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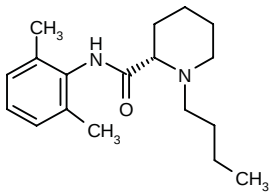
Levobupivacaine

Local Anesthetic

Prop INN;BAN

Chirocaine™

(–)-(*S*)-1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide
(–)-(*S*)-1-Butyl-2',6'-pipecoloxylidide



$C_{18}H_{28}N_2O$ Mol wt: 288.4370

CAS: 027262-47-1

EN: 220671
EN: 091311 (as racemic)

Synthesis

Levobupivacaine has been obtained by two different ways: Scheme 1.

1) The deamination of *N*-benzoyloxycarbonyl-L-lysine (I) with $NaNO_2$/acetic acid gives 6-acetoxy-2(*S*)-(benzyloxycarbonylamino)hexanoic acid (II), which is amidated with 2,6-dimethylaniline (III) and dicyclohexylcarbodiimide (DCC) to the expected amide (IV). The deacetylation of (IV) with K_2CO_3 in methanol affords compound (V), which is tosylated as usual with tosyl chloride giving intermediate (VI), which is stereospecifically cyclized by means of K_2CO_3 in ethanol yielding *N*-(2,6-dimethylphenyl)piperidine-2(*S*)-carboxamide (VII). Finally, this compound is alkylated with butyl bromide and K_2CO_3 or by reductoalkylation with butyraldehyde (1, 2).

2) The amidation of piperidine-2-carboxylic acid (VIII) with 2,6-dimethylaniline (III) by means of $SOCl_2$ in toluene gives the corresponding amide (IX), which is alkylated with butyl bromide as before yielding racemic bupivacaine (X) (3). This compound is then submitted to optical resolution by treatment with (*S*,*S*)-(–)-tartaric acid followed by crystallization of the resulting tartrate and acidification with HCl in isopropanol (4).

Introduction

In 1884, 45 years after its isolation from the leaves of the coca plant, cocaine was introduced as a local anesthetic. The search for a cocaine substitute represents the first major attempt to harness organic chemistry in order to improve upon the therapeutic properties of a natural product. Local anesthetics are classified according to their chemical structures as esters or amides. Table I presents local anesthetics by their year of introduction.

One such agent, bupivacaine, is a long-lasting local anesthetic that is widely used for spinal anesthesia. However, inadvertent intravenous (i.v.) injection of bupivacaine results in cardiotoxic effects (5-8). In addition to the direct myocardial depressant effects associated with the compound, deaths reported with i.v. injection are thought to be due to severe cardiac dysrhythmia (6, 7). Studies have also shown that the central nervous system is involved in the observed cardiotoxic response to bupivacaine (9-12).

The enantiomers of bupivacaine, ropivacaine and mepivacaine, have been reported to differ in both potency and toxicity (13, 14). Moreover, since ropivacaine (a single enantiomer) has lower cardiac toxicity than bupivacaine, interest has been generated in evaluating the enantiomer-specific differences in the action of bupivacaine (15-17).

Bupivacaine is an equimolar (racemic) mixture of (*S*)-(–)-bupivacaine (or levobupivacaine) and (*R*)-(+)-bupivacaine. Experimental studies have demonstrated that the potency and duration of levobupivacaine *in vivo* were equal to or in some cases greater than those of (*R*)-(+)-bupivacaine (14, 18, 19). Levobupivacaine was also less toxic, with an LD_{50} 30-40% lower than that of the (*R*)-(+)-enantiomer when administered i.v. in rats, mice and rabbits (14, 18). Levobupivacaine was thus selected for development by Chiroscience in view of its improved safety profile as compared to bupivacaine.

