

Phase Ia and Ib Study of Amitriptyline for Ulnar Nerve Block in Humans

Side Effects and Efficacy

Peter Fridrich, M.D.,* Sunil Eappen, M.D.,† Walter Jaeger, Ph.D.,‡ Eva Schernhammer, M.D., Dr.P.H.,§ Anthony M. Zizza, B.A.,|| Ging Kuo Wang, Ph.D.,# Peter Gerner, M.D.†

Background: The antidepressant amitriptyline is used as an adjuvant in the treatment of chronic pain conditions. Among its many actions, this drug also blocks ion channels, such as Na⁺ channels. Preliminary animal studies suggested that amitriptyline would be a longer-lasting local anesthetic than bupivacaine, with potentially fewer side effects. Therefore, the authors investigated the adverse effects and effectiveness of this drug when given for ulnar nerve blockade in human volunteers.

Methods: After obtaining written institutional review board approval and informed consent, a typical phase Ia trial was conducted by administration to the ulnar nerve at the level of the wrist in an open-label, dose-escalating fashion. Amitriptyline hydrochloride, 4 ml, at concentrations of 5, 10, and 20 mM (n = 4-9/group) was used for each volunteer. If no major side effects and nerve block were encountered, comparison in a randomized, double-blinded trial of amitriptyline (20 mM) to placebo and bupivacaine (4 mM) (n = 4-9/group), was to follow. A blunt needle was used to grade the pain, and motor blockade was assessed by the Froment test.

Results: There was no significant statistical difference in terms of side effects (pain, swelling, erythema, and sedation) among any groups. The analgesic effects of 20 mM amitriptyline and 4 mM bupivacaine solution were significantly higher than those of the placebo solution.

Conclusions: Because of the lack of evidence that amitriptyline provides better nerve blockade than current local anesthetics and the potential for neurotoxicity, its use for peripheral nerve blockade in humans seems limited.

THE antidepressant amitriptyline is used as an adjuvant in the treatment of a variety of chronic pain conditions.¹ Inhibition of norepinephrine and serotonin reuptake² are only one of its many potential mechanisms of action. There is also evidence that amitriptyline blocks α_2 -adren-
ergic,³ nicotinic,⁴ muscarinic cholinergic,⁵ N-methyl-D-aspartate,⁶ and histaminergic receptors⁷ and interacts

with opioid and adenosine receptors.⁸ In addition, amitriptyline has been shown to block various voltage-gated ion channels, including Na⁺, K⁺, and Ca⁺ channels.⁹⁻¹²

Because blocking Na⁺ channels is a major feature of local anesthetics, it was hypothesized that amitriptyline may have local anesthetic properties. Further experimentation has shown that amitriptyline has greater efficacy than both lidocaine and bupivacaine when used to produce sciatic nerve blockade in rats.¹³

To date, there has been no report on the use of amitriptyline for nerve blockade in humans. When a new drug or new indication for an already approved drug is tested clinically, the United States Food and Drug Administration mandates a phase Ia trial (which is designed to detect adverse effects) followed by a phase Ib trial (designed to compare the new treatment against placebo, standard drugs, or both) in healthy volunteers.¹⁴⁻¹⁶ Our goal was to conduct a phase Ia study to evaluate the side effect profile of amitriptyline when used as a local anesthetic for peripheral nerve blockade in the usual dose escalating fashion. If any severe side effect was present, the study was to be halted immediately. If it seemed that the side effect profile of amitriptyline was similar to that seen with currently available local anesthetics and clear signs of nerve blocking capabilities were present, a phase Ib study to evaluate the efficacy of this drug in comparison with bupivacaine and placebo was to follow.

Preclinical Safety Data

Safety must be the most important consideration in the clinical investigation of new drugs or indications.¹⁷ Cardiac toxicity and neurotoxicity are the major concerns for local anesthetics and are therefore the most important to consider before embarking on a clinical trial. In rats, intravenous amitriptyline administration has been found to be less cardiotoxic than bupivacaine as a bolus injection (simulating accidental intravascular injection during regional anesthesia). Also, cardiac toxicity has not appeared as a major concern in the decades of intravenous use in Europe in much higher dosages.¹⁸

We conducted a number of pilot studies with repeat percutaneous injections of amitriptyline for rat sciatic nerve blockade at high dosages (0.2 ml amitriptyline, 40 mM, every day for 3 days; n = 6) to preliminarily evaluate direct neurotoxicity. Neurobehavioral examination (response to pinch of the fifth toe and motor strength) seemed to have returned to baseline after sev-

* Attending Anesthesiologist, Trauma Hospital Lorenz Boehler. † Assistant Professor, # Associate Professor, || Research Assistant, Pain Research Center, Department of Anesthesiology, Perioperative and Pain Medicine, § Instructor, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. ‡ Professor, Institute of Pharmaceutical Chemistry, University of Vienna, Vienna, Austria.

