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Inclusion complexation of amide-typed local anesthetics with β-cyclodextrin and its derivatives. III. Biopharmaceutics of bupivacaine-SBE7-βCD complex following percutaneous sciatic nerve administration in rabbits

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Abstract

The effect of a new modified β-cyclodextrin derivative, sulfobutylether7-β-cyclodextrin (SBE7-βCD) on the biopharmaceutics of local anesthetic bupivacaine (BVC) was studied in a rabbit sciatic model. Phase-solubility study revealed the formation of a 1:1 complex of the *Al* type between BVC and SBE7-βCD, with an apparent stability constant of $149 \pm 7\ M^{-1}$. Then, BVC hydrochloride (BVC-HCl) and BVC complexed with SBE7-βCD (BVC-SBE7-βCD) were administered around the sciatic nerve both as solutions, in a randomized cross-over design in six New Zealand rabbits. The plasma concentrations of BVC, the onset and duration of motor blockade were evaluated. For the dose of BVC injected (5 mg in 2.5 ml), complexation with SBE7-βCD led to a decrease in the maximum plasma concentration (C_{max}) of BVC, while the time to reach C_{max} (T_{max}) was increased. Complexation also delayed the onset of motor block and did not modify its duration. This decrease in absorption rate of BVC following complex administration was confirmed by Loo-Riegleman absorption analysis. The effect of SBE7-βCD concerned mainly the faster absorption phase, responsible for side effects, but had also an impact on the slower phase, even if not stastistically significant, shown by a flip-flop in the elimination constant. Complexation may be useful to improve the therapeutic index of local anesthetics, allowing greater amounts of drug to be injected in order to prolong nerve blockade.

Keywords: Bupivacaine; Sulfobutylether7-β-cyclodextrin; Inclusion complex; Phase-solubility analysis; Percutaneous administration; Sciatic nerve block; Systemic absorption

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1. Introduction

Blocking nerves by local anesthetics (LAs) is commonly used in the management of many forms of acute and chronic pain. However, there is a need to improve regional administration of LA drugs, allowing a longer duration of action and a decrease of systemic uptake, transient high plasma levels being responsible for toxic side effects (Stanley, 1988). Among different formulations that could be considered in order to reach that goal, i.e. microspheres (Le Corre et al., 1995; Curley et al., 1996), liposomes (Grant et al., 1994; Boogaerts et al., 1995), hyaluronic acid formulations (Doherty et al., 1995, 1996), biodegradable polymer matrix (Masters et al., 1993)..., we also studied cyclodextrins (CDs), especially parenterally safe derivatives. In previous works we have shown that i) complexation between LAs and CDs exists in aqueous as well as in solid state (Dollo et al., 1996) and ii) epidurally administered BVC-hydroxypropyl-β-cyclodextrin complex could prolong duration of action and decrease systemic uptake of BVC (Fréville et al., 1996).

Natural CDs are cyclic oligosaccharides containing six (αCD), seven (βCD) or eight (γCD) α-1,4-linked glucopyranose units able to entrap many drugs in their hydrophobic cavities to form non covalent inclusion compounds (Duchêne, 1987). This may improve physical and/or chemical properties of the inside guest molecule such as stability, solubility, bioavailability... (Loftsson and Brewster, 1996). Alkylated derivatives of βCD, such as hydroxypropyl-β-cyclodextrin (HP-βCD) and, more recently, variably substituted sulfobutyl ether cyclodextrin derivatives (SBE-βCD) have been developed due to improved complexing ability, greater water solubility and lesser toxicity allowing parenteral administration (Järvinen et al., 1994; Rajewski et al., 1995). In sulfobutyl ether 7 β-cyclodextrin (SBE7-βCD), a derivative with an average degree of substitution of seven, an anionic sulfonate group is spaced from the cavity by a butyl chain (Fig. 1).

The aim of this investigation was to study the feasibility of using complexes with SBE7-βCD as controlled drug delivery systems for local anesthetic drugs. For that purpose, we have evaluated the biopharmaceutics and the pharmacodynamics of bupivacaine-SBE7-βCD complex following percutaneous sciatic nerve block in rabbits.

