Controlled Release of Lidocaine from Injectable Gels and Efficacy in Rat Sciatic Nerve Block

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Purpose. Methods of delaying the action of local anesthetics are important, since short duration of action limits their use in the treatment of postoperative and chronic pain. The present study evaluated the use of low-viscosity gels in prolonging the release of lidocaine.

Methods. Release of lidocaine from 2% lidocaine·HCl containing methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), sodiumcarboxymethyl cellulose (CMC), and poloxamer 407 (PO) gels was studied in phosphate buffer, pH 7.4, at 37°C. Commercial metylcellulose gel (MC_{com}) served as control. The *in vivo* efficacy of the respective gel formulations were evaluated in rats. The gel was injected into the vicinity of the sciatic nerve and nociception and motor function were tested.

Results. The cumulative amount of lidocaine released during 8 hr was slowest from the PO gel, followed by the CMC, HPMC and MC gels. The antinociceptive effect was not prevented by the motor block and lasted longest with the PO gel. Good linear and rank order correlation was obtained between *in vitro* and *in vivo* results. The microscopic examination of the tissue samples revealed only mild or no irritation of the skeletal muscle tissue by the PO, HPMC, and CMC gels.

Conclusions. Based on these results poloxamer gel proved to be the most promising carrier for lidocaine.

KEY WORDS: controlled release; gel; lidocaine·HCl; nerve block; *in vitro-in vivo* correlation.

INTRODUCTION

Local anesthetics are widely used in the treatment of both acute and chronic pain, but their usefulness is limited by the short duration of action. Catheter infusions and repeated injections have been used in order to achieve long and constant pain relief. However, complications may result from these techniques, they may be contraindicated or impractical in certain patients. A long-acting single-dose injection would be of clinical importance. Many chemical, physical and biomedical alternatives have been studied, including the use of epinephrine (1), dextran (2), lipid solutions (3), cyclodextrins (4), and liposomes (5). The results have been to some extent conflicting and few have been introduced to clinical use.

Inert, hydrophilic polymers form a colloidal gel-type solution in water and can affect the solution behavior and diffusion of drug molecules (6). The injection of a viscous solution would also be better localized to the injection site than a regular water solution, thus reducing the absorptive area of the drug, minimizing the systemic absorption and the possibility of toxic side effects.

Celluloses are highly hydrophilic polymers which, because of the cross-linked covalent bonds, cannot dissolve in water. The molecular layers of celluloses swell in aqueous solutions and become surrounded by a hydration sheath (7,8). Although celluloses have a low toxicity, being macromolecules they may cause irritation at the injection site. Poloxamer is widely used in medical and pharmaceutical systems and the non-toxic properties make it suitable also for parenteral drug delivery (9). Reverse phase thermal gelation is typical for aqueous solutions of poloxamers above 20% (w/w) concentrations; the solutions are highly viscous gels at room temperature, but liquid at refrigerated temperatures (10). This allows injection of a fluid solution which forms a gel *in situ* at a physiological temperature.

All nerve fibers are sensitive to local anesthetics. However, a differential block where the smaller diameter pain fibers (A-delta and C) are blocked with lower concentrations which leave the large motor fibers almost intact, would be most desirable. Studies on single mixed nerve blocks may help to predict the effects of sustained release local anesthetic also in more complicated nervous systems like in epidural and spinal anesthesia.

The aim of this investigation was to study the feasibility of using gels as injectable sustained-release vehicles for local anesthetic agents. One important factor in choosing the simple composition for the preparation was that it could be easily prepared for example in hospital pharmacy. *In vitro* release of lidocaine from four different experimental gels was studied, and the respective effects on the duration of the sciatic nerve block in rats were evaluated. In addition, histological effects were studied.