Pharmacological Actions

Levobupivacaine is a long-acting, highly potent local anesthetic. Studies have been performed to compare the

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Scheme 1: Synthesis of Levobupivacaine

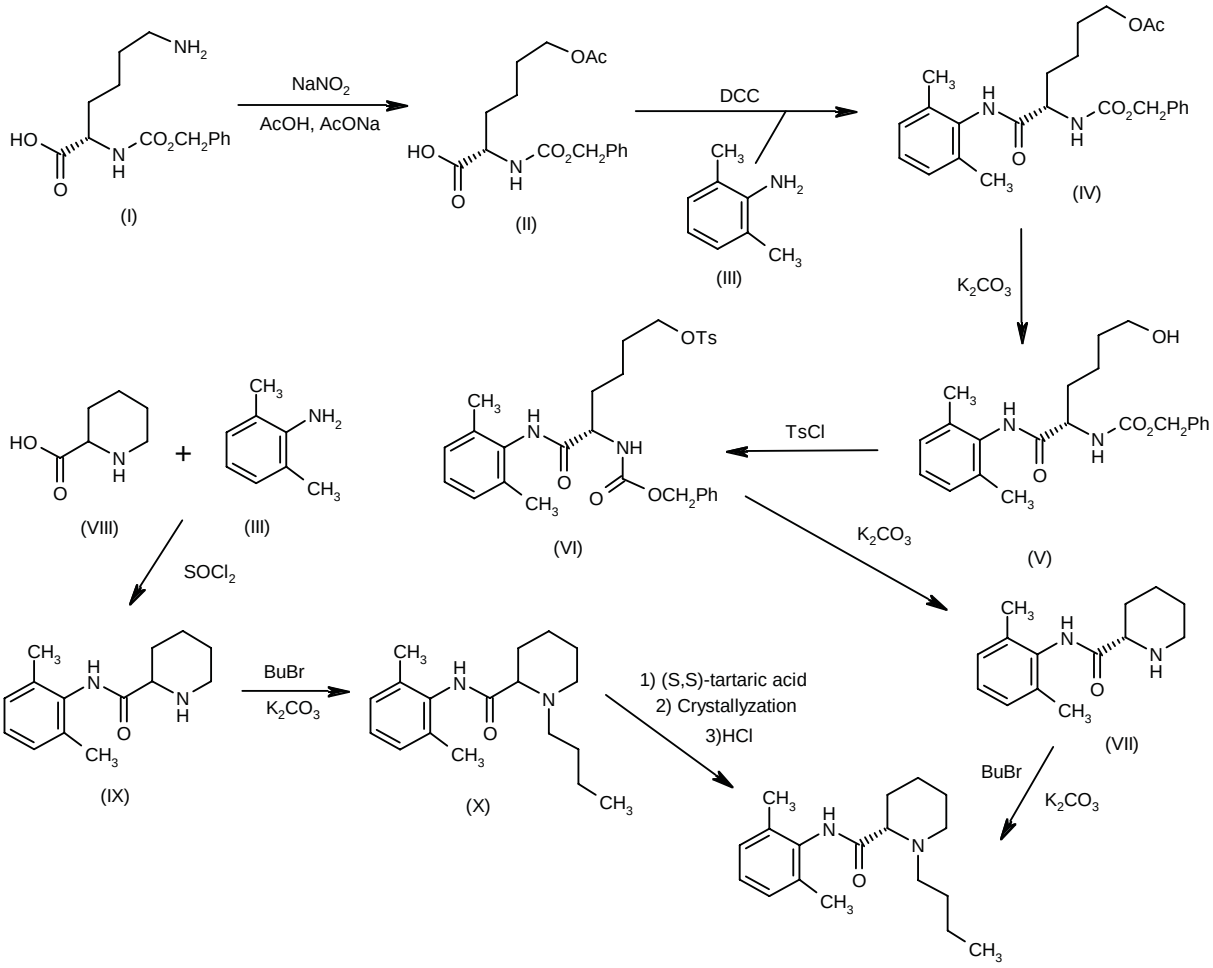

Table I: Year of introduction of local anesthetics/chemical group.

1884	Cocaine[1]	Ester
1900	Benzocaine[1]	Ester
1905	Procaine HCl[2]	Ester
1941	Tetracaine HCl[1,2]	Ester
1947	Lidocaine HCl[1,2]	Amide
1957	Mepivacaine HCl[2]	Amide
1967	Bupivacaine HCl[2]	Amide
1974	Etidocaine HCl[2]	Amide
1996	Ropivacaine HCl[2]	Amide

[1]Topical (surface) application; [2]Injection.

