Controlled Release Gel of Ibuprofen and Lidocaine in Epidural Use—Analgesia and Systemic Absorption in Pigs

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Purpose. Reduction of the frequency of injections and localization of the absorption of drug molecules to the injection site would be of great advantage in epidural pain treatment. The epidural use of a controlled release gel of lidocaine and ibuprofen was studied.

Methods. The effect of a poloxamer gel (25%) containing 2% lidocaine·HCl and 2% ibuprofen·Na on the duration of analgesia after epidural administration to pigs was compared with drug in solution. Analgesia was assessed by observing the motor function and the nociceptive reflex–withdrawal response to painful pressure stimulation on the feet. Pharmacokinetic and histological examinations were performed.

Results. Analgesia lasted significantly longer after epidural lidocaine gel injection in comparison with the solution. The gel prolonged the systemic absorption, thereby increasing the epidural availability of lidocaine for spinal analgesia. Although the absorption of ibuprofen was prolonged after epidural gel injection, the duration of analgesia as compared with the solution was not prolonged. After epidural injection, only slight inflammatory changes were observed in the tissue structures of the epidural space, but none in the spinal cord.

Conclusions. These results demonstrate poloxamer gel to be a promising controlled-release, injectable epidural formulation for the management of pain.

KEY WORDS: ibuprofen·Na; lidocaine·HCl; injectable poloxamer gel; epidural analgesia; systemic absorption; histology.

INTRODUCTION

Controlled release formulations are important in parenteral administration to achieve sustained and constant drug levels in the target body area. In epidural treatment, it would be important to reduce the frequency of injections and to localize the absorption of drug molecules to the site of injection. A long-acting single-dose epidural preparation would insure a constant drug concentration in the spinal nervous tissue and a longer duration of analgesic action, i.e., pain-suppressing activity. It would improve the treatment of various pain states by allowing for catheter-free administration.

The fate of drugs given epidurally is complicated. The analgesic and anesthetic effect is to a major extent determined by the amount of drug transferred across the spinal meninges and entering the spinal nerve tissues (1). On the other hand, the systemic absorption of drugs following epidural administration is of great importance in predicting the extent of possible side effects and toxicity of a controlled release formulation. It also enables estimation of the amount of drug available for the effect at the spinal level.

To prevent the risk of adverse effects of spinal opiates, nonsteroidal anti-inflammatory drugs (NSAIDs) for subarachnoidal and epidural pain treatment have been studied (2). Since NSAIDs act through the enzymatic system instead of receptors, tolerance, resistance, and dependence are unlikely to develop. The NSAIDs have, however, a fairly short biological half-life; for ibuprofen, for instance, it is approximately 2 hr (3). Because of a short duration of action and a short half-life limit, the usefulness of a commonly used local anesthetic, lidocaine, a long-acting, injectable epidural gel preparation of these analgesic and anesthetic drugs, would also be beneficial.

In our previous *in vitro* studies, we have demonstrated the controlled release of lidocaine from injectable poloxamer gel and the effect on the sciatic nerve block (4). In comparison with the solution, the gel significantly prolonged the effect of the drug. The aim of the present study was to investigate the injectable controlled release poloxamer hydrogel of ibuprofen and lidocaine in *in vivo* epidural use. The duration of analgesia (pharmacodynamics) and drug concentrations in plasma (pharmacokinetics) after epidural injection of the gel to pigs were measured. In addition, the tissue irritability of the treatment was studied.

MATERIALS AND METHODS

Drug Formulation

The poloxamer gel was prepared as previously (4) using the cold preparation method (5). An appropriate amount of poloxamer 407 (Lutrol F-127, BASF, USA) (25% w/w) was added to a cold solution (5–10°C) while maintaining constant agitation with a magnetic stirrer. The gel was stored at 4°C until a clear solution was formed. The gel was autoclaved. Ibuprofen·Na (Knoll Pharm., England) (2% w/w corresponding to 1.6% ibuprofen) was added in the gel and the pH was adjusted to 7. Alternatively, lidocaine·HCl (Ph.Eur.) (2% w/w corresponding 1.6% lidocaine) was added to the gel and the pH was adjusted to 5. The pH was adjusted carefully with solutions of HCl or NaOH, and was measured at 4°C with the pH meter (Mettler, delta 320). The placebo gels were prepared in an identical way but drug was not added. Ibuprofen·Na-saline solution (2%) and lidocaine·HCl-saline solution (2%) were used as controls.