MATERIALS AND METHODS

Gel-Forming Agents

Two types of polymers were used to form gels. The celluloses used were methylcellulose (MC) (Methocel A4M; Dow Chemical Company, USA), hydroxypropylmethylcellulose (HPMC) (Methocel E4M; Dow Chemical Company, USA) and sodium carboxymethylcellulose (CMC) (21903; BioFluka Chemica, Switzerland). The polyoxyethylene-polyoxypropylene copolymer used was poloxamer 407 (PO) (Lutrol F-127; BASF, USA). The model drug was lidocaine·HCl (Ph.Eur.). The commercial lidocaine·HCl gel composed of methylcellulose (MC_{com}) (Lidocain gel 2%; Orion-Farmos, Finland) and lidocaine·HCl-saline solution

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Notation: MC, methylcellulose; HPMC, hydroxypropylmethylcellulose; CMC, sodiumcarboxymethyl cellulose; PO, poloxamer 407; MC_{com}, commercial methylcellulose gel; Sol, lidocaine·HCl-saline solution (20 mg/ml); HCl, hydrochloride.

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(Sol) (Lidocain 20 mg/ml; Orion-Farmos, Finland) served as controls.

Preparation of Lidocaine-Containing Gels

The cellulose gels were prepared by adding the weighed amount of cellulose powder to one third of the final amount of distilled water at 80–90°C. After the cellulose had been wetted, cold water was added to an appropriate quantity while stirring. The gel formed gradually as the solution cooled in an ice bath for 1 hr. The concentration of MC in the gel was 2.7% (w/w). The HPMC and CMC content was 2.5% (w/w). The gels were sterilized by autoclaving (120°C, 20 min). After sterilization, the gels were shaken until cooled to room temperature, and were stored in a refrigerator for 24 hr. Lidocaine·HCl (2% w/v corresponding 1.6% w/v lidocaine) was dissolved in each gel, and the pH was adjusted to 5.

The poloxamer-gel was prepared by the cold method described by Schmolka (10). An appropriate amount of poloxamer 407 (25% w/w) was slowly added to cold distilled water (5–10°C) while maintaining constant agitation with a magnetic stirrer. The beaker was left in the refrigerator until a clear solution was formed (6–12 hr). The gel was autoclaved (120°C, 20 min) and stored in the refrigerator for 24 hr. Lidocaine·HCl (2% w/v) was dissolved in the cold solution and the pH was adjusted to 5.

Viscosity of Gels

The viscosities of the cellulose gels were measured at 37.0 ± 0.1°C applying the viscosity measurement described in the European Pharmacopoeia and using capillary (U-tube) viscosimeters (KPG Ubbelohde IIIa and IV, Scott-Geräte, Germany) (n = 3). The measured kinematic viscosity values (cSt) were converted to dynamic viscosity values (mPas).

Drug Release Experiments

A two compartment *in vitro* method was used to study the release of lidocaine from various gels (Fig. 1). In this system cellulose membrane (Spectrapore, mwco 12000–14000, Thomas Scientific, USA) separated the gel (2.0 g) in the donor compartment from the acceptor compartment, which was phosphate buffer sink pH 7.4 at 37°C (150 ml). The cellulose membrane was selected after screening different types of membranes to preclude the membrane acting as a rate-limiting factor in the drug release process. The effective diffusion area was 3.8 cm^2. The acceptor solution was stirred with a magnet bar at 350 rpm. The system was connected to a flow-through spectrophotometer (Ultrospect II, LKB Biochrom LTD, England) via a peristaltic pump (Watson-Marlow 503S, Smith and Nephew, England). Samples were withdrawn from the acceptor compartment and the absorbances in 10-mm flow-through cells were measured automatically at regular intervals using a wavelength 263 nm. Measurements of absorbances were controlled by a computer running TDS software (LKB Biochrom, England). The absorbances were converted to the amount of lidocaine released using a calibration curve based on standard solution in phosphate buffer pH 7.4.

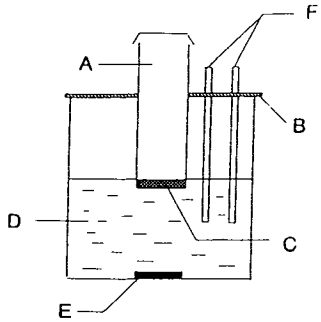

Fig. 1. Experimental system for the *in vitro* drug release measurement. A. Glass cylinder (donor compartment); B. Plexiglass cover; C. Membrane; D. Sink solution (acceptor compartment); E. Stirring bar; F. Sampling port.