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Address reprint requests to Dr. Gerner: Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. Address electronic mail to: pgerner@partners.org. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

eral days. Then, the animals were euthanized, and the sciatic nerves were excised. After fixation, cross-sections of the sciatic nerve were taken, embedded in paraffin, and stained with hematoxylin and eosin. None of these rats revealed histopathologically detectable nerve damage. Therefore, we concluded that a human trial was justified. However, this percutaneous approach does not guarantee that the drug is actually applied in close proximity to the nerve. The limitations of this approach are presented in detail in the Discussion section.

Materials and Methods

Written approval for the use of human subjects was obtained from the local Human Research Committee of the Trauma Hospital Lorenz Boehler, Vienna, Austria. Financial compensation was offered for participation.

Inclusion Criteria

Inclusion criteria were as follows:

1. Healthy men and women between the ages of 19 and 65.
2. A negative pregnancy examination within 24 h of study for female subjects. (A pregnancy test is deferred if the female subject is not of childbearing potential [defined as postmenopausal for at least 1 yr] or is surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]. If subject is of childbearing potential, she was categorized as not pregnant if confirmed by negative serum pregnancy test at time of screening.)
3. Subject has voluntarily signed and dated an informed consent form.

Exclusion Criteria

Exclusion criteria were as follows:

1. Subjects with dermatologic conditions in the area of application.
2. Subjects with neurologic or neuromuscular diseases.
3. Female subjects who are or may be pregnant.
4. Subjects who have received investigational treatment within the previous 30 days.
5. Subjects who are using any prescription drugs.
6. Subjects with a history of heart problems.
7. Subjects with a history of hypersensitivity to any of the study treatments, including amitriptyline or other tricyclic antidepressants.

Enrollment

After obtaining institutional review board approval, subjects were recruited by advertising with flyers. Subjects were informed that with nerve blockade, perma-

nent and irreversible nerve damage was a possibility and were again made aware of that possibility immediately before the procedure.

The phase Ia safety assessment study was conducted using a dose-escalating, open-label style. Initially, only subjects for the phase Ia study were enrolled for the 5 mM ($n = 9$) concentration. Only in the absence of predefined significant side effects was the study to proceed to a doubled concentration of 10 mM ($n = 9$) and finally to 20 mM ($n = 4$). The phase Ib efficacy assessment study was randomized (by a computer-generated list) and double blinded. All phase Ib subjects including the bupivacaine and the normal saline group were also evaluated for side effects to compare the incidence and severity of side effects.

Drugs

Amitriptyline hydrochloride (Saroten[®], 50 mg/2 ml; Lundbeck Inc., Copenhagen Valby, Denmark) was diluted with sodium chloride (0.9%) and adjusted to pH 6.0–6.2 with sodium bicarbonate by an experienced pharmacist under strict sterile conditions. Each subject received 4 ml of one of the following solutions: 5, 10, or 20 mM amitriptyline in vehicle—resulting in a total dose of 6.3, 12.6, or 25.2 mg amitriptyline, respectively, 4 mM (0.125%, 5.0 mg) bupivacaine or normal saline.

Ulnar Nerve Block

This procedure was performed by an anesthesiologist experienced in this technique, as previously described.¹⁹ In brief, the area of the left wrist was disinfected with Betadine (Purdue Pharma, Stamford, CT), and a 25-gauge needle was inserted on the medial side of the ulnar artery and advanced between it and the flexor carpi ulnaris to the level of the ulnar styloid. The left side was used, as all subjects were right handed. When a paresthesia was elicited, the needle was retracted 1–2 mm, and, after a negative test result for aspiration of blood was obtained, 4 ml test solution was injected.