Animals and Drug Administration

The experiment protocol was approved by the Committee on Animal Care and Use of the Helsinki University Central Hospital. Female land-race pigs weighing 19–24 kg were used. The pigs were anesthetized with intravenous propofol (3–5 mg/

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kg) and halothane inhalation (1.5–2% v/v) through a mask. For epidural catheterization, the pigs were placed in the lateral decubitus position. The epidural puncture was performed with an epidural needle (18G, Tuohy-type, Portex Ltd., Hythe, U.K.) either at the 4th, 5th, or 6th lumbar interspace using the loss-of-resistance technique. An epidural catheter (20G, Portex Ltd., Hythe, U.K.) was advanced 2 cm past the tip of the needle in the caudal direction to the epidural space. If blood was aspirated, the catheter was withdrawn and a new puncture was made at an adjacent interspace. The catheter was cut, leaving 10 cm outside the skin. Before drug administration, the pigs were allowed to recover from the anesthesia. One pig had to be sacrificed after the epidural catheterization due to obvious hind leg paralysis. For this animal, the catheterization was difficult to perform and several punctures were required. Dissection of the spinal region revealed holes in the *dura mater* as well as major bleeding in the spinal cord and the epidural space.

The pigs were randomly divided into the following four groups: lidocaine gel group (n = 10) and lidocaine solution group (n = 6), ibuprofen gel group (n = 6), and ibuprofen solution group (n = 6). In addition, four pigs received placebo poloxamer gel epidurally and two pigs received physiologic saline epidurally. The injection (4 ml) was administered in divided portions: between each milliliter, the catheter was flushed with 0.5 ml of physiologic saline. The preparations were injected cold (4–8°C) when the gels were in the liquid state. For pharmacokinetic comparison, another three pigs received 4 ml of ibuprofen·Na intravenously. It should be noticed that six of the ten animals of the lidocaine gel group received epidural lidocaine solution injection two days prior to the gel injection and were thus catheterized twice. As the pharmacokinetic results of these animals (n = 6) were indistinguishable from those of the animals treated only once (n = 4), all the animals (n = 10) were considered to belong to the same gel group.

Pharmacodynamic Experimentation

The duration of analgesia was tested by measuring the motor function and the nociceptive responses of the feet. The tests were performed 5, 10, 20, and 30 min after epidural injection and thereafter every 30 min until complete recovery.

Motor Functions

The motor function testing (motor blockade) was performed by letting the animal stand and walk on an even surface. A three-point scale was devised: 0 = normal stability and strength (able to stand without support), 1 = faint legs, and 2 = total paralysis of legs (unable to stand).

Nociception

The nociceptive response (sensory blockade) was tested by clamping the toe of the animal at the border of the nail and skin with a large surgical hemostat with taped claws, and closing the hemostat to the first ratchet. The very same instrument was used in all experiments. If there was no reflex-withdrawal response, the hemostat was released after 5 sec. The response was graded as 0 = instantaneous (normal) withdrawal, 1 = visible reflex-contraction or delayed withdrawal, and 2 = no withdrawal of legs or visible reflex-contraction of muscles.

The results are expressed as number of animals with the different degrees of effect. Pairwise comparisons for motor function and nociceptive data were performed according to the non-parametric Mann-Whitney U-test. Intergroup comparisons for all data were performed using analysis of variance (ANOVA). Values of $p < 0.05$ were considered statistically significant.

Pharmacokinetic Experimentation

Plasma Concentration Assay

Venous blood samples were collected into EDTA tubes from an indwelling cannula in the hind leg of the pigs 5, 10, 20, 30, 60, 120, 180, and 240 minutes after the injection. Plasma was separated by centrifugation at 3000 rpm for 10 min and stored in plastic tubes at -20°C until analysis.