The release data of lidocaine were plotted against the square-root-of time equation. Statistical analyses were performed using unpaired Student's t-test or one-way analysis of variance.

Animals and Drug Administration

Female Wistar rats weighing 245–310 g were used. The rats were housed five to a cage with free access to food and water. The animal room was light-cycled (12 hr light, 12 hr dark), and the temperature was 20°C. All experiments, approved by the Animal Care and Use Committee of Helsinki University Hospital, were carried out during the light phase.

The animals were anesthetized with halothane (1.5–2% v/v) during the identification of the sciatic nerve and the injection. The nerve was identified with a nerve stimulator (Stimuplex^R 22G diameter, B. Braun Melsungen AG, Germany). Each animal received a single injection (0.5 ml) of a lidocaine containing gel or solution on one side and the corresponding placebo gel or solution on the contralateral side. The investigators were unaware whether the injection was placebo or lidocaine, respectively.

Nociceptive Testing

Before nociceptive testing the animals were adapted to the test situation on three consecutive days. Nociception and motor function were tested every 30 min after drug administration, and the values were compared with the control values obtained prior to anesthesia and nerve block.

Motor function of the hind limbs was tested by observing the flexor movement during walking. For graphic clarity a 3-point scale was devised: 0 = normal movement, 1 = unable to flex the extremity completely, and 2 = total paralysis of the extremity.

Nociception (paw-pressure test) was tested with the Randall Selitto Analgesiameter (IITC Inc., Life Science Instruments, Woodland Hills, California, USA) (11). The paw of the animal was placed between the blunt tips of two plexiglass cones of the test apparatus. The test measured the pressure which the animal could tolerate before either vocalizing or moving the paw from the pressure. To prevent tissue damage, the cut-off pressure used was 200 mmHg; approximately 2.5 times that which normally evokes a withdrawal response. The test was performed two times on both hind paws. The data were converted to the maximum percentage effect (MPE%) according to the following equation:

$$MPE\% = [(B-A):(c-A)] \times 100\%$$

where A is the mean predrug response, B is the mean post-drug response and c is the cut-off response pressure (12).

To compare the time courses of antinociception produced by lidocaine-solution and different lidocaine gels, the data were expressed as the area under the curve (AUC) using the MPE% values from time zero to the time MPE% values had returned to baseline level. The AUC values were calculated using the trapezoidal method, where height was the MPE% and the base was time. The results are expressed as means ± SEM. Intergroup comparisons for all data were performed using two-way analysis of variance (ANOVA). The pairwise comparisons were performed using a non-parametric Mann-Whitney U-test. A p-value <0.05 was considered significant.

Microscopy

Half of the animals were killed in random order with an overdose of halothane, 20–28 hr after the nerve block, while the other half were killed two weeks after the block. The sciatic nerves were carefully removed, and thin transversal sections were placed in formalin. Three small samples, from the skeletal muscle surrounding the sciatic nerve were also cut out and placed in formalin. After dehydration, embedding in paraffin, slicing, and staining with hematoxylin and eosin, the sections were examined in light microscopy.

RESULTS

Effect of Gel-Forming Polymer and Viscosity on Drug Release

The concentration of the polymers in the experimental gels were chosen based on our previous studies to produce cellulose gels with similar viscosities (Table I). This enables the comparison of different celluloses. Because of the thermogelling property of poloxamer, the viscosity of the PO gel is different from celluloses and could not be measured with the method used.

The cumulative amount of lidocaine released from the gels *in vitro* (%) during the 8-hr perioid was markedly reduced with HPMC ($p<0.05$), CMC ($p<0.01$), and PO ($p<0.001$) as compared with the release from commercial control gel (MC_{com}) (Fig. 2). After 2 hr the release of lidocaine from the MC gel was also significantly ($p<0.05$) slower than from the control. The release rate of lidocaine decreased as a function of time with the cellulose gels but almost a steady-state release was obtained with the PO gel after 3 hr. The PO gel had the lowest diffusion: after 3 hr, only 24% of lidocaine was released. The overall *in vitro* drug release from the gels followed the well-known square-root-of-time equation (Table I). The delay at the beginning of the release (lag-time) was about 2 min.