Evaluation of Side Effects

The safety of amitriptyline was assessed by asking subjects to rate paresthesias or tingling sensations, pain, swelling, erythema, and sedation. All subjective ratings were classified as none, mild, moderate, or severe (scored as 0, 1, 2, and 3, respectively) at 5, 10, 15, 30, and 60 min, then every 30 min until 6 h, and then daily until resolution. Subjects were encouraged to mention any possible adverse effect at any time and were also asked to complete a symptom checklist (potential side effects included drowsiness, nausea, dry mouth, pruritus, as well as the sensation of “burning”) at the end of the first and second days of the study. They were given a brief physical examination at the beginning of the study and at the end of the first and second days to further assess the safety of amitriptyline.

Electrocardiogram (baseline before initiation of the ulnar nerve block and before discharge), blood pressure, and heart rate before the procedure and at 1, 3, and 5 h were recorded. Particular attention was paid to evidence of QT and QRS prolongation or development of any intracardiac conduction delays.

Clinical Testing of Nociception

A 16-gauge blunt needle was used to grade the pain (visual analog scale; 0 = complete analgesia, 100 = normal pain sensation) at the hypothenar eminence at 5, 10, 15, 30, and 60 min, then every 30 min until 6 h, and then daily until resolved. Testing was conducted by the same investigator, who was trained to apply a reproducible force on the skin with the blunt needle tip and who was also blinded to the treatment group. This individual was also unaware of the test results obtained during earlier time points. Specifically, three brisk stimuli within approximately 1 s were applied to a predetermined area of the left hypothenar and then compared with the same area contralaterally. If the subjects were undecided as to how to rate the pain sensation (which was quite common), the testing was repeated, up to three times, after which a number indicating the pain sensation had to be volunteered by the subjects.

Clinical Testing of Motor Function

Blockade of the ulnar nerve at the wrist leads to weakness of the adductor pollicis brevis muscle. Therefore, a test using the motor strength of adducting the thumb (Froment test) as well as evaluating the movement of the first toward the fifth finger was chosen to assess the degree of motor block.²⁰ Subjects were assigned a score of 3 (full motor blockade, *i.e.*, unable to touch the tip of the fifth finger with the tip of the thumb), 2 (able to touch but unable to hold a sheet of paper between thumb and index finger), 1 (able to hold a sheet of paper but unable to hold a book, weight approximately 770 g), or 0 (full motor strength as demonstrated by ability to hold a book).

Measurements of Plasma Concentrations of Amitriptyline

Blood samples (5 ml) were collected from the contralateral antecubital vein at 1, 3, and 5 h after amitriptyline application. The blood was immediately centrifuged, and the plasma was stored at -80°C until analysis. The concentration of amitriptyline in plasma was measured by high-performance liquid chromatography. Briefly, plasma samples (1 ml) and the internal standard (200 μl desipramine, 1 $\mu\text{g}/\text{ml}$) were vortex-mixed for 10 s and passed through extraction cartridges (Oasis HLB, 1 ml; Waters, Milford, MA) equilibrated with 1 ml methanol and water, respectively. The cartridges were washed with water and amitriptyline and the internal standard were eluted with methanol (100%, 0.5 ml). The

recovery of extraction of amitriptyline and desipramine generally exceeded 90%. One hundred microliters of the methanolic solution was injected onto the high-performance liquid chromatography column. The chromatographic assay included a Merck "La Chrom" system (Merck, Darmstadt, Germany) equipped with an L-7250 injector, an L-7100 pump, an L-7300 column oven (set at 35°C), a D-7000 interface, and an L-7400 UV detector (210 nm). Separation of amitriptyline was performed using a Luna 5 μm C18 column (5 μm , 250×4.6 mm ID; Phenomenex, Torrance, CA) preceded by a Luna 5 μm C18 column precolumn (5 μm , 10×4.6 mm ID) at a flow rate of 1 ml/min. The mobile phase was 10 mM phosphate buffer pH 7.0-acetonitrile-water (16:74:10). Linear calibration curves were performed from the peak areas of amitriptyline to the internal standard by spiking drug-free human plasma with standard solutions of amitriptyline. The limit of detection, defined as a signal-to-noise ratio of 3, was 2 ng/ml for the drug.

