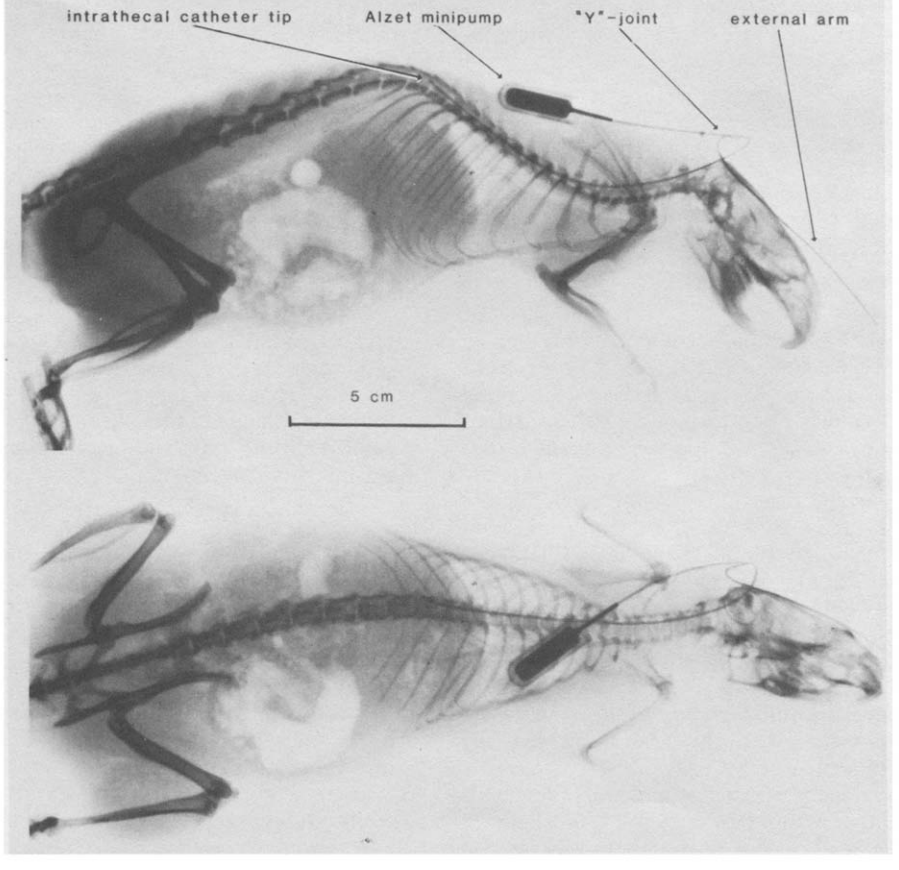

FIG. 2. X-ray showing the orientation of the Alzet® minipump and the external and intrathecal segments of the "Y" connection. A: Lateral view; B: Dorsal view.

tween the finger tips and the tubing is joined. The wires thus maintain the patency of the connection between the three catheters during the heating and sealing process. The tubing is then cooled and a small drop of cranioplast cement (Fastcure®, Kerr Sybron, Romulus, MI) is placed on the joint. The cranioplast provides a rigid lock on the orientation of the catheters, and prevents the stress of bending to act directly on the joint. The occluding wires are then removed.

Once prepared, the spinal segment of the catheter is cut to the desired length. If a smaller dead volume for the spinal segment of the catheter is desired, this portion of the catheter may now be stretched, effectively drawing down the lumen of the catheter and essentially reducing the dead volume by up to half.

The "Y" catheters are then tested for leakage by forcing 3 cc of distilled water with maximal pressure of a hand-held syringe through the PE-60 arm. Any catheter with leakage at the joint or failing to emit a fine stream of water from both PE-10 ends is considered defective and discarded. Currently, the failure rate of these catheters after their initial manufacture is less than 1%. An individual, once shown the method, can easily prepare 25–30 catheters in an hour.

LOADING OF PUMP AND "Y" CATHETER

To load the catheter system before implantation, a drug filled syringe is connected to the PE-60 arm of the "Y" catheter and all tubing is filled. The long PE-10 length is then sealed by capillary tube sealer (Critoseal®, Sherwood Medical, St. Louis, MO). The short PE-10 arm is left open while the minipump is attached to allow for displacement of solution. After the minipump is attached, taking care not to introduce any air backward into the pump and PE-60 arm, the short PE-10 arm is then sealed. When the animal is prepared for introduction of the intrathecal catheter, the long PE-10 stem is measured to 8.5 cm from the junction and the sealed end cut.

