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The Meningeal Permeability of R- and S-bupivacaine Are Not Different

Evidence that Pharmacodynamic Differences between the Enantiomers Are Not the Result of Differences in Bioavailability

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MANY drug molecules exist as one or more enantiomers, and recent evidence indicates that different enantiomers of the same drug may have different biologic properties.¹⁻⁸ These differences are presumed to exist because enantiomers differ in their interaction with chiral centers at their target site.^{3,4,8,9}

There is an alternative explanation that must also be given consideration: enantiomers may differ in their ability to reach the target site because of differential interaction with the chiral proteins, lipids, and carbohydrates in both the intracellular and the extracellular spaces. Multiple studies show that human skin^{10,11} and the blood-brain barrier^{12,13} differ in degree of permeability for enantiomers of the same drug.

The purpose of this study was to determine whether the two enantiomers of bupivacaine (*R*(+)-dextrobupivacaine and *S*(-)-levobupivacaine) differ in ability to move through tissue. To address this question, we used a previously described *in vitro* diffusion cell model¹⁴⁻¹⁷ to

quantitate the permeability of both bupivacaine isomers in the spinal meninges of the monkey (*Macaque nemestrina*).

Materials and Methods

All studies were approved by the University of Washington Animal Care and Use Committee, Seattle, Washington. All monkey (*M. nemestrina*) meningeal tissue was obtained from animals killed as part of the Tissue Distribution Program of the University of Washington Regional Primate Research Center.

Details of the method have been previously described.¹⁴⁻¹⁷ Briefly, postage stamp-sized pieces of intact meningeal tissue—dura, arachnoid, and pia mater—were excised from the animal and placed over the pore connecting two reservoirs of a temperature-controlled (37°C) diffusion cell. At time 0, 0.5 mg *S*- or *R*-bupivacaine (Celltech Chiroscience, Ltd., Cambridge, UK) was added to the donor reservoir, along with approximately 3 kBq of the corresponding ³H-labeled enantiomer (Amersham Life Science, Arlington Heights, IL): *S*-bupivacaine-specific activity, 2,072 GBq/mM; radiochemical purity, 98%; *R*-bupivacaine-specific activity, 3,145 GBq/mM; radiochemical purity, 98%. Thereafter, at 10 min-intervals for 100 min, 100 μl was removed from both reservoirs and placed in separate scintillation vials for later scintillation counting.

As previously described, bupivacaine concentration was determined by use of radiotracer methods using an Ecoscint scintillation cocktail (National Diagnostics, Atlanta, GA) and a liquid scintillation counter (Tri-Carb 2000; Packard Instruments, Downer's Grove, IL).¹⁴⁻¹⁷

Bupivacaine flux was determined from linear regression of the bupivacaine-*versus*-time data. These data were plotted and the permeability coefficient was calculated from the equation

$$P = Q/(C \times A)$$

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where P = permeability coefficient (cm/min), Q = bupivacaine flux ($\mu\text{g}/\text{min}$), C = bupivacaine concentration in the donor reservoir ($\mu\text{g}/\text{ml}$), and A = tissue area (cm^2).

Statistical Analysis

The permeability coefficients for *R*- and *S*-bupivacaine were compared using the unpaired Student *t* test. Differences were considered to be statistically significant if $P < 0.05$. Data are reported as mean \pm SD.

Results

Each enantiomer was studied in 10 tissue specimens. The r^2 for regression lines used to determine bupivacaine flux averaged 0.973 ± 0.031 (range, 0.887–0.998), indicating excellent fit of the data to a linear model. The permeability coefficient averaged $1.6 \pm 1.1 \times 10^{-3}$ cm/min for *S*-bupivacaine and $1.5 \pm 0.7 \times 10^{-3}$ cm/min for *R*-bupivacaine ($P = 0.786$).

Discussion

To our knowledge, this is the first study to investigate whether there are differences between local anesthetic enantiomers regarding ability to move through tissue. This is a particularly important question to be addressed with local anesthetics because their use in anesthesiology relies on their ability to diffuse through tissue to reach their target sites. The data clearly indicate that there is no difference in the meningeal permeability of the *R*- and *S*-enantiomers of bupivacaine. In addition, the permeability coefficients measured in this study are nearly identical to those previously reported by our laboratory for the racemic bupivacaine mixture ($1.6 \pm 0.4 \times 10^{-3}$ cm/min).¹⁴ This finding shows the reproducibility and reliability of this model.