Statistical Analysis

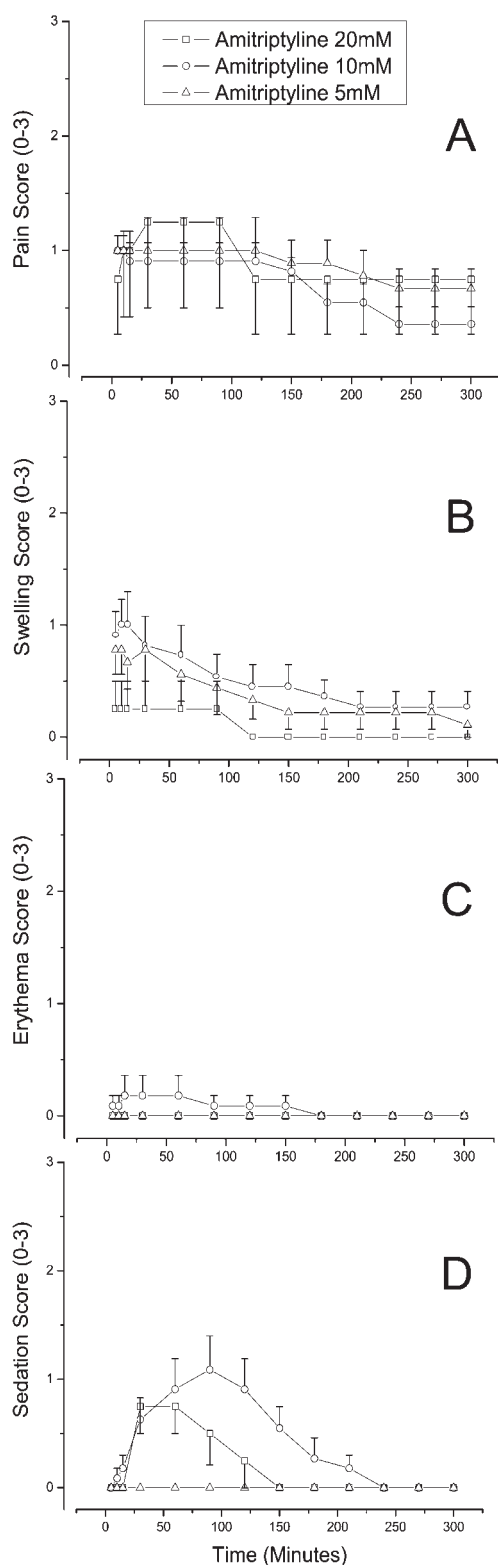
Power calculations to determine the number of individuals necessary to detect clinically relevant differences in efficacy of amitriptyline as compared with placebo and bupivacaine were performed on the basis of animal data from a previous study¹³ ($\alpha = 0.05$, $\beta = 0.20$). These analyses showed that samples from at least three individuals per group were required to detect statistically significant differences. Therefore, a total of four to nine subjects per group (taking into account potential dropouts) were enrolled.

Differences in plasma concentrations of amitriptyline at 1, 3, and 5 h after injection were evaluated, using the Student *t* test. Natural logarithms of the plasma amitriptyline values were used in these analyses to improve normality.

To test whether the mean analgesic (visual analog scale scores) and motor effects (motor scores) of amitriptyline, bupivacaine, and/or placebo were different, analysis of variance models were fitted. For *post hoc* analyses (pairwise comparison of different amitriptyline concentrations, bupivacaine, and/or placebo), the Scheffé procedure was used.

Differences of side effects of the subjects in the phase I b trial (between amitriptyline at a concentration of 20 mM, bupivacaine and placebo) were reported by dichotomizing side effect scores into groups of subjects with scores of less than 2 and 2 or greater and by comparing the proportion of subjects who reported a score of 2 or greater in the amitriptyline groups *versus* those with a report of a score of 2 or greater in the placebo and bupivacaine groups. We used the Fisher exact test to assess statistically significant differences at the 0.05 level between the groups.

All statistical tests were two-sided. We used the SAS statistical package for all analyses (SAS Institute, Cary, NC).²¹



Results

A total of 40 healthy volunteers aged 23–53 yr (18 male, 22 female) with no history of cardiovascular disorders or neurologic conditions participated. All of the volunteers completed the study.