PREPARATION OF ANIMAL

Male Sprague-Dawley rats (250–300 g, Harlan Industries, Indianapolis, IN), are anesthetized with halothane. The animal is then placed in a stereotaxic head holder with the head flexed forward. The occipit is shaved closely, the area scrubbed with an iodine tincture, and a midline incision is made exposing the occipital crest. The musculature is bluntly dissected 1–2 mm on either side of midline and atlanto-occipital membrane over the cisterna magna exposed. The cisterna membrane is then pierced using the bent tip of a 22-ga needle, allowing the escape of cerebrospinal fluid and an entrance to the intrathecal space. The cisternal membrane is retracted and the 8.5 cm length of PE-10 tubing is then inserted carefully to the lumbar intrathecal level. The Alza minipump is then slid into the subcutaneous pocket, with every effort being made to avoid placing torque on the intrathecal catheter which is in place. The externalized part of the PE-10 catheter is then tunneled by a 19-ga trochar which is run subcutaneously from the top of the head to the incision on the back of the neck. The PE-10 injection catheter is thus externalized. The wound is closed with cutaneous sutures and the animal allowed to recover from the anesthetic.

Figure 2 presents radiograms displaying the orientation of the Alzet® minipump and the catheter.

OUTCOME

To date, we have implanted over 250 rats with the intrathecal infusion system as described. In a random sample of 36 rats after 7 days of chronic infusion, the animals were sacrificed and the integrity of the minipump catheter preparation examined. At this time, inspection of the "Y" joint revealed that in all animals this joint would hold the maximal pressure achieved with a hand-held 3-cc syringe. In animals thus far prepared, no instance of infection or motor dysfunction have been observed secondary to the chronic infusion of saline vehicle.

The one drawback of the "Y" catheter is that the contents of the catheter must be flushed before the probe drug can be injected. For this reason, the dead volume of the spinal segment of the catheter should be kept as small as possible. If dead volumes are critical, e.g., as with short infusion intervals, the spinal catheter may be stretched and thereby reduced in size. In our own work, we flush the catheter with the appropriate volume 3 hr prior to the test drug, obtain our baseline at the appropriate time and then inject the probe drug.

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REFERENCES

1. DeLander, G. E. and A. E. Takemori. Spinal antagonism of tolerance and dependence induced by systemically administered morphine. *Eur J Pharmacol* **94:** 35–42, 1983.
2. Goeders, N. E., J. D. Lane and J. E. Smith. Self-administration of methionine enkephalin into the nucleus accumbens. *Pharmacol Biochem Behav* **20:** 451–455, 1984.
3. Schmauss, C., Y. Shimohigashi, T. S. Jensen, D. Rodbard and T. L. Yaksh. Studies on spinal opiate receptor pharmacology. III. Analgetic effects of enkephalin dimers as measured by cutaneous-thermal and visceral-chemical evoked responses. *Brain Res* **337:** 209–215, 1985.
4. Tseng, L.-F. Tolerance and cross tolerance to morphine after chronic spinal D-Ala^2-D-Leu^5-enkephalin infusion. *Life Sci* **31:** 987–992, 1982.
5. Tung, A. S. and T. L. Yaksh. *In vivo* evidence for multiple opiate receptor mediating analgesia in the rat spinal cord. *Brain Res* **247:** 75–83, 1982.
6. Wiesenfeld, Z. and L. L. Gustafsson. Continuous intrathecal administration of morphine via an osmotic minipump in the rat. *Brain Res* **247:** 195–197, 1982.
7. Wiesenfeld-Hallin, Z. The effects of intrathecal morphine and naltrexone on autotomy in sciatic nerve sectioned rats. *Pain* **18:** 267–278, 1984.
8. Yaksh, T. L. Spinal opiate analgesia: characteristics and principles of action. *Pain* **11:** 293–346, 1981.
9. Yaksh, T. L., J. R. Howe and G. J. Harty. Pharmacology of spinal pain modulatory systems. In: *Advances in Pain Research and Therapy, Vol 7*, edited by C. Benedetti *et al.* New York: Raven Press, 1984, pp. 57–70.
10. Yaksh, T. L., R. L. Kohl and T. A. Rudy. Induction of tolerance and withdrawal in rats receiving morphine in the spinal subarachnoid space. *Eur J Pharmacol* **42:** 275–284, 1977.
11. Yaksh, T. L. and R. Noueihed. The physiology and pharmacology of spinal opiates. *Annu Rev Pharmacol Toxicol* **25:** 433–462, 1985.
12. Yaksh, T. L. and T. A. Rudy. Chronic catheterization of the spinal subarachnoid space. *Physiol Behav* **17:** 1031–1036, 1976.