Ibuprofen plasma concentrations were determined by means of high performance liquid chromatography (HPLC) at a wavelength of 222 nm using a slightly modified version of the method described by Avgerinos and Hutt (6). A reversed-phase C_{18} column (μBondapak 10 μm, 125 Å, 3.9 x 300 mm) (Waters Ltd., USA-Milford) combined with a guard column (μBondapak) was used at ambient temperature. The isocratic mobile phase was acetonitrile:0.1 M sodium acetate (35:65 v/v), and the pH was adjusted to 6.2 with glacial acetic acid. The flow rate was 2 ml/min. The standard curve was linear over a concentration range of 0.05–30 μg/ml ($r > 0.999$). The accuracy of the method was investigated according to recommendations (7). The reproducibility of the method was investigated by the repeated analysis (n = 6) of plasma samples spiked with ibuprofen at concentrations of 0.1 and 20 μg/ml. The coefficient of variation of intra-assay variability was 2% or less. The detection limit was 0.05 μg/ml.

Lidocaine plasma concentrations were determined by means of gas chromatography (GC) according to the method by Mather and Tucker (8). Plasma concentrations as low as 0.01 μg/ml could be determined. The coefficient of variation of intra-assay variability was 3% or less.

Pharmacokinetic Parameters and Statistics

The pharmacokinetic parameters assessed were the maximum plasma concentration (C_{max}), the time of peak plasma concentration (t_{max}), the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), the area under the concentration-time curve from time zero to the last measured point (AUC_{0-t}), the apparent plasma elimination half-life ($t_{1/2}$), and the mean residence time (MRT). The measured C_{max} and t_{max} values were used as such. The AUC and MRT values were calculated according to the trapezoidal method without logarithmic transformation. The results are expressed as means ± SEM. Statistical analysis were performed using Student's t-test, the analysis of variance (ANOVA), and the non-parametric Mann-Whitney U-test.

Histological Examination

A toxic intravenous overdose of ketamine was given to animals 24 hr after the epidural blockade. A thoracotomy was performed and the animal was exsanguinated by cardiac punc-

ture. The epidural space was carefully exposed after lumbar region vertebral laminectomy. Tissue samples were taken from the *ligamentum flavum* and epidural fat near the site of the drug administration. Thereafter, the spinal cord covered by *dura mater* and *pia arachnoidea* was carefully removed and placed on a dissection plate. These meninges were inspected for mechanical damage and hemorrhage. Pieces of *dura mater* and cross sections of the spinal cord at the level of the epidural puncture were taken. The samples were immediately submerged in phosphate-buffered formalin for histologic processing. After dehydration and embedding in paraffin, sections were cut and stained with hematoxylin-eosin for light microscopy.

RESULTS

Analgesic Effects (Antinociception)

Epidural administration of ibuprofen gel and ibuprofen solution resulted in an antinociceptive response (sensory blockade) both to the hind and the front legs (Fig. 1a, 1b). As compared with the intravenous ibuprofen solution, epidural injection of the gel or the solution prolonged the response significantly, almost by 100% ($p < 0.001$). The duration of analgesia was, however, not prolonged after the epidural gel injection as compared with the epidural solution. Sensory blockade lasted maximally 150 min in the hind legs and 180 min in the forelegs. Ibuprofen did not cause any motor blockade of the legs.

Antinociceptive response after epidural lidocaine gel injection lasted 60 min longer ($p < 0.01$) and was more effective over time in comparison with epidural lidocaine solution (Fig. 2a). Sensory blockade was not observed in the forelegs after lidocaine administration. All the animals developed a maximum motor blockade of the hind legs (Fig. 2b). With the lidocaine gel, the motor blockade lasted 90 min longer ($p < 0.001$) than with the lidocaine solution.

Sensory or motor blockade was not observed either in the placebo poloxamer gel or in the saline group.