Table I. Viscosity Values for 2% Lidocaine·HCl-Containing Gels (n = 3), Correlation Coefficient (r) and Lag-Time According to the Square-Root-of-Time Equation, Time for 50% of Lidocaine Released T(50%), and Amount of Lidocaine Released in 3 hr A(3hr) *in Vitro* (n = 5)

Gel	Viscosity (mean ± SD) (mPas)	Correlation coefficient (r)	Lag time (min)	$T(50_{\%})$ (hr)	T(3hr) (%)
MC	4018 ± 87.7	0.989	2.86	3.5	47.9
HPMC	4024 ± 36.7	0.992	0.24	4.0	44.4
CMC	4291 ± 67.3	0.994	0.02	5.0	39.7
PO	[a]	0.998	1.00	>8.0	23.9
MC_{com}	804 ± 24.4	0.996	0.46	3.0	52.2

[a] Not possible to measure at 37 °C with the method used.

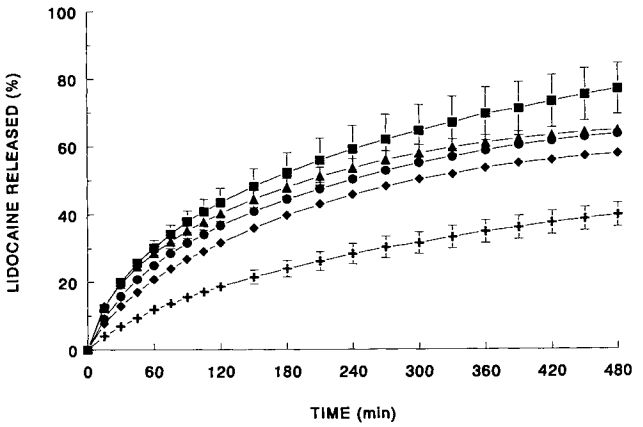

Fig. 2. Cumulative release of lidocaine (%) from different gels into phosphate buffer pH 7.4. Means ± SD (n = 5) are presented. Symbols: ▲ MC, ● HPMC, ♦ CMC, + PO, ■ MC_{com}.

Effect of Lidocaine Gels on Sciatic Nerve Block

Nociception. The maximal antinociceptive response in the paw-pressure tests occurred with all preparations during the first 60 min (Fig. 3). In comparison with the control lidocaine-solution and gel group the HPMC, CMC and PO gels prolonged the mean duration of the response significantly ($p<0.01$). The duration of the antinociceptive effect was longest, 240 min, with the PO gel, i.e., 90 min longer than with lidocaine-solution controls or MC gel ($p<0.001$). The corresponding placebo gels had no effect.

Motor Function. All rats injected with the lidocaine containing preparations had a motor block in the hind limb at

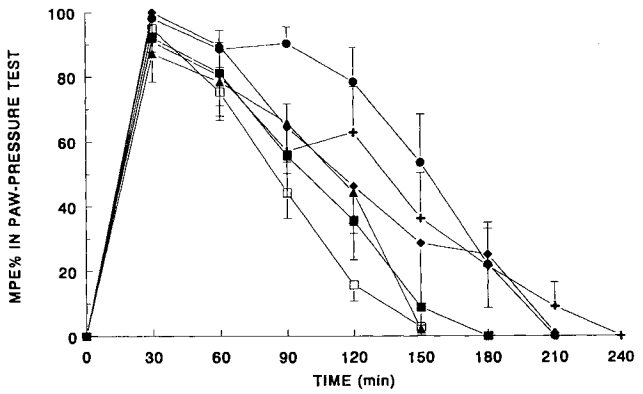

Fig. 3. Plots of maximum percentage effect (MPE%) versus time for the paw-pressure test values after injection of gel or solution containing 10 mg dose of lidocaine·HCl. Means ± SEM are presented. Symbols: ▲ MC(n = 10), ● HPMC(n = 8), + PO(n = 10), ♦ CMC(n = 7), ■ MC_{com}(n = 10), □ Sol(n = 29).