Fig. 1. Subjects' reports of spontaneous pain, swelling, erythema, and sedation (0 = none, 1 = mild, 2 = moderate, 3 = severe). *N* = 9 for the 5 mm amitriptyline group, *n* = 9 for the 10 mm amitriptyline group, and *n* = 4 for the 20 mm amitriptyline group. (A) Subjects' reports of spontaneous pain. Of note, amitriptyline at all concentrations caused some degree of pain at all time points. (B) Swelling at the area of and adjacent to the injection site. After approximately 1 h (probably when the 4 ml injected solution had been resorbed), most swelling had subsided. (C) Erythema at the area of and adjacent to the injection site. Minimal erythema was detectable. (D) Subjects' reports of perceived sedation. Interestingly, sedation was highest in the 10 mm amitriptyline group; however, this is also the group that had the highest mean plasma concentrations at 1 h after initiation of ulnar nerve blockade.

Phase Ia Safety Assessment Study

Adverse Effects. On injection of the drugs, most subjects experienced some mild paresthesias, but the incidence and severity of them was indistinguishable among groups and subsided at the latest by the time the block became effective. However, one subject in the 5 mm amitriptyline group reported mild paresthesia in the innervation area of the ulnar nerve distal to the injection site that began after the block had resolved and lasted for 2 days. Pain, swelling, and erythema at the injection site and sedation were not significantly different than from that reported in comparable literature (figs. 1A–D). The amount of pain in all amitriptyline groups was fairly consistent during the first day after drug application and resolved completely in all subjects except one by the next morning (one subject had mild pain for 48 h).

All electrocardiographic readings were unchanged from baseline to discharge. Blood pressure and heart rate measurements did not differ by more than 10–15% at any recorded time, even in the subjects who had the highest amitriptyline plasma concentrations or those who reported a higher sedation score.

Efficacy assessment was not part of this phase I study; however, a brief assessment of the sensory and motor function in the innervated area clearly showed a dose-dependent block.

Plasma Concentrations. Mean geometric amitriptyline plasma concentrations at 1, 3, and 5 h are shown in table 1. No statistically significant differences were found among the groups for plasma concentrations at 1, 3, and 5 h. However, the overall decline of plasma concentrations from 1 to 3 to 5 h after injection was statistically significant. Of note, mean plasma concentrations in the highest concentration (20 mM) were lower at 1 and 3 h than in the 10 mM group at 1 h. Also, no metabolites (nortriptyline) were found in any of the samples.

Phase Ib Efficacy Assessment Study

Five subjects participated in the placebo group, four participated in the bupivacaine group, and 9 partici-

Table 1. Geometric Means of Plasma Concentrations

Amitriptyline Concentration, mm	Plasma Concentration (1 h), ng	Plasma Concentration (3 h), ng	Plasma Concentration (5 h), ng
5	35.2	14.2	10.7
10	147.0	40.4	26.0
20	100.5	120.0	47.9

Mean amitriptyline plasma concentrations of all subjects at 1, 3, and 5 h after administration for ulnar nerve block with amitriptyline at various concentrations. The toxic range has been reported to be greater than 700 ng/ml, which was reached in one subject at 1 h; however, no signs of toxicity (except moderate tiredness) were observed. Because of the high variability, no statistical difference was found between each of the amitriptyline groups. When all groups medians were compared, the plasma concentration was significantly lower between 1 and 3 h as well as 3 and 5 h. $P < 0.05$ for 5-mm vs. 10-mm groups; $P < 0.05$ for 10-mm vs. 20-mm groups.

pated in the amitriptyline 20 mm group. After unblinding, four subjects in the amitriptyline group were found to have no signs of block. However, none of these subjects were excluded from the analysis.

Testing by Pinprick. The analgesic effects of amitriptyline are significant ($P < 0.05$) at a concentration of 20 mm when compared with the effects of placebo (fig. 2). No significant difference was found between the 4 mm bupivacaine group and the 20 mm amitriptyline group. One subject in the bupivacaine group reported complete analgesia, lasting for 6 h, but none of the subjects at the 20 mm concentration of amitriptyline reported complete analgesia.

Motor Function. Similar results for the motor blockade were found as for the visual analog scale scores (fig. 3). There was significantly greater motor block in the treatment groups when compared with placebo but no statistically significant difference between the bupivacaine and amitriptyline groups.

Adverse Effects of Amitriptyline versus Bupivacaine and Placebo. Although safety and adverse effects were not the focus of this phase Ib trial, detailed observation and follow-up studies of the nine subjects in the 20 mm amitriptyline group were compared with those of the bupivacaine and placebo groups. There was no significant difference among those groups.