Systemic Absorption

The epidural injection of 80 mg of ibuprofen solution or gel prolonged the absorption of ibuprofen as compared with

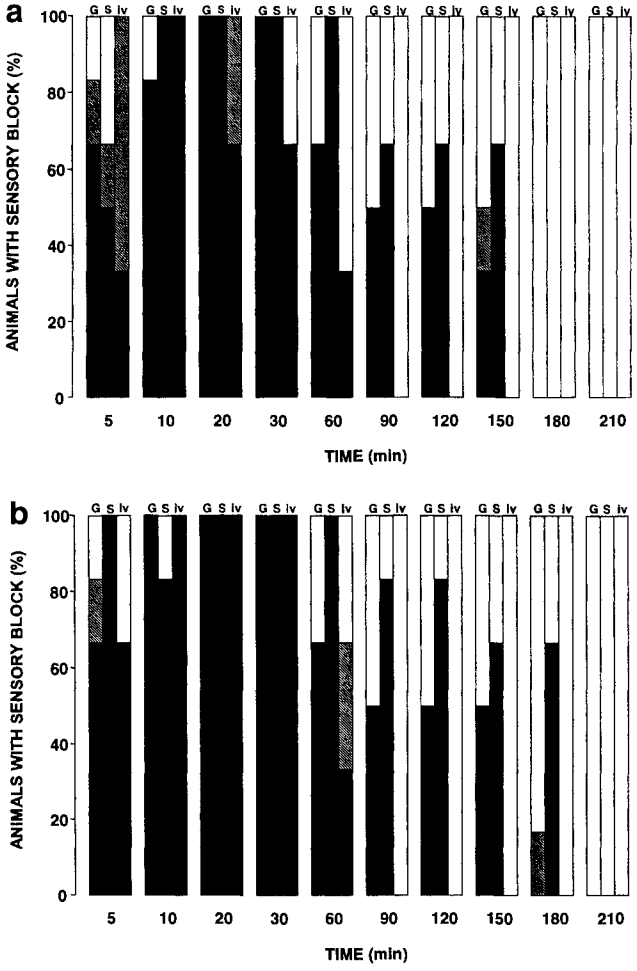

Fig. 1. Number of pigs (%) with complete sensory blockade (black bar), with partial sensory blockade (striped bar), and pigs recovered (white bar) following epidural injection of 80 mg of ibuprofen gel or solution, or i.v. injection of solution a) in the hind legs, and b) in the front legs. Symbols: **G** = gel (n = 6), **S** = solution (n = 6), **iv** = i.v. solution (n = 3).