30 min (Fig. 4). The most complete block, i.e., the percentage of rats within the group with a motor block score 2, was in the lidocaine-solution group (72%) while the weakest block was in the PO group (30%). The motor block lasted longest in the HPMC and PO gel groups in which 3 rats in each did not recover from the motor block until after 210 min. All lidocaine-solution group rats (n = 29) had complete motor recovery already 150 min after the injection. The difference in the mean duration of the motor block was statistically significant either between the PO or HPMC groups ($p<0.05$) and both the lidocaine-solution and the MC group ($p<0.05$).

Tissue Reactions. All rats recovered uneventfully from the nerve blocks and no signs of skin injury or neurological deficits were evident. At 24 hr a clear lump of gel was observed at the injection site around and in the vicinity of the sciatic nerve in all rats injected with a gel. Macroscopically, the tissues surrounding the gel had a normal appearance. After two weeks, dissection and visual inspection revealed that no gel was present any more.

The most prominent and consistent changes in light microscopy were observed in the skeletal muscle samples taken after 24 hr from rats which had been injected with 2% lidocaine·HCl-solution (Table II); seven rats of ten had marked myositis, but no necrosis, as compared with none on the side of saline injection. In the muscle and nerve samples taken 24 hr after gel injections, only the CMC group showed no pathological changes. After two weeks, intramuscular and perineural inflammatory changes occurred most frequently in the MC placebo group samples, while there were only single or no changes in the other groups. Macrophages and lymphocytes were present in several of the muscle tissue samples. However, necrosis or intraneural inflammation was not observed. A consistent finding was that placebo HPMC, PO, and CMC gels had not caused any inflammatory changes.

Table II. Summary of Marked Inflammatory Changes (Number of Rats) in the Skeletal Muscle Tissue Surrounding the Sciatic Nerve (*Myositis*) and in the Immediate Perineural Tissue (*Perineuritis*) After Injection of Various 2% Lidocaine·HCl Gels, 2% Lidocaine·HCl Solution, Various Placebo Gels and Saline Solution[a]

	Inflammatory changes/total number			
	Myositis		*Perineuritis*	
Formulation	24hr	2 weeks	24hr	2 weeks
2% lidocaine·HCl in				
MC	0/5	0/5	2/5	0/5
HPMC	0/4	0/4	2/4	1/4
CMC	0/3	1/3	0/4	0/4
PO	2/5	1/5	2/5	0/5
MC_{com}	0/5	1/5	2/5	1/5
Sol	7/10	0/10	3/10	1/10
Placebo				
MC	1/5	1/5	3/5	3/5
HPMC	0/4	0/4	0/4	0/4
CMC	0/3	0/3	0/4	0/4
PO	0/5	0/5	0/5	0/5
MC_{com}	0/5	1/5	2/5	1/5
Sol	0/10	0/10	1/10	0/10

[a] The samples were taken either at 24 hr or 2 weeks after the injection.

In Vitro-in Vivo Correlation

The results from the cumulative AUC values (MPE%×min) of the nociceptive test compared with the cumulative amount of lidocaine released (%) showed a linear correlation for all gel types during the time interval from 30 to 150 min (Fig. 5). The correlation between the *in vitro-in vivo* data was best for the PO gel ($r=0.999$; $p<0.001$). The correlation was good also for the CMC and HPMC gels, followed by the control MC_{com} gel and MC gel. The correlation coefficients were $r=0.997$ ($p<0.01$), $r=0.991$ ($p<0.01$), $r=0.996$ ($p<0.01$), and $r=0.987$ ($p<0.01$), respectively. A clear rank order correlation between the gels existed (Figs. 2,5).