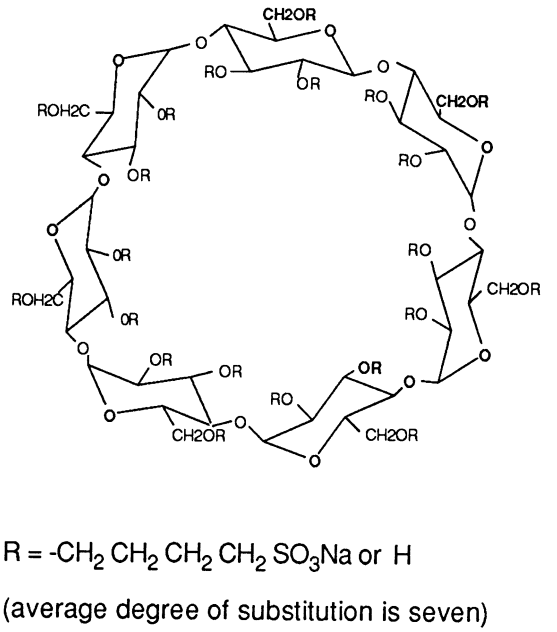

Fig. 1. Chemical structure of SBE7-βCD.

2. Materials and methods

2.1. Reagents

SBE7-βCD (CAPTISOL™; ref. 7585-39-9; DS = 6.4; M_W = 2163 g/mole) was kindly supplied by Cydex, Overland Park, USA.

Bupivacaine hydrochloride was supplied by Astra (Sortjalde, Sweden). The base (Fig. 2) was obtained by precipitation from an alkaline (3% aqueous NH_4OH solution) saturated solution of the hydrochloride. The precipitate were rinsed by

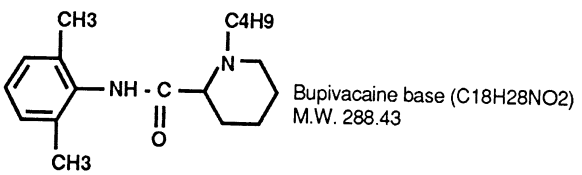

Fig. 2. Chemical structure of bupivacaine.

distilled water until a neutral pH filtrate was obtained. The base were then dried (+40°C) before its purity was established in comparison with hydrochloride standard by HPLC. Unless specified otherwise, doses and concentrations of bupivacaine were expressed in term of base equivalent. All other reagents and solvents (Merck, Darmstadt, Germany) were of analytical grade. Freshly prepared distilled water was used as medium throughout the study.

2.2. Phase-solubility studies

Solubility measurements were determined according to the method of Higuchi and Connors (1965). Excess amounts of bupivacaine (30 mg) were weighted into 1 ml screw-cap polypropylene tubes to which were added aqueous solutions containing increasing concentrations of SBE7-βCD, ranging from 0 to 10% (w/v). The suspensions formed were then rotated on a top to bottom shaker, thermostatically controlled at 37 ± 0.1°C. After solubility equilibrium for 48 h, an aliquot was filtered through a cotton filter, appropriately diluted with the mobile phase (in a 5/1000 ratio) and total concentration of bupivacaine in the filtrate was analyzed by HPLC (see below). The experiment was carried out in triplicate and the stability constant (K_s) was then calculated from the linear portion of the phase solubility diagrams (reporting drug concentration vs SBE7-βCD concentration), assuming that a 1:1 stoichiometric ratio complex was formed at the initial step (slope smaller than one) according to Eq. (1) (Higuchi and Connors, 1965):

$$K_s = \frac{\text{slope}}{s_0(1 - \text{slope})} \quad (1)$$

where s_0 is the drug solubility in water.

2.3. Quantitative determinations

The quantitative determinations were performed on a reverse-phase high-performance liquid chromatographic (HPLC) system according to Le Guévello et al. (1993). The analytical chromatography column was a Waters Model μBondapak C_{18} (250 × 4 mm I.D.; particle size 10 mm) thermostated at 30°C. The mobile phase was a mixture of acetonitrile and 0.01 M sodium dihydrogenphosphate solution (30:70). The pH of the aqueous solution was brought to 2.1 after addition of 15 N phosphoric acid. The flow rate was 1 ml/mn and the detector was operated at 205 nm.

2.4. Animals

The study was approved by the local Committee of Laboratory Animal Care in accordance with the rules and guidelines concerning the care and use of laboratory animals. New Zealand albino female rabbits, weighing 2.9–3.2 kg, were housed individually in standard cages on a 12-h light/dark cycle. The animals were given free access to food and tap water and were not tested for at least 7 days after their arrival from the supplier.