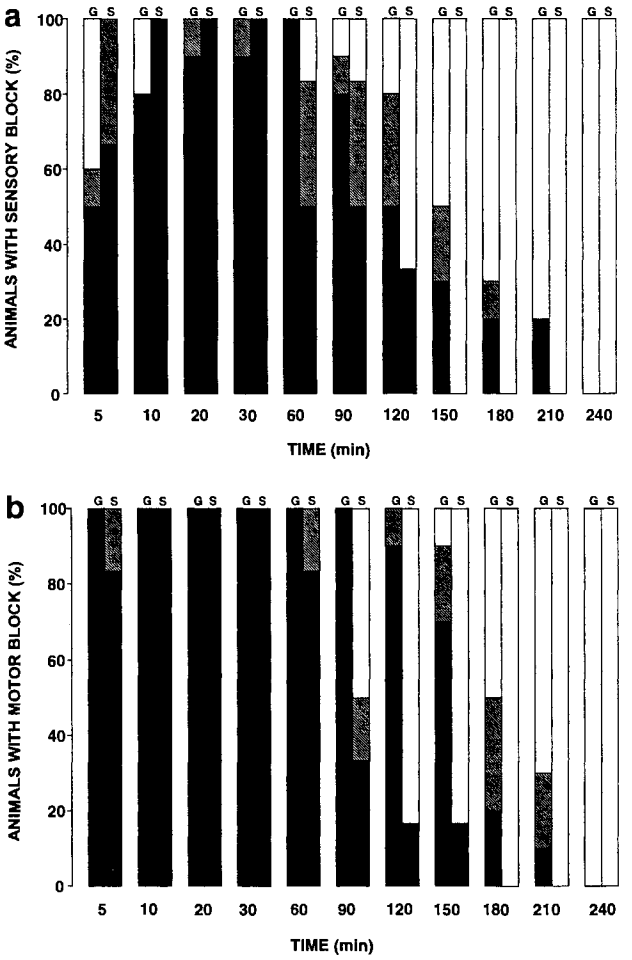

Fig. 2. a) Number of pigs (%) with complete sensory blockade (black bar), with partial sensory blockade (striped bar), and pigs recovered (white bar), and b) number of pigs (%) with complete motor blockade (black bar), with partial motor blockade (striped bar), and pigs recovered (white bar) following epidural injection of 80 mg of lidocaine gel or solution. Symbols: **G** = gel (n = 10), **S** = solution (n = 6).

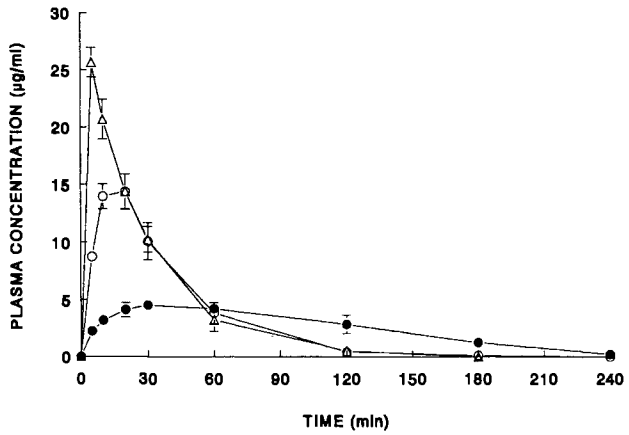

Fig. 3. Mean plasma concentrations of ibuprofen in pigs after epidural injection of 80 mg of ibuprofen gel or solution, or intravenous injection of ibuprofen solution. Means ± SEM are presented. Symbols: ● gel (n = 6), ○ solution (n = 6), △ i.v. solution (n = 3).

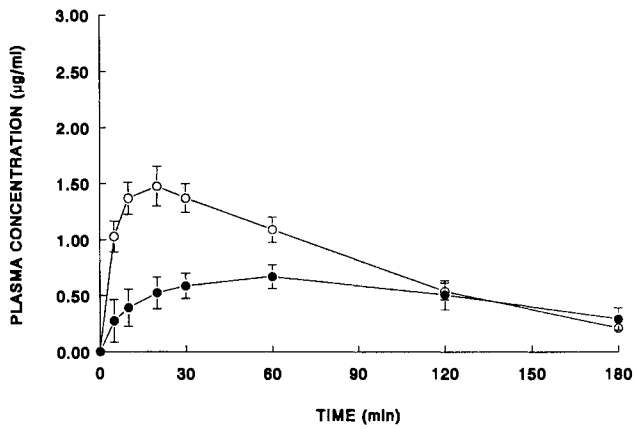

Fig. 4. Mean plasma concentrations of lidocaine in pigs after epidural injection of 80 mg of lidocaine gel or solution. Means ± SEM are presented. Symbols: ● gel (n = 10), ○ solution (n = 6).

intravenous injection of ibuprofen solution (Fig. 3). The C_{max} value (14.8 µg/ml) was observed 18 min after epidural injection of the solution, while the apparent C_{max} (25.6 µg/ml) after intravenous injection was reached within 5 min (Table I). After epidural injection of ibuprofen gel, the peak ibuprofen concentration (C_{max} = 5.6 µg/ml) was reached in 30–60 min. Also the $t_{1/2}$ and MRT values were significantly longer after epidural gel injection than after epidural solution. The AUC values of the epidural gel group (699 µg/ml·min^{-1}) and the epidural solution group (703 µg/ml·min^{-1}) were, however, similar.