duration of sensory and motor suppression in periphery nerve blocks induced by several local anesthetics. Levobupivacaine and bupivacaine (0.125%, 0.25% or 0.5% solutions) and ropivacaine and pethidine (0.25%, 0.5% and 1.0% solutions) were injected into male rats subjected to infraorbital (IONB) or sciatic nerve block (SNB). Sensory blocks of similar duration were induced by equimolar doses of the anesthetics. However, in both IONB and SNB animals, bupivacaine was more potent than its vasoconstrictive enantiomer, levobupivacaine. The pethidine-induced motor block was shorter than blocks induced by bupivacaine and levobupivacaine. Furthermore, ropivacaine displayed an inverse relation between dose and duration of motor block which could not be explained. The log(dose)-log(effects) lines for bupivacaine, levobupivacaine and ropivacaine did not deviate from parallelism in IONB animals. In SNB animals, however, only the log(dose)-log(duration) lines for bupivacaine *vs.* levobupivacaine did not deviate from parallelism. It should be noted that the differences in peripheral nerve blocks observed between anesthetics used in this study were modest or nonsignificant (20).

The enantiomer-specific component and cardiotoxicity of bupivacaine action have been demonstrated in a study examining the effects of (*R*)-(+)-bupivacaine and levobupivacaine on the cell firing rate (CFR) at the nucleus tractus solitarius (NTS) and on the cardiovascular system. Rats were administered arrhythmogenic doses

(2 mg/kg i.v.) of either enantiomer. Both bupivacaine enantiomers significantly decreased CFR , blood pressure and heart rate and an inversion in electrical axis was observed 2-3 sec after injection. However, severe bradycardia accompanied by hypotension and eventual apnea and death were observed in all animals receiving the (*R*)-(+)-enantiomer. In contrast, while all animals continued to breathe, 4 levobupivacaine-treated animals exhibited mild bradycardia and only 2 animals died. These results support the enantiomer-specific component of bupivacaine's actions on the NTS and cardiovascular system (21).

The mechanisms of the cardiotoxic effects of levobupivacaine and bupivacaine were investigated in longitudinal crossover studies in sheep, demonstrating that levobupivacaine is the clinically safer enantiomer. Sheep (2 groups of 7) were administered either levobupivacaine or bupivacaine via right atrial catheter in the following dose ranges: subconvulsive (6.25-37.5 mg diluted in 10 ml saline over 1 min) or toxic (37.5-200 mg diluted in 40 ml saline over 3 min). Similar time- and dose-dependent reductions in left ventricular systolic contractility were observed with both drugs when administered at subconvulsive doses, and minor changes in heart rate and blood pressure were observed. In contrast, convulsions were observed with doses of ≥ 75 mg of bupivacaine and ≥ 100 mg levobupivacaine, in addition to decreased cardiac output and myocardial blood flow, ventricular arrhythmias and QRS widening. However, fewer and significantly less severe arrhythmias were observed in levobupivacaine-treated animals. Moreover, while doses of 100, 150 and 200 mg levobupivacaine resulted in only nonfatal arrhythmias, the same doses of bupivacaine resulted in sudden onset of ventricular fibrillation and death in 3 animals (22).

A possible explanation for the differential toxicity observed with the two bupivacaine enantiomers was provided by a study which examined the direct myocardial effects of levobupivacaine and (*R*)-(+)-bupivacaine through monitoring of transmembrane action potentials in the guinea pig isolated papillary muscle. Although both enantiomers caused a reduction in the maximal rate of rise (V_{max}) of action potential amplitude and duration at a concentration of 10 μM, the reduction was greater in the presence of (*R*)-(+)-bupivacaine (K_d = 16 μM) as compared to levobupivacaine (K_d = 39 μM). Moreover, membrane potential recovery following hyperpolarizations was also slower and action potential duration was shortened in the presence of (*R*)-(+)-bupivacaine (23). Similarly, another study examining the direct effect of the enantiomers on the human cardiac delayed rectifier channel (hKv1.5) has demonstrated that the stereochemical conformation of the racemate influences its interaction with cardiac cell membranes. Although both enantiomers were shown to have similar voltage dependencies, the steady-state block induced by levobupivacaine was 31 ± 2% (K_d = 27.3 μM), as compared to 80 ± 3% (K_d = 4.1 μM) induced by (*R*)-(+)-bupivacaine. These results indicate that, although the blocking action of both enantiomers occurs at the same site at the internal mouth of the hKv1.5 channel pore, the block is stereoselective with a difference in binding energies between the enantiomers (24).