2.5. Study formulations

Two formulations were compared, BVC-HCl and BVC complexed with SBE7-βCD (BVC-SBE7-βCD), both as solutions containing BVC at a concentration of 2 mg/ml. The complex between BVC and SBE7-βCD was formed by complete dissolution of 20 mg of BVC in 10 ml of an aqueous solution of SBE7-βCD (30% w/v). The mixture was shaken during 48 h to ensure complete dissolution of BVC and then stored at 4°C. BVC-HCl solution was prepared by dissolution in isotonic NaCl solution. All solutions were sterilized by filtration just before administration (over a 0.22 μm filter, Minisart® NML, Sartorius, Göttingen, Germany), after the lack of non specific adsorption of bupivacaine to the filter membrane has been checked.

2.6. Study design

The biopharmaceutics as well as motor block duration of BVC-HCl and BVC-SBE7-βCD were compared in a group of six animals following a cross-over (side of injection, formulation injected) and randomized administration in the vicinity of the sciatic nerve of a 5 mg dose of bupivacaine

with a one-week wash-out period between the administrations. We used a model of percutaneous sciatic block described by Grant for the rat (Grant et al., 1992), modified for the rabbit, with a nerve stimulator to locate the sciatic nerve accurately. After the animal was held in lateral recumbency with the limb to be injected forming a right angle with the longitudinal axis of the trunk, the groove between the great trochanter of the femur and the ischial tuberosity was identified by palpation. A 22 gauge beveled teflon-shielded injection needle (Stimuplex®-Kanüle A, B. Braun, Melsungen, Germany, i. d. 0,7 mm, length 50 mm) attached to a nerve stimulator (Stimuplex GLR 61®, B. Braun, Melsungen, Germany) was advanced into the groove from dorsolateral direction at a 45° angle and stimulated at 1 Hz, with an initial intensity of 3 mA. Close proximity of the needle tip to the sciatic nerve was confirmed by a flexion of the hindpaw at a stimulus intensity ≤ 0.3 mA. Then, while the needle was held steady, the injection (5 mg/2.5 ml) was made through a catheter attached to the needle. During the whole study, no animal ever showed any sign of stress, or side effect or trauma induced by the injection needle, either immediately after the injection or several hours or days later. Prior to each unilateral injection, the integrity of both sciatic nerves was clinically checked. Blockade was reversible and all animals recovered motor function normally. For biopharmaceutic purposes, an intravenous administration of BVC-HCl (2 mg) was performed one week after the last percutaneous administration of bupivacaine.

2.7. Drug sampling and analysis

Prior to any administration, each rabbit received heparin sodium (3 ml, 5000 UI/ml) (Leo SA, St Quentin en Yvelines, France). Blood samples were drawn from a catheter placed in a marginal vein of the ear before the injection and then at 0.5, 1, 2, 3.5, 5, 7.5,10, 15, 20, 30, 45, 60, 120, 240 and 360 min. Blood was collected by fractions of 30 s. during the first 5 min (lower than 1 ml) and then by samples of 1 ml. After centrifugation (3 min at 900 g) the plasma was collected in polypropylene tubes and stored frozen at -20°C until analysis.

Bupivacaine plasma concentrations were determined by a reversed phase liquid chromatographic method with UV detection (conditions previously described). The accuracy, the within-day and between-day reproducibilities ($n = 10$) at a plasma concentration of 50 ng/ml were 2.7, 3.9 and 4.7%, respectively. All calibration curves ranging from 2 to 1000 ng/ml were linear ($r^2 = 0.9995$).

2.8. Biopharmaceutics

The maximum plasma concentration of bupivacaine in plasma (C_{max}) and the time to reach C_{max} (T_{max}) were derived from raw data. The area under the plasma concentration–time curves from the time of drug administration up to the last sampling point [AUC (0–360)] following hind limb and i.v. administration was computed by the trapezoidal rule. The area under the plasma concentration–time curves from the time of the last sampling point to infinity [AUC (360–∞)] was calculated by dividing the plasma concentration at 360 min by the apparent elimination rate constant.