The absorption of lidocaine was prolonged by epidural gel (Fig. 4). The C_{max} value (1.48 µg/ml) was reached 20 min after the injection of lidocaine solution, while (0.94 µg/ml), after lidocaine gel injection, was reached in 87 min (Table II). The plasma concentrations were low and stable. The $t_{1/2}$ and MRT values in plasma were significantly ($p < 0.05$) longer after the epidural lidocaine gel injection than after the epidural solution. The AUC value of the gel group (200 µg/ml) was not significantly larger than that of the solution group (167 µg/ml).

Histology

The macroscopic examination revealed minor epidural hemorrhage in almost every pig that had had an epidural catheter. There were no signs of mechanical damage in the *dura mater* or the spinal cord. On the other hand, in each epidural group, inflammatory changes (lymphocyte accumulation) were observed in the microscopic examination in *ligamentum flavum*, epidural fat, and *dura mater*. In the majority of cases, mild inflammatory changes appeared also along *pia mater* but never inside the spinal cord (Fig. 5). The most severe changes were seen in two of the six pigs that received two epidural injections; lidocaine solution at the first day and lidocaine gel two days later. After epidural ibuprofen, the inflammatory changes were clearly the mildest. The degree of change was similar after ibuprofen gel and solution. The observed changes were not different from those seen after epidural injection of the placebo gel or saline solution.

Correlation Between Plasma Concentrations and Nociceptive Effect

Pearson analysis was performed to evaluate whether the plasma concentration correlated with the analgesic effect. In this test the mean drug plasma concentration value was compared with the mean value of nociceptive effect at time 0, 5, 10, 20, 30, 60, 120, and 180 minutes. The results of the analysis showed a good correlation ($r > 0.97$; $p < 0.001$) between the analgesia and drug plasma concentrations after the epidural injection of lidocaine solution, while the correlation after the epidural injection of lidocaine gel was not significant ($r > 0.77$; $p < 0.06$). On the other hand, correlation between analgesia and drug plasma concentrations after the epidural injection of

Table I. Pharmacokinetic Parameters After Epidural Injection of 80 mg Dose of Ibuprofen Gel (n = 6) or Solution (n = 6) Including Intravenous Injection of Ibuprofen Solution (n = 4)[a]

Parameter	Gel	Solution	i.v. solution
$AUC_{0-\infty}$(µg/ml-min^{-1})	699 ± 281	703 ± 220	815 ± 274
AUC_{0-t}(µg/ml-min^{-1})	627 ± 219	697 ± 224	815 ± 274
C_{max}(µg/ml)	5.61 ± 1.16**[b]	14.8 ± 3.1	25.6 ± 3.1**[c]
t_{max}(min)	35.0 ± 19.0*	18.3 ± 4.0	5.0 ± 0.0***[c]
MRT (min)	54.8 ± 19.3*	23.6 ± 4.6	28.5 ± 7.5
$t_{1/2}$ (min)	12.5 ± 1.91	11.8 ± 3.1	13.6 ± 1.9

[a] Means ± SEM are presented.
[b] Significant difference with epidural solution * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[c] The C_{max} and t_{max} are apparent values.

Table II. Pharmacokinetic Parameters After Epidural Injection of 80 mg Dose of Lidocaine Gel (n = 10) or Solution (n = 6)[a]

Parameter	Gel	Solution
$AUC_{0-\infty}$(µg/ml-min^{-1})	200 ± 55	167 ± 45
AUC_{0-t}(µg/ml-min^{-1})	132 ± 33	146 ± 35
C_{max}(µg/ml)	0.94 ± 0.31**[b]	1.48 ± 0.44
t_{max}(min)	87.0 ± 45.0***	20.0 ± 6.3
MRT (min)	137.0 ± 66.0*	83.4 ± 32.4
$t_{1/2}$ (min)	99.4 ± 47.2*	59.8 ± 24.7

[a] Means ± SEM are presented.
[b] Significant difference with solution * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