For pain scores, one of nine subjects (11%) in the 20 mm amitriptyline group, zero of four subjects in the bupivacaine group, and zero of five subjects in the placebo group reported a score of 2 or more. For erythema scores, one of nine subjects (11%) in the amitriptyline group, zero of four subjects in the bupivacaine group, and zero of five subjects in the placebo group reported a score of 2 or more. For swelling scores, zero of nine subjects in the amitriptyline group, one of four subjects in the bupivacaine group (25%), and zero of five subjects in the placebo group reported a score of 2 or more. For sedation scores, one of nine subjects (11%) in the ami-

triptyline group, zero of three subjects in the bupivacaine group, and zero of five subjects in the placebo group reported a score of 2 or more. One amitriptyline-treated subject in this phase Ib trial reported a moderate paresthesia at the site of injection radiating proximally at the ulnar side of the forearm to the elbow area; this resolved after 1 week.

Discussion

We have shown that the side effect profile of amitriptyline for ulnar nerve blockade in human volunteers is not significantly different from currently clinically used local anesthetics,²² therefore justifying the progression to a phase Ib trial. The overall efficacy of amitriptyline at 20 mm was not significantly different from that of bupivacaine at 4 mm despite the fivefold greater concentration used. The very dense and long-lasting block with this concentration of bupivacaine (4 mm \approx 0.125%) correlates well with earlier work.

Interestingly, earlier *in vitro* and *in vivo* work with amitriptyline revealed it to be much more potent than bupivacaine in blocking peripheral nerves in rats.^{12,23,24} However, our data show a relatively weak clinical local anesthetic effect of amitriptyline when administered for ulnar nerve blockade in humans. There are a number of reasons detailed below that may explain this paradox. First, this difference may be due to the difference in thickness of surrounding fascias and nerve sheaths as well as the presence of a much better developed epineurium in peripheral nerves of humans. This is in contrast to the lack of such obstructions when conducting *in vitro* experiments and the relatively thin fascial and nerve sheaths in the previous animals tested. Second, the log P value (octanol-buffer coefficient) of amitriptyline is relatively high, approximately 4.9,** indicating that it is an extremely lipophilic substance; this would make passage through various barriers in the relatively large human ulnar nerve difficult.²⁵ This may also explain why four subjects in the amitriptyline group had no measurable blockade after the ulnar nerve injection. Of course, this could also represent a technical failure. However, if there is very low permeability across nerve sheaths and the drug is not applied in close proximity to the nerve, it could be expected that amitriptyline would be much less effective than bupivacaine because of a diminished amount of drug molecules available for diffusion into the nerve core. Considering this possibility, the observation that the onset of amitriptyline block in the rat sciatic nerve model (this nerve has a diameter of approximately 2 mm) was significantly slower than with bupivacaine²⁶ in that specific rat model supports the idea that the larger diameter human nerve provides more of a barrier than smaller diameter rat sciatic nerve to amitriptyline. Furthermore, any small