Individual plasma concentration data obtained after i.v. administration were analyzed according to an open-system model with first-order elimination from the central compartment. A model was fitted to the data using a least-squares nonlinear regression analysis with the SIPHAR software package (Simed, Créteil, France). The choice of the best weighting scheme and model was based on inspection of standardized weighted residuals versus time plots, and on statistical evaluation of the weighted sum of squared residuals (Boxenbaum et al., 1974).

Individual absorption kinetics after percutaneous administration of BVC-HCl and BVC-SBE7-βCD were evaluated by Loo–Riegelman absorption analysis (Loo and Riegleman, 1968). Time corresponding to 10, 50 and 90% absorbed (T_{10}, T_{50} and T_{90}) were derived from raw data and T_d (63.2% absorbed) was calculated from the fit of the percent absorbed–time plots using the Weibull equation. The absolute bioavailability of bupivacaine following hind limb administration of BVC-HCl and BVC-SBE7-βCD around the sci-

atic nerve was determined by the AUC $(0-\infty)$ ratio.

2.9. Pharmacodynamics

Motor activity of the animals was evaluated by a blinded experimentator unaware of the formulation studied, using a modified motor scale adapted from Langerman's scale (Langerman et al., 1991) and the model validated by Feldman for the rat (Feldman and Covino, 1988), motor block being graded from level 0 for which no deficit was seen (normal movements) to level 3, state of total paralysis of the hind limb. Because the scale is principally based on grip strength and due to the difficulty to clearly evaluate in the rabbit the different steps from level 3 to level 2 and level 1, we only evaluated i) the onset of motor blockade, i.e. the time after the injection when the rabbit lost motor control of the foot as evidenced by dragging the hind limb and/or by closing of the foot with digits together, as compared to a normal foot with digits open and far apart and ii) the duration of motor blockade, i.e. the time from onset of motor blockade to the time when these signs disappeared. The intensity of the motor activity was checked continuously and recorded 5 min after the injection and then every 30 min until recovery, i.e. level 0 was reached. Prior to the injection, the lack of motor blockade was checked, so was the absence of neurological deficit in the contralateral limb after the injection.

2.10. Statistics

Data are presented as mean $\pm$ standard deviation (S.D.). Biopharmaceutic differences among groups were evaluated by one-way analysis of variance (ANOVA) (all values were normally distributed). Following a significant ANOVA, comparisons were made using the Protected Least Significant Difference test. Pharmacodynamic differences between the two formulations were checked by a paired t-test. A value of $p < 0.05$ defined statistical significance.

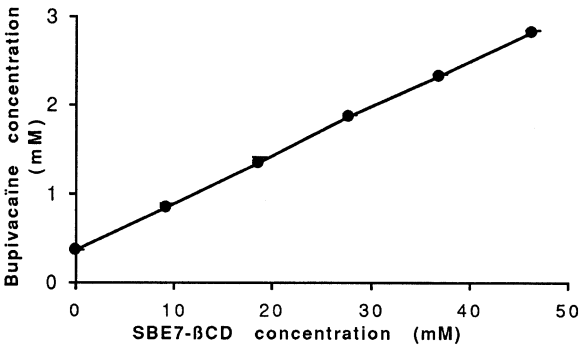

Fig. 3. Phase-solubility diagram of bupivacaïne-SBE7-βCD system in distillated water at 37°C. Each data point is the mean ($\pm$S.D.) of three determinations.

3. Results and discussion

3.1. Phase-solubility studies

The complexing capacity of the anionically charged SBE7-βCD with BVC in aqueous solution at 37°C was quantified using the solubility method. The *Al*-type equilibrium phase-solubility diagram obtained is presented in Fig. 3. The linear increase for BVC solubility as a function of SBE7-βCD concentration suggests the formation of a 1:1 soluble complex, according to Higuchi and Connors (1965). According to Eq. (1), the apparent stability constant of the complex formed (K_s) was found to be $149 \pm 7\ M^{-1}$, in accordance with the values already obtained between local anaesthetics and other cyclodextrin derivatives (Dollo et al., 1996).