When administered to near-term pregnant ewes, levobupivacaine, bupivacaine and ropivacaine were found to have similar actions on uterine blood flow. Chronically instrumented animals received 2 infusions of one of the three local anesthetics, starting with 0.07 mg/kg/min for 15 min followed by another infusion of 0.035 mg/kg/min for 45 min. No significant differences were observed in maternal and fetal serum anesthetic concentrations following infusion and no significant changes in uterine blood flow or intraamniotic pressure were observed with any of the anesthetics (25).

Pharmacokinetics

The myocardial uptake kinetics were found to be similar for levobupivacaine, (*R*)-(+)-bupivacaine and the racemate when examined using the isolated rabbit heart model. Similar steady-state tissue/perfusate concentration ratios and rapid decreases in outflow concentration after removal of drugs were observed for the three anesthetics. However, although QRS widening and severe arrhythmias were observed in all preparations, these responses were, again, less severe with levobupivacaine treatment as compared to (*R*)-(+)-bupivacaine and the racemate (25).

A partial crossover systemic and regional pharmacokinetic study in the brains of ewes administered bupivacaine or levobupivacaine has demonstrated that the pharmacokinetics of each anesthetic were similar and independent of dose. Sheep received bupivicaine or levobupivacaine (6.25-37.5 mg in 10 ml saline over 1 min) through a catheter inserted near the aortic arch, in the right atrium or in the coronary sinus. Both anesthetics displayed a mean myocardial tissue concentration of 1-4% of the dose between 3-5 min and a mean brain concentration of 0.2%-1% of the dose at 2 and 4 min postadministration. No dose-dependent pharmacokinetics or systemic toxicity were observed for either drug. However, (*R*)-(+)-bupivacaine was found to have a higher mean total body clearance as compared to levobupivacaine. The systemic pharmacokinetics of levobupivacaine were found to be the same whether administered alone or as a component of the racemic mixture (27).

The pharmacokinetics of the enantiomers of bupivacaine were further investigated in 10 healthy male volunteers, with results demonstrating that the enantiomer-selective differences observed may be due to differences in plasma binding. Bupivacaine (30 mg) was administered via infusion through a cannula inserted into an antecubital vein at a constant rate for 10 min. Mean total plasma clearance was found to be significantly higher for (*R*)-(+)-bupivacaine than for levobupivacaine. However, the plasma clearance for unbound (*R*)-(+)-bupivacaine was significantly lower than that of levobupivacaine. The terminal half-life and mean residence time of (*R*)-(+)-bupi-

vacaine were also significantly longer than those of levobupivacaine (210 ± 95 and 215 ± 74 min *vs.* 157 ± 77 and 172 ± 55 min for (*R*)-(+)-bupivacaine and levobupivacaine, respectively), providing further evidence of enantiomer-selective pharmacokinetics (28).

Investigation of the pharmacokinetics has also provided support for the use of single enantiomers as opposed to the racemate in local anesthesia. Six healthy patients scheduled for minor surgery received a total of 51 mg of bupivacaine hydrochloride via injections (into the epidermal space) of 3 ml of 0.5%, followed by an additional 20 ml 3 min later. Peak plasma concentrations of (*R*)-(+)-bupivacaine were significantly lower than those of levobupivacaine (389 ± 93 ng/ml *vs.* 449 ± 109 ng/ml, respectively) with significantly larger unbound peak concentrations of (*R*)-(+)-bupivacaine (20 ± 11 ng/ml) as compared to levobupivacaine (15 ± 9 ng/ml). Although systemic absorption did not vary between enantiomers, differential distribution and elimination displayed enantiomer-selective characteristics (29).

Clinical Studies

Similar anesthetic effects were induced by levobupivacaine and bupivacaine when compared in a double-blind study. Seventy-four patients undergoing elective surgery received either 0.4 ml/kg of 0.25% or 0.5% levobupivacaine or 0.5% bupivacaine; supraclavicular brachial blocks were applied to each patient and sensory and motor blocks were assessed using pinpricks and the Bromage scale, respectively. No significant differences were observed between the three treatment groups with respect to onset, duration and quality of sensory and motor block indicating similar activities of the three treatments (30). Moreover, another randomized, double-blind study evaluating the efficacy and safety of levobupivacaine and bupivacaine for use as extradural anesthesia also demonstrated that the two anesthetics induce clinically indistinguishable sensory and motor blocks. Eighty-eight patients undergoing elective lower limb surgery requiring extradural anesthesia received 15 ml of levobupivacaine (0.5% or 0.75%) or bupivacaine (0.5%). Again, no significant differences were observed between onset and intensity of sensory or motor block. However, the duration of the sensory block tended to be longer, although not significantly so, in patients receiving 0.75% levobupivacaine (31).