** Available at: <http://esc.syrres.com/interkow/kowdemo.htm>. Accessed November 1, 2003.

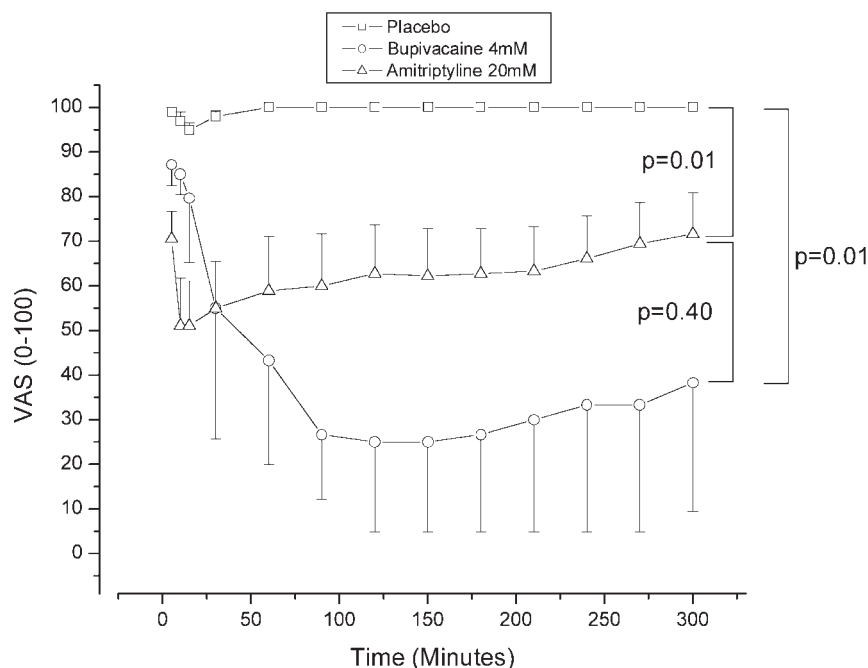


Fig. 2. Analgesia after ulnar nerve block of placebo/vehicle only ($n = 5$) and amitriptyline at a concentration of 20 mM ($n = 9$) and bupivacaine at a concentration of 4 mM ($n = 4$). Blinded subjects were tested at specific time points with a blunt needle at a designated test area *versus* a control area on the contralateral hand. The respective visual analog scale (VAS) score was reported to the blinded experimenter. Data are presented as mean \pm SEM. Overall significance was determined by analysis of variance for repeated measurements. *Post hoc* analysis (pairwise comparison of different concentrations, placebo, or both at each time point) was performed by the Scheffé method. All subjects had normal pain sensation by the next morning. $P < 0.05$ for placebo *versus* 20 mM amitriptyline and placebo *versus* 4 mM bupivacaine.

distance the amitriptyline is deposited away from the nerve makes blockade even more unlikely.

Also, the pH value of amitriptyline was 6.0–6.2. Considering the high pK_a (9.4) of this drug, this means that only approximately 0.1% of drug existed in the uncharged form and was therefore available to pass through the nerve membranes.²⁷ Concomitantly, a higher pH could have increased the potency closer to that observed in animal experiments. However, increasing the pH could increase the potential for causing direct neurotoxicity because more drug is available in the unionized form.

We assessed the effect of placebo/bupivacaine/amitriptyline by pin-prick test and visual analog scale score. Undoubtedly, different modes of evaluation (e.g., von Frey hair testing, thermal or electrical stimulation) might lead to slight variability in the data. However, after testing similar methods for assessing analgesia as reported in previous studies,^{28,29} we concluded that the above-mentioned technique yielded the most reproducible results, thus producing the least variability.

Cardiac toxicity as measured by electrocardiogram, heart rate, and blood pressure changes seemed to be negligible at the dosages used. This is supported by