3.2. Pharmacodynamics

To study the effect of SBE7-βCD on pharmacodynamics of bupivacaine after administration near the sciatic nerve, mean onset time and total block duration for both formulations were compared, based on the time of disappearance of the motor force maintaining foot digits far apart. The administration of SBE7-βCD (30% w/v solution) in the same conditions in two rabbits at the end of the study did not induce any motor block. The duration of motor blockade of bupivacaine following administration of the complex BVC-SBE7-

βCD was not significantly different to the one induced by BVC-HCl solution (4.5 ± 1.5 vs 4.9 ± 1.8 h, $p = 0.06$). On the other hand, difference in rapidity of onset of motor block between both formulations was observed, the onset was about four times slower with the complex (22.7 ± 5.1 vs 5.4 ± 1.2 min with BVC-HCl solution, $p < 0.001$). This suggested that when bupivacaine is complexed with SBE7-βCD its dissociation may be the rate-limiting step of the transfer across nervous membranes. The results showed great intra-individual variations concerning both formulations, for the onset (c.v. > 20%) but more markedly for the duration of motor blockade (c.v. > 33%). This could explain no significant difference in duration was found for both solution tested, the number of animals being probably too small. Both formulations allowed similar uptake by the nerve membrane, or similar intraneural BVC concentration profiles. The initial quantity of base form (diffusing most readily across the nerve sheath and membrane) available in the complex (about 5%) was probably too small to allow rapid onset, a sufficient quantity to be released from the complex was needed in order to reach the minimum blocking concentration. For BVC-HCl solution however, even if it is mainly ionized (less than 1% of the base form is available following the injection), in vivo buffering systems may rapidly produce the active base from the hydrochloride in a faster way than the release from a complex. The administration of BVC-HCl immediately followed by complex administration would perhaps be interesting in order to obtain a rapid onset but also an increase in blockade duration.

3.3. Biopharmaceutics

During peripheral nerve block, only a small amount of injected local anesthetic penetrates within and along the nerve, depending on its lipids affinity, to produce the observed functional deficits. Indeed, in addition to systemic uptake leading to a decrease in pharmacological effect but also responsible for cardiac as well as neurological toxicities, the nerve sheath perineurium is a very effective diffusion barrier to drugs leading to a substantial fraction of the delivered bupivacaine being absorbed locally by connective tissue and muscle surrounding the nerve (Popitz-Bergez et al., 1995). When complexed to SBE7-βCD, bupivacaine will dissociate, following mass action law as a function of complex stability constant. As this dissociation occurs progressively, free bupivacaine will reach the sciatic nerve or will undergo systemic absorption. The effect of complexation with SBE7-βCD on the biopharmaceutics of bupivacaine is shown in Table 1 and illustrated by Fig. 4. The transfer rate of BVC into the blood stream can be appreciated with model independent parameters C_{max} and T_{max}. Compared to BVC-HCl solution, the administration of BVC-SBE7-βCD complex around the sciatic nerve led to C_{max} values about 2.5 times smaller (154 ± 59 vs 380 ± 139 ng/ml), with T_{max} values four times greater (58 ± 36 vs 14 ± 9 min) suggesting a decrease in the absorption rate in the systemic circulation.

Mean plasma concentration–time profile of BVC following sciatic administration of the complex shows a flip-flop effect, explained by a slow release of BVC from the complex limiting its systemic absorption, the apparent elimination half-life ($T_{1/2\beta}$) is in fact corresponding to the apparent slow-absorption half-life ($T_{1/2abs2}$). The evaluation of the absorption kinetics was achieved by constructing the individual percent absorbed–time plots following sciatic administration of both formulations, BVC-HCl and BVC-SBE7-βCD. The pharmacokinetic modeling of plasma concentrations following intravenous administration of BVC-HCl indicated that the drug behavior was best described by a two-compartment open-system model requiring the percent absorbed–time plots to be constructed according to the Loo–Riegelman method (Loo and Riegleman, 1968). The mean profiles of the percent drug absorbed into the systemic circulation following administration around the sciatic nerve of BVC-HCl and BVC-SBE7-βCD showed that the cyclodextrin formulation led to a decrease in absorption rate (Fig. 5). Significant differences were evidenced in time parameter derived from raw data (T_{10}) and from fitted parameter (T_d) (Table 1). Moreover, the percent remaining to be absorbed versus time

Table 1
Biopharmaceutic parameters of bupivacaine after percutaneous administration around the sciatic nerve of BVC-HCl and BVC-SBE7-βCD (5 mg/2.5 ml) and intravenous administration of BVC-HCl (2 mg/1 ml)