The clinical characteristics of 0.75% levobupivacaine were further described when the anesthetic was used for epidural anesthesia in a randomized, double-blind study. Fifty-six patients undergoing major elective abdominal surgery were administered 20 ml of either 0.75% levobupivacaine or bupivacaine over 5 min injected at the L2-3 or L3-4 interspace; sensory and motor blockade and abdominal relaxation were monitored by pinprick, the modified Bromage scale or the rectus abdominis muscle test, respectively, after injection of the anesthetic. Fifty-three of the 56 patients successfully completed surgery with the initial dose of anesthetic. No significant differences were observed in onset and regression of sensory blockade between the treatment groups, and the duration of the motor blockade was similar for both anesthetics. However, a significant, although slight, increase in duration of the sensory block was observed in patients receiving levobupivacaine (32).

Chiroscience has signed a licensing agreement with Zeneca for commercialization of levobupivacaine (Chirocaine™). Chiroscience filed for regulatory approval in Europe in December 1997 and an NDA has been submitted to the FDA (33, 34).

Manufacturer

Chiroscience, Ltd. (GB), licensed to Zeneca, Ltd. (GB).

References

1. Adger, B., Dyer, U., Hutton, G., Woods, M. *Stereospecific synthesis of the anaesthetic levobupivacaine.* Tetrahedron Lett 1996, 37: 6399-402.

2. Hutton, G.E. (Chiroscience, Ltd.). *The manufacture of levobupivacaine and analogues thereof from L-lysine.* WO 9611181.

3. Langston, M., Skead, B.M. (Chiroscience, Ltd.). *Progress for preparing levobupivacaine and analogues thereof.* WO 9612700.

4. Langston, M., Skead, B.M. (Chiroscience, Ltd.). *Crystallization of levobupicavaine and analogues thereof.* WO 9612699.

5. Mallampati, S.R., Liu, P.L., Knapp, R.M. *Convulsions and ventricular tachycardia from bupivacaine with epinephrine: Successful resuscitation.* Anesth Analg 1984, 63: 856-9.

6. Kotelko, D., Shnider, S., Dailey, P. et al. *Bupivacaine-induced cardiac arrhythmias in sheep.* Anesthesiology 1984, 60: 10-8.

7. Gregg, R.V., Turner, P.A., Denson, D.D. et al. *Does diazepam really reduce the cardiotoxic effects of intravenous bupivacaine?* Anesth Analg 1987, 67: 9-14.

8. Feldman, H.S. *Toxicity of local anesthetic agents.* In: Anesthetic Toxicity, S.A. Rice, K.J. Fish (Eds.), Raven Press, New York, 1994, 107-33.

9. Heavner, J.E. *Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricle of cats.* Anesth Analg 1986, 65: 133-8.

10. Thomas, R.D., Behbehani, M.M., Coyle, D.E., Denson, D.D. *Cardiovascular toxicity of local anesthetics: An alternative hypothesis.* Anesth Analg 1986, 65: 444-50.

11. Richter, R.R., Denson, D.D., Behbehani, M.M. *The effect of an arrhythmogenic intravenous dose of bupivacaine on the activity of cortical and medullary cells.* Anesthesiology 1988, 69: A865.

12. Denson, D.D., Behbehani, M.M., Gregg, R.V. *Effects of an intravenously administered arrhythmogenic dose of bupivacaine at the nucleus tractus solitarius in the conscious rat.* Reg Anesth 1990, 15: 76-80.

13. Aberg, G., Wahlstrom, B. *Mechanical and electrophysiological effects of some local anaesthetic agents and their isomers on the rat portal vein.* Acta Pharmacol Toxicol 1972, 31: 255-66.

14. Aberg, G. *Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds.* Acta Pharmacol Toxicol 1972, 31: 273-86.

15. Akerman, B., Hellberg, I.B., Trossvik, C. *Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103).* Acta Anaesthesiol Scand 1988, 32: 571-8.