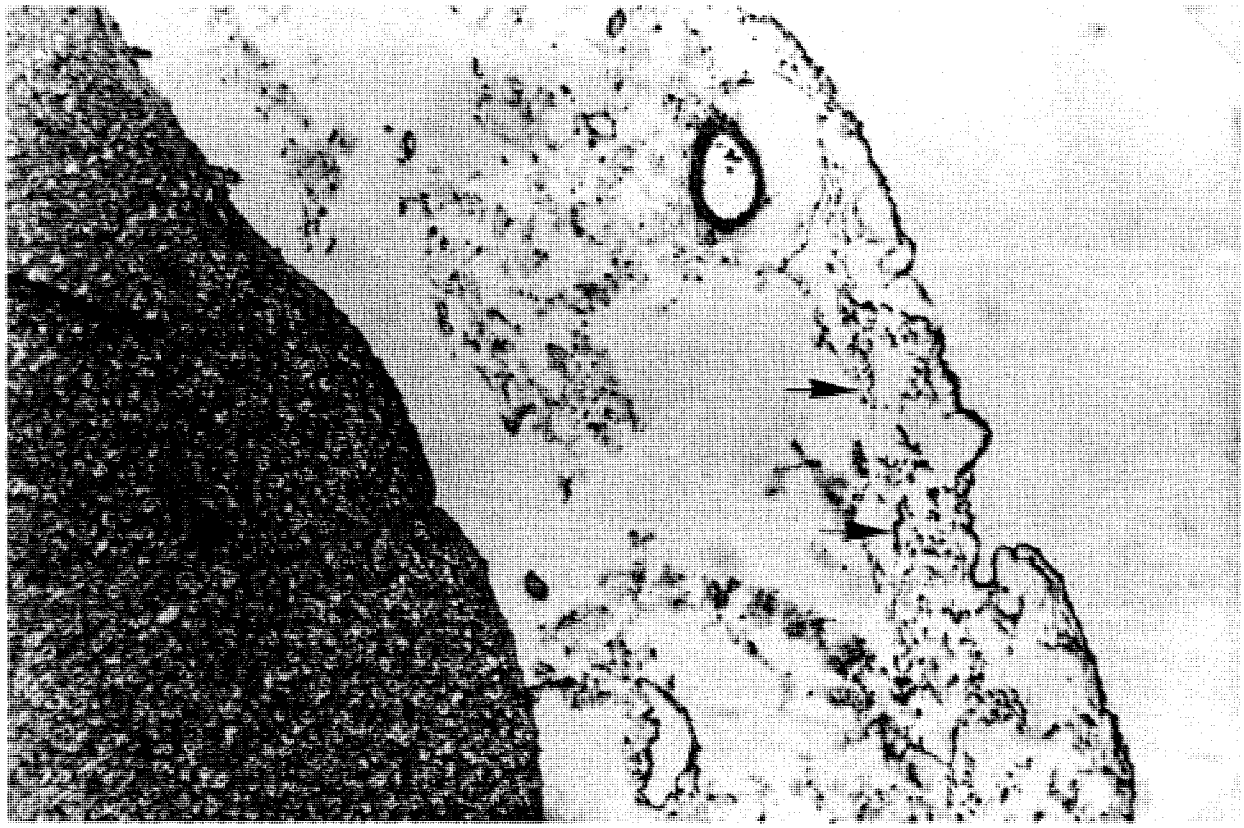

Fig. 5. A microphotograph of a cross section of the spinal cord of a pig after epidural injection of lidocaine gel. Note the lining inflammation of lymphocytes and histiocytes (black arrows) along *pia mater* outside the spinal cord. The appearance of spinal cord histology is normal. Original magnification 250x.

ibuprofen gel was quite good ($r > 0.95$; $p < 0.001$), but after the epidural solution it was not significant ($r > 0.720$; $p < 0.06$). After intravenous injection of ibuprofen a correlation was observed between analgesic effect and plasma concentrations ($r > 0.852$; $p < 0.05$).

DISCUSSION

Reverse-phase thermal gelation is typical of aqueous solutions of poloxamer above 20% (w/w) concentrations. The solutions are highly viscous gels at room temperature, but liquid at refrigerated temperatures (5). This allows injection of a cold fluid solution which forms a gel *in situ* at a physiologic temperature (4). The injection of a viscous gel-type solution can be better targeted to the injection site than a regular water solution. Thus, the absorption area of a drug is limited, and the systemic absorption and the risk of systemic toxic side effects can be expected to be minimized. In the present study, the dissections performed on pigs 24 hours after the epidural injection revealed that the gel had spread initially within a region of about 2–3 cm in length. It was felt as a sticky even layer. There were no signs of neurological deficit in the pigs after the recovery of the local anesthetic blockade, and no signs of ischemic damage in the spinal cord.