Parameter	Administration around the sciatic nerve		Intravenous administration
	BVC-HCl	BVC-SBE7-βCD	BVC-HCl
C_{max} (ng/ml)[a,b,c]	380 ± 139	154 ± 59	1510 ± 622
T_{max} (mn)[a]	14 ± 9	58 ± 36	
AUC (0–360) (ng mn/ml)	43105 ± 8493	35545 ± 4612	15353 ± 3229
AUC (360–∞) (ng mn/ml)	6983 ± 7416	27270 ± 16916	967 ± 602
$T_{1/2\beta}$ (mn)[a,c]	118.8 ± 66.1	308.0 ± 131.0	81.9 ± 12.1
F (0–360)	1.12	0.93	
$T_{1/2abs1}$ (mn)[a]	16.1 ± 19.1	50.0 ± 45.5	
$T_{1/2abs2}$ (mn)[d]	229.9 ± 70.0	311.7 ± 162.3	
T_{10} (mn)[a]	9 ± 6	21 ± 14	
T_{50} (mn)[d]	118 ± 40	190 ± 68	
T_{90} (mn)[d]	386 ± 48	445 ± 118	
T_d (mn)[a]	183 ± 24	246 ± 59	

Each datum represents the mean ± S.D. ($n = 6$ rabbits).
[a] $p < 0.05$ between sciatic BVC-HCl and BVC-SBE7-βCD.
[b] $p < 0.05$ between sciatic BVC-HCl and intravenous BVC-HCl.
[c] $p < 0.05$ between sciatic BVC-SBE7βCD and intravenous BVC-HCl.
[d] Non significant difference.

displayed a biexponential decay suggesting that drug absorption near the sciatic nerve can be described by two parallel first-order processes (Gibaldi and Perrier, 1982). Such biphasic absorption patterns have already been found in different models, by our team after epidural administration of BVC-HCl in rabbits (Fréville et al., 1996), as well as by an australian team after epidural administration of lidocaine–hyaluronic acid ionic complex in dogs (Doherty et al., 1996). With regard to the rapid phase, the absorption half-life ($T_{1/2abs1}$) of bupivacaine following BVC-HCl was smaller than following BVC-SBE7-βCD (16.1 ± 19.1 vs 50.0 ± 45.5 min, $p < 0.05$) while no significant difference was observed between absorption half-life of the slower phase ($T_{1/2abs2}$) (229.9 ± 70.0 vs 311.7 ± 162.3 min). These results suggested that the complexation of bupivacaine with SBE7-βCD may serve as a controlled release formulation around the sciatic nerve, i.e. that the rate of dissociation of bupivacaine from SBE7-βCD may be the rate-limiting step in the absorption into the systemic circulation. As in the epidural model previously described (Fréville et al., 1996), the cyclodextrin influenced only the rapid absorption phase which is responsible for the high plasma concentrations. The relative percents absorbed during each phase can be obtained easily from the bi-exponential equation giving the percent remaining to be absorbed (PRA) as a function of time:

$$\mathrm{PRA} = A\mathrm{e}^{-k_{abs1}} + B\mathrm{e}^{-k_{abs2}} \quad (2)$$

It results that A% of the drug is absorbed with a half-life ($0.693/k_{abs1}$), while the remaining B% is absorbed with a half-life of ($0.693/k_{abs2}$) (Loo and Riegleman, 1968). Mean percent absorbed during rapid absorption phase was found to be 34.9 ± 17.7% for BVC-HCl versus 18.0 ± 8.2% for the BVC-SBE7-βCD complex, $p < 0.05$. As hydroxypropyl-β-cyclodextrin in the epidural model, SBE7-βCD also decreased the rapid phase but systemic impact were different in these models, for which the contribution of each phase (i.e. slow or rapid absorption phase) was different. That is, in the sciatic model there is also an impact of complexation on slow absorption phase (concerning about 82% of the drug), limiting BVC elimina-