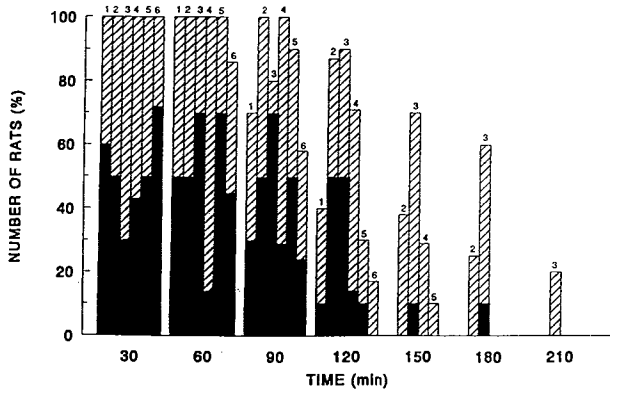

Fig. 4. Number of rats (%) with complete motor block (black bar) or partial motor block (striped bar) after injection of gel or solution containing 10 mg dose of lidocaine·HCl. Means ± SEM are presented. Symbols: 1 = MC(n = 10), 2 = HPMC(n = 8), 3 = PO(n = 10), 4 = CMC(n = 7), 5 = MC_{com}(n = 10), 6 = Sol (n = 29).

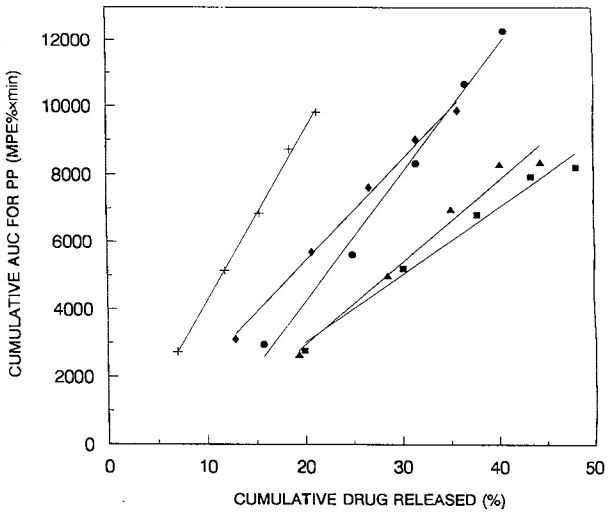

Fig. 5. Correlation between *in vitro* cumulative lidocaine released in phospahte buffer, pH 7.4, and *in vivo* area under the cumulative antinociceptive response curve in paw-pressure test. Symbols: ▲ MC, ● HPMC, + PO, ◆ CMC, ■ MC_{com}.

DISCUSSION

Drug Release *in Vitro*

The criterion for the viscosity used for the gels studied was to obtain an easily injectable gel. Although the apparent viscosities of the MC, HPMC, and CMC gels were about the same, the actual intrinsic viscosity through which the drug molecules diffuse most likely differs (6), probably reflecting the different release rates of lidocaine. The kinetics of release of lidocaine from gels *in vitro* appeared to follow the controlled square-root-of-time mechanism ($r>0.99$), which indicates that the diffusion coefficient for lidocaine was the same regardless of the position in the gel matrix, and the gel acted as a monolithic system. The physical reason for the slow release rate of drug from the cellulose gels is most probably the formation of a highly viscous diffusion layer of hydrated polymer chains which entraps the access of water and thus reduces migration of drug molecules (13). The differences in the release of lidocaine between various cellulose gels are likely due to the chemical factors, like molecular weight and nature of polymers. HPMC probably forms harder polymer chain structures and networks at pH 7.4 than MC. However, an anionic polymer has been found to strengthen the gel structure even more than neutral or cationic polymer. Complex formation between the drug and the polymer may also occure to some extent. As the drug molecules bind to the macromolecular structures by hydrogen bonding and van der Waals forces, the complex-forming capacity of the macromolecules is directly comparable to the amount of reactive groups (14). On the other hand, an interaction between lidocaine·HCl and anionic CMC gel is possible and it might result in the formation of slightly soluble migration products.

Unlike celluloses poloxamer forms micelles in aqueous systems and the gel structure is composed of cubic orientation of micellar subunits (liquid crystals) (10). Above 25°C up to 40°C the critical micelle concentration decreases and larger and spheroidal micelles are formed. The size of the water channels and the concentration of drug between the micellar and water phase, as well as the microviscosity of the extramicellar fluid control the release of the drug (15,16). Lidocaine diffuses through extramicellar aqueous channels and the microviscosity of the water channels controls the release.