16. Reiz, S., Haggmark, S., Johansson, G., Nath, S. *Cardiotoxicity of ropivacaine: A new amide local anaesthetic agent.* Acta Anaesthesiol Scand 1988, 33: 93-8.

17. Moller, R., Covino, G.B. *Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic.* Anesthesiology 1990, 72: 322-9.

18. Luduena, F.P., Bogado, E.F., Tullar, B.F. *Optical isomers of mepivacaine and bupivacaine.* Arch Int Pharmacodyn 1972, 200: 359-69.

19. Aps, C., Reynolds, F. *An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine.* Brit J Clin Pharmacol 1978, 6: 63-8.

20. Dyhre, H., Lang, M., Wallin, R., Renck, H. *The duration of action of bupivacaine, levobupivacaine, ropivacaine and pethidine in peripheral nerve block in the rat.* Acta Anaesthesiol Scand 1997, 41: 1346-52.

21. Denson, D.D., Behbehani, M.M., Gregg, R.V. *Enantiomer-specific effects of an intravenously administered arrhythmogenic dose of bupivacaine on neurons of the nucleus tractus solitarius and the cardiovascular system in the anesthetized rat.* Reg Anesth 1992, 17: 311-6.

22. Huang, Y.F., Pryor, M.E., Mather, L.E., Veering, B.T. *Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep.* Anesth Analg 1998, 86: 797-804.

23. 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.* Brit J Pharmacol 1991, 103: 1275-81.

24. Valenzuela, C., Delpa2n, E., Pfrez, O., Tamkun, M.M., Tamargo, J., Snyders, D.J. *Stereoselective bupivacaine block of the human cardiac delayed rectifier Kv1.5 channel.* Biophys J 1994, 66: A205.

25. Yun, E., Karpel, B., Noble, G., Santos, A., Finster, M. *The effects of levobupivacaine, bupivacaine, and ropivacaine on uterine blood flow.* Anesthesiology 1996, 85(3A): Abst A881.

26. Mazoit, J.X., Bobfco, O., Samii, K. *Myocardial uptake of bupivacaine: II. Pharmacokinetics and pharmacodynamics of bupivacaine enantiomers in the isolated perfused rabbit heart.* Anesth Analg 1993, 77: 477-82.

27. Mather, L.E., Huang, Y.F., Veering, B., Pryor, M.E. *Systemic and regional pharmacokinetics of levobupivacaine and bupivacaine enantiomers in sheep.* Anesth Analg 1998, 86: 805-11.

28. Burm, A.G.L., van der Meer, A.D., van Kleef, J.W., Zeijlmans, P.W.M., Groen, K. *Pharmacokinetics of the enantiomers of bupivacaine following intravenous administration of the racemate.* Brit J Pharmacol 1994, 38: 125-9.

29. Groen, K., Mantel, M., Zeijlmans, P.W.M., Zeppenfeldt, B., Olieman, W., Stienstra, R., van Kleef, J.W., Burm, A.G.L. *Pharmacokinetics of the enantiomers of bupivacaine and mepivacaine after epidural administration of the racemates.* Anesth Analg 1998, 86: 361-6.

30. Checketts, M.R., Cox, C., MacKenzie, N., Bannister, J., Scott, N.B. *Comparison of levobupivacaine and bupivacaine in supraclavicular brachial plexus blockade.* Reg Anesth 1997, 22(2, Suppl.): 64.

31. Cox, C.R., Faccenda, K.A., Gilhooly, C., Bannister, J., Scott, N.B., Morrison, L.M.M. *Extradural S(–)-bupivacaine: Comparison with racemic RS-bupivacaine.* Brit J Anaesth 1998, 80: 289-93.

32. Kopacz, D.J., Allen, H.W., Thompson, G.E. *Double-blind randomized trial of 0.75% levobupivacaine compared to 0.75% bupivacaine for epidural anesthesia in patients undergoing major elective abdominal surgery.* Anesth Analg 1998, 86(2, Suppl.): Abst S281.

33. *Chiroscience: Year-end 1997 highlights.* Prous Science Daily Essentials May 15, 1998.

34. *Chiroscience submits NDA to FDA for Chirocaine.* Prous Science Daily Essentials May 4, 1998.