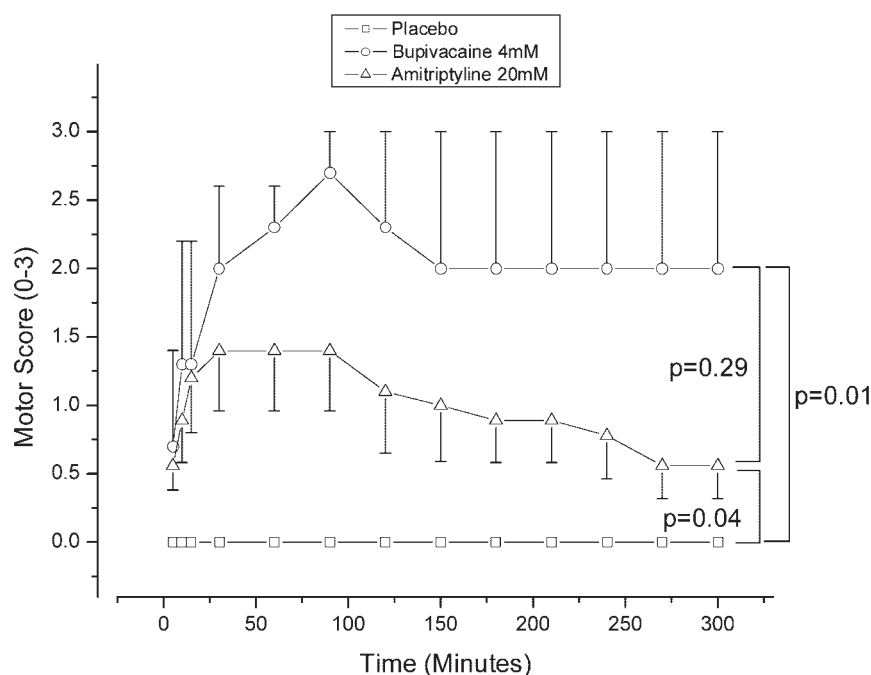


Fig. 3. Motor block after ulnar nerve block with placebo/vehicle only ($n = 5$) and amitriptyline at a concentration of 20 mM ($n = 9$) and bupivacaine at a concentration of 4 mM ($n = 4$). Similar to the visual analog scale score (fig. 2), statistical significance was found only between amitriptyline and placebo groups, not between amitriptyline and bupivacaine. All subjects had fully recovered motor function by the next morning.

earlier work,¹⁸ where 80 patients receiving 100–150 mg of either intravenous or oral amitriptyline daily for 28 days showed no significant cardiovascular toxicity.

On injection and before the block was established, the incidence of paresthesias were found to be similar in all groups and to occur in the distribution of the ulnar nerve. However, neurotoxicity may not be seen on initiation of nerve blockade and may only be clinically detectable when the block has resolved. Therefore, the one subject in the 5 mm amitriptyline group (paresthesia for 2 days) and the one subject in the 20 mm amitriptyline group (paresthesia for 7 days) may be indicative of some degree of neurotoxicity. One could argue that paresthesias after ulnar nerve block are relatively common with bupivacaine³⁰ or ropivacaine³¹ and could also represent needle trauma. Our study did not attempt to elucidate these possibilities.

Adverse Effects of Amitriptyline versus Bupivacaine and Placebo

In phase Ib subjects, we compared pain, swelling, erythema, and sedation after administration of 20 mm amitriptyline, 4 mm bupivacaine, and/or placebo.

Pain on injection was present in all groups. However, the pain subsided in the bupivacaine group within 30 min but was present for 2 days in one subject who received 20 mm amitriptyline. This is an interesting phenomenon because the pain was present despite the presence of the nerve block and may indicate that amitriptyline is itself pain generating. The mechanism of this pain is unknown.

Moderate erythema was present at the injection site in one subject in the 20 mm amitriptyline group, which did not occur in any of the bupivacaine or placebo groups. Aseptic techniques were used when performing the ulnar nerve block. Although we did not perform any microbiology testing of the drugs involved, bacterial contamination is unlikely because no redness occurred in the other subjects. In addition, the amitriptyline was prepared under sterile conditions by an experienced pharmacist. A potential mechanism of this erythema could be that amitriptyline is toxic to neutrophils in relatively low concentrations, as well as inducing membrane damage in *Xenopus* oocytes.^{32,33}

Moderate sedation was also present in one subject of the 20 mm amitriptyline group, lasting for several hours, but this was not associated with any worrisome effects.

Plasma Concentrations

Except in one subject, the plasma concentrations of amitriptyline were far below the toxic range. This one individual's high plasma concentration seemed to correspond with the clinical impression of moderate sedation. All subjects had negative test results for aspiration of blood before injection. However, because the variation is very large and the highest plasma concentration was

found in the 10 mm group, at least partial injection into the vascular system cannot be fully excluded. Alternatively, it may have been due to variable deposition and absorption of the drug around the vasculature as well as variable pharmacokinetics in the volunteers. In any case, plasma concentrations decreased in all groups by 5 h, which might indicate that less monitoring is appropriate after that time under the conditions stated.

Neurotoxicity

After completion of our study, data became available that demonstrated severe axon and Schwann cell degeneration after rat sciatic nerve injection with amitriptyline starting at 20 mm.³⁴ The model used in their study uses a more sophisticated technique (incision of the skin and dividing the muscle above the sciatic nerve, thereby allowing exposure of the sciatic nerve, and injecting directly subfascial under vision onto the nerve, but leaving the fascia surrounding the nerve intact.^{35,36} This ensures that all of the injected drug comes into the direct vicinity of the nerve and is therefore most sensitive for toxicity evaluation.

In summary, the lack of any clear analgesic benefit of peripheral nerve blockade with amitriptyline over currently used local anesthetics combined with the reported side effect profile makes it unlikely that amitriptyline will find clinical utility for this purpose. We would discourage further clinical use of this drug for the purpose of nerve blockade until additional animal studies warrant justification of human investigation.

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