Drug Effects *in Vivo*

An effective concentration of lidocaine in the nerve tissue was best maintained by the HPMC gel as compared with the other cellulose gel types probably due to the tight gel structure of HPMC. The antinociceptive effect of anionic CMC gel was first very efficient but it stabilized with time being quite steady before the termination (Fig. 3). Lidocaine diffuses through the gel to the nerve tissue. Dilution and erosion of the gel-matrix in the body fluid is also possible, which could explain the quite sharp decline observed with MC gel after 120 min. When the concentration of lidocaine released is high, it is probably transported faster to the circulation, reducing the local effect. The cross-linking between the carboxyl group and the hydroxyl group are greater than between molecules of the same species (9). Therefore, mixtures of non-ionic and ionic cellulose might form more compact gels and could reduce the drug release into the neuraxis. The tight structure of the PO gel was maintained also in the living biological environment. This suggests that the carrier functions of the PO gel could possibly be extended much beyond the time observed by increasing the lidocaine concentration in the gel formulation.

The recovery from motor block occurred before the sensory block had recovered completely (Fig. 3,4). The animals could move their hind limb and interrupt the stimulus in spite of the partial motor insufficiency. Since the responsiveness to nociception was not prevented by motor block, lidocaine gel preparations could be considered practical for clinical use.

In Vitro-in Vivo Correlation

The simple *in vitro-in vivo* correlation analysis showed good linear correlation between the amount of drug released and the pharmacological effect by each individual gel. The correlation found reinforces that the main release mechanism for lidocaine from the gels was diffusion, both *in vitro* and *in vivo*. As the amount of drug released *in vitro* from the different gels in 150 min varied markedly the differences between the slopes of correlation curves are relatively great and a general correlation between gels could not be demonstrated. The rank order correlation found between *in vitro* release and *in vivo* results reflects the efficiency of the effect. In this case the often used three level correlation, definded in the descending order of quality as the A, B and C correlation (17), was rejected because of the small number of animals used in the study.

Tissue Reactions

Certain striking and consistent tissue reactions were caused by the various gels (Table II). There was a complete lack of neurological (e.g. *paralysis*) and visible macroscopic tissue defects, in spite of some inflammatory changes, even around the sciatic nerves. The gels were accurately localized to the injection site, since a lump of gel was present in the sciatic nerve reagion at dissection site.

The most marked inflammation observed in the muscle of rats injected with 2% lidocaine-solution was not unexpected. Amide-type local anesthetics are known to cause local myotoxicity in skeletal muscle cells (18,19). The acute degeneration is usually followed by complete regeneration in approximately four weeks (19). The reason for the occasional occurrence of perineural inflammation in most study groups remains speculative. The long-lasting presence of the gel material in the sciatic nerve groove could have induced local chemical irritation and disturbance in the circulation. It is unlikely that potential needle injury would be the major reason for inflammatory changes observed, since the nerves were virtually unaffected in the saline group.

The methylcellulose gels (MC and MC_{com}) were more often than the others associated with some inflammatory changes. On the other hand, both the carboxylated and hydroxypropylated methylcellulose gels were non-irritating to the tissue although the small number of rats and single-dose administration in the various study groups do not allow any definite conclusions in this respect. Longer exposure to gels

may, however, result in toxicity since subcutaneous application of CMC for more than a year in rats has caused fibrosarcoma (20). The PO gel was also non-irritating. Poloxamer has previously been used in various pharmaceutical formulations (9,10), but not as a carrier for nerve blocking agents.

CONCLUSIONS

The chemical and ionic nature of the polymers controlled the dissolution rate and the pharmacological nerve block effects of lidocaine. As the gels remained at the injection site, the dilution rate and the biological degradation of the gels seems to determine the duration of the action of lidocaine. The release of lidocaine from the gels followed square-root-of-time kinetics indicating that the release was diffusion. Since the *in vitro* results correlated well with *in vivo* results, the chosen *in vitro* dissolution test can be used in predicting the *in vivo* effects. Poloxamer proved to be the most promising carrier for prolonging lidocaine release. However, the prolongation of the antinociceptive effect was shorter than assumed, probably because after a certain time the amount of drug released will become insufficient to maintain a nerve blocking concentration inside the sciatic nerve. It seems possible to further prolong the release by formulative factors.

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