Several studies have shown pharmacodynamic differences between *R*- and *S*-bupivacaine. For example, Kopacz *et al.*¹⁸ demonstrated in humans that levobupivacaine produced significantly longer sensory block than did the racemic mixture of *R*- and *S*-bupivacaine. Our data suggest that this finding is the result of differential actions of the *R*- and *S*-enantiomers at the target site and is not the result of differences in ability to reach the target from the epidural space.

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References

- Hancock PJ, Stamford JA: Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. *Br J Anaesth* 1999; 82:603–8
- Sidebotham DA, Schug SA: Stereochemistry in anaesthesia. *Clin Exp Pharmacol Physiol* 1997; 24:126–30
- Valenzuela C, Delpon E, Tamkun MM, Tamargo J, Snyders DJ: Stereoselective block of a human cardiac potassium channel (Kv1.5) by bupivacaine enantiomers. *Biophys J* 1995; 69:418–27
- Franqueza L, Longobardo M, Vicente J, Delpon E, Tamkun MM, Tamargo J, Snyders DJ, Valenzuela C: Molecular determinants of stereoselective bupivacaine block of hKv1.5 channels. *Circ Res* 1997; 81:1053–6
- Vanhoutte F, Vereecke J, Verbeke N, Carmeliet E: Stereoselective effects of the enantiomers of bupivacaine on the electrophysiological properties of the guinea-pig papillary muscle. *Br J Pharmacol* 1991; 103:1275–81
- Trejtnar F, Wsol V, Szotakova B, Skalova L, Pavek P, Kuchar M: Stereoselective pharmacokinetics of flufen in rats. *Chirality* 1999; 11:781–6
- Spiegelstein O, Yagen B, Levy RH, Finnell RH, Bennett GD, Roeder M, Schurig V, Bialer M: Stereoselective pharmacokinetics and pharmacodynamics of propylisopropyl acetamide, a CNS-active chiral amide analog of valproic acid. *Pharm Res* 1999; 16:1582–8
- Cordato DJ, Chebib M, Mather LE, Herkes GK, Johnston GA: Stereoselective interaction of thiopentone enantiomers with the GABA(A) receptor. *Br J Pharmacol* 1999; 128:77–82
- Nau C, Vogel W, Hempelmann G, Brau ME: Stereoselectivity of bupivacaine in local anesthetic-sensitive ion channels of peripheral nerve. *ANESTHESIOLOGY* 1999; 91:786–95
- Kommuru TR, Khan MA, Reddy IK: Effect of chiral enhancers on the permeability of optically active and racemic metoprolol across hairless mouse skin. *Chirality* 1999; 11:536–40
- Suedee R, Brain KR, Heard CM: Differential permeation of propranolol enantiomers across human skin in vitro from formulation containing an enantioselective excipient. *Chirality* 1999; 11:680–3
- Baudry S, Pham YT, Baune B, Vidrequin S, Crevoisier C, Gimenez F, Farinotti R: Stereoselective passage of mefloquine through the blood-brain barrier in the rat. *J Pharm Pharmacol* 1997; 49:1086–90
- Pham YT, Nosten F, Farinotti R, White NJ, Gimenez F: Cerebral uptake of mefloquine enantiomers in fatal cerebral malaria [published correction appears in *Int J Clin Pharmacol Ther* 1999; 37:316]. *Int J Clin Pharmacol Ther* 1999; 37:58–61
- Bernards CM, Hill HF: Physical and chemical properties of drug molecules governing their diffusion through the spinal meninges. *ANESTHESIOLOGY* 1992; 77:750–6
- Bernards CM: Flux of morphine, fentanyl, and alfentanil through rabbit arteries in vivo. Evidence supporting a vascular route for redistribution of opioids between the epidural space and the spinal cord. *ANESTHESIOLOGY* 1993; 78:1126–31
- Bernards CM, Kopacz DJ, Michel MZ: Effect of needle puncture on morphine and lidocaine flux through the spinal meninges of the monkey in vitro. Implications for combined spinal-epidural anesthesia [see comments]. *ANESTHESIOLOGY* 1994; 80:853–8
- Bernards CM, Kern C: Palmitoyl carnitine increases the transmeningeal flux of hydrophilic but not hydrophobic compounds in vitro. *ANESTHESIOLOGY* 1996; 84:392–6
- Kopacz D, Allen H, Thompson G: A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. *Anesth Analg* 2000; 90:642–8