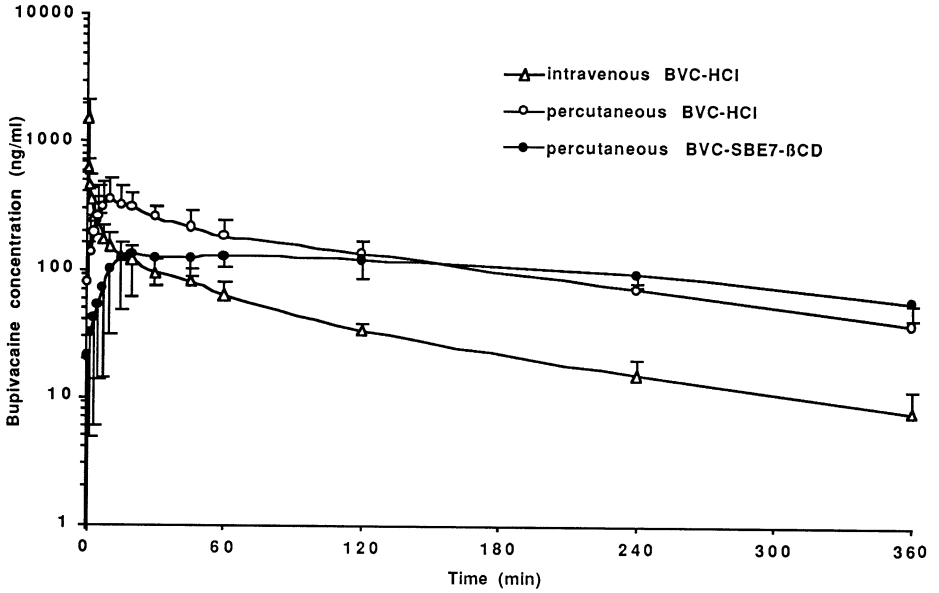

Fig. 4. Mean (± S.D.) plasma concentration–time curves of bupivacaine after single administration around the sciatic nerve in six rabbits of 5 mg bupivacaine as BVC-HCl (○) and BVC-SBE7-βCD (●), and after intravenous administration of 2 mg bupivacaine as BVC-HCl (△).

tion (flip-flop effect). With BVC-HCl however, sciatic administration do not exhibit a flip-flop, slow absorption is no more limiting the elimination, evidenced by its slower half-life and because this phase implicates a smaller fraction of drug (about 65% of the drug). Considering that drug absorption is a first-order process, the decrease in the absorption rate should be attributed to a decrease in the diffusional gradient of free drug across the vascular membrane resulting from drug complexation. Indeed, the low initial dilution of the complex near the sciatic nerve may prevent its rapid dissociation. Such a feature should be clinically interesting to improve the cardiovascular and neurologic toxicities of local anesthetics resulting from high and transient plasma concentrations. However, complex with higher affinity constants should be of interest to further limit the rate of systemic absorption.

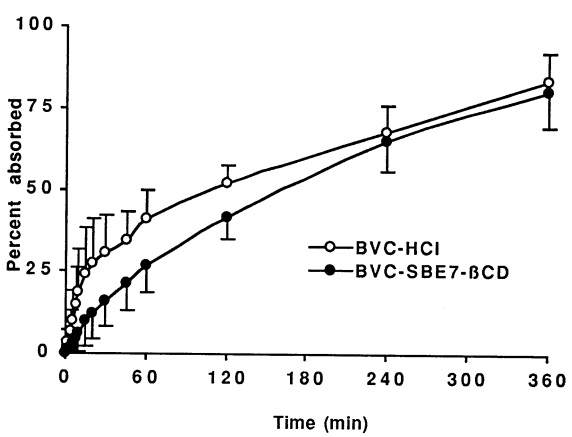

Fig. 5. Mean (± S.D.) percent absorbed time–plots of bupivacaine after single administration around the sciatic nerve in six rabbits of 5 mg bupivacaine as BVC-HCl (○) and BVC-SBE7-βCD (●).

Comparison of AUC showed that the absolute bioavailability of bupivacaine following administration around the sciatic nerve was complete, and that the complexation of bupivacaine did not apparently modify the extent of bioavailability. Thus, complexation of bupivacaine altered the rate, but not the extent, at which the drug entered the systemic circulation.

In summary, injectable aqueous formulation of BVC complexed with SBE7-βCD allowed an improvement of the therapeutic index of BVC after percutaneous sciatic nerve administration. With

regard to plasmatic profiles, it is possible to inject a greater amount of BVC in order to gain into blockade duration. Additional work is in progress to evaluate complexes with higher affinity constants between anionic SBE7-βCD and cationic BVC-HCl.

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