The epidural injection of ibuprofen solution caused almost three times longer analgesia than the intravenous injection. The spinal site of action, not the systemic, has been suggested to account for most of the antinociceptive effect of epidurally administered ibuprofen (9). After direct administration of ibuprofen into the cerebrospinal fluid, the spinal attenuation of pain (analgesia) has been 100 to 500 times greater than after systemic administration (10). The spinal action of NSAIDs is assumed to be caused by blocking the excessive sensitivity to pain induced by the activation of the spinal glutamate and substance P receptors (10). As neurotransmission is mediated through many different interneurons, the mechanism of action of ibuprofen in the spinal area may even be a more complicated process.

Although quite effective, the analgesic effect of ibuprofen was not prolonged after epidural gel in comparison with epidural solution. The plasma concentrations of ibuprofen after epidural gel were low and quite constant over the evaluation time, but the epidural availability of ibuprofen was not increased by the gel in comparison with the solution. It is possible that the amount of ibuprofen released from the gel and transferred to the spinal cord is too low to prolong effective analgesia. On the other hand, ibuprofen caused no motor blockade in the pigs. In this respect, ibuprofen is an ideal drug for epidural postoperative pain treatment, while it would facilitate the patients' movement capability (9,11). Analgesia was, however, observed both in the hind and forelegs after epidural injection of the ibuprofen gel or solution. Surprisingly, the effect in the forelegs was slightly stronger in intensity, although not longer, than in the hind legs. The reason for this remains speculative and a systemic effect of ibuprofen has to be considered.

The analgesia produced after epidural injection of lidocaine gel was more effective and also longer lasting than after epidural injection of lidocaine solution. The kinetics of lidocaine after epidural injection of a solution is well characterized (1,12). In the present study, the peak plasma concentration in pigs after epidural injection of lidocaine solution was reached in 20 min, which is in accordance with that in humans (t_{max} = 15 min) (13). Epidural gel injection prolonged the systemic absorption of lidocaine (t_{max} > 1 hr), although the amount of drug absorbed was not reduced. The amount of drug released and delivered from the gel through the dural membrane to the nerve tissue of the spinal cord and to nerves crossing the epidural space was sufficient to produce effective analgesia in pigs. Therefore, the local availability of lidocaine in the epidural space was increased by the use of the poloxamer gel. Based on the known kinetic characteristics of lidocaine (1,12) and on the present plasma concentration results it seems to be possible to increase the concentration of lidocaine in the gel without causing toxic effects.

The inflammatory changes in the tissue structures of the epidural space after ibuprofen or lidocaine gel or solution injection were generally mild. No signs of cellular damage were observed and the spinal cord structure appeared unaffected. Because the inflammatory changes were also similar after the injection of physiologic saline, the main reason for the changes observed seems to be a mechanical irritation caused by the catheter. This is in accordance with the previous findings by Kyttä et al. (14), when bupivacaine was injected epidurally to pigs twice a day for one week.

CONCLUSIONS

The duration of the analgesia of lidocaine was prolonged with the epidural injection of poloxamer gel preparation. Lidocaine was slowly released from the gel and a sufficient amount of drug was delivered through the dural membrane into the nerve tissue of the spinal cord. Although the amount of ibuprofen absorbed was significantly reduced by the use of the gel preparation, the difference in the duration of analgesia produced by epidurally administered ibuprofen gel or solution was not significant. Poloxamer gel preparations reduced the systemic absorption of both drugs, but increased the epidural availability only in the case of lidocaine. Because only slight inflammatory changes in the epidural space tissue samples were observed, the results support the possibility of using poloxamer gel as a controlled-release, injectable epidural formulation. It also seems to be possible to increase the concentration of drug in the gel.

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