

Topical Amitriptyline in Healthy Volunteers

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Background and Objectives: The antidepressant amitriptyline is used as an adjuvant in the treatment of a variety of chronic pain conditions. This drug interacts with many receptors and ion channels, such as Na⁺ channels. In a randomized, double-blinded, and placebo-controlled trial, we investigated whether amitriptyline also is capable of providing cutaneous analgesia when applied topically in 14 healthy volunteers.

Methods: Amitriptyline hydrochloride was prepared as a 45% water/45% isopropanol/10% glycerin solution and titrated to pH 8.5 with sodium hydroxide. Four areas, 2 on each arm, of approximately 1 cm² each were marked on the ventral aspect of the upper arm. A piece of gauze, placed on each of the marked areas and affixed to the arm with an occlusive plastic dressing, was saturated via syringe with placebo and amitriptyline solutions (10 mmol/L, 50 mmol/L, and 100 mmol/L). After 1 hour, the dressings and gauze were removed. A 16-G blunt needle was used to grade the pain at the marked area once per hour (1 = complete analgesia, 10 = normal pain sensation).

Results: The analgesic effects of 50 mmol/L and 100 mmol/L solutions of amitriptyline were significantly higher than those of the placebo or the 10 mmol/L solution. However, no significant difference was found between the analgesia provided by the placebo solution versus the 10 mmol/L solution or between the 50 mmol/L versus the 100 mmol/L solution. The only side effect observed was a concentration-dependent redness of the skin.

Conclusions: Topically applied amitriptyline is effective as an analgesic in humans. Different vehicles may improve its efficacy and decrease the skin redness observed. *Reg Anesth Pain Med* 2003;28:289-293.

Key Words: Amitriptyline, Analgesia, Topical, Transdermal.

The antidepressant amitriptyline is used in pain clinics as an adjuvant in the treatment of a variety of chronic pain conditions.¹ Inhibition of norepinephrine and serotonin reuptake² is only one of its many potential mechanisms of action. In addition, amitriptyline was shown to block various voltage-gated ion channels (e.g., Na⁺, K⁺, and Ca⁺ channels).³⁻⁶ Furthermore, it blocks α_2 -adrenergic, nicotinic, muscarinic, cholinergic, N-methyl-D-as-

partate, and histaminergic receptors⁷⁻¹¹ and interacts with opioid and adenosine receptors.^{12,13}

Because local anesthetics function by blocking Na⁺ channels, it was hypothesized that amitriptyline may have local anesthetic properties. Further experimentation has shown that amitriptyline is indeed a potent local anesthetic, as evidenced by its improved efficacy over both lidocaine and bupivacaine in producing rat sciatic nerve blockade.¹⁴

In animal models of pain, amitriptyline has been administered through practically every route possible (i.e., enteral and parenteral, intraperitoneal, intrathecal, and peripheral locally).^{13,15} Although amitriptyline has been used clinically as an antidepressant for several decades, administration has largely been limited to the peroral route. Intramuscular and subcutaneous injections are available if peroral administration is not feasible, although intravenous injection/infusion has not been approved by the U.S. Food and Drug Administration (FDA). Topical application of amitriptyline has not been FDA approved, although there is literature precedent for this route of administration. Scott et al.¹⁶ reported the use of an amitriptyline gel in a patient with chronic pain and depression, and 2 formulations of amitriptyline gel are reported in the

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International Journal of Pharmaceutical Compounding.^{17,18} However, none of these studies evaluated potential analgesia of the skin.

Currently 2 formulations containing local anesthetics for topical analgesia are available: eutectic mixture of local anesthetics (EMLA) cream, available from AstraZeneca LP, Wilmington, DE, and Lidoderm, from Endo Laboratories, Chadds Ford, PA. Unfortunately, both of these drugs have a long onset time and short duration. For example, EMLA cream is a popular FDA-approved topical anesthetic containing 2.5% lidocaine and 2.5% prilocaine. However, its analgesic effects persist for only 1 to 2 hours after removal of the occlusive dressing (per package insert).

Most recently, infiltration block by subcutaneous injection in rats was found to be longer with amitriptyline than with bupivacaine,¹⁹ and transdermally applied amitriptyline was found to be more effective than lidocaine in providing cutaneous analgesia in rats.²⁰ On the basis of these preclinical studies on the topical application of amitriptyline in rats, we investigated whether amitriptyline also provides cutaneous analgesia when applied topically in humans.

Potential benefits of topical amitriptyline include the treatment of chronic pain, such as neuropathic pain, back pain, neuralgia, and the prevention of pain in procedures such as intravenous cannulation, vaccination, circumcision, dermatological procedures, and skin grafting. Because safety is the most important consideration in the clinical investigation of new drugs or indications, we also have attempted to evaluate the side effect profile.

Methods

Approval for the use of human subjects was obtained from the Human Research Committee of Brigham and Women's Hospital/Massachusetts General Hospital. Fourteen healthy volunteers aged 23 to 53 years with no history of cardiovascular disorders or dermatological conditions participated in this study.

Amitriptyline hydrochloride was prepared as a 45% water/45% isopropanol/10% glycerin solution (titrated to pH 8.5 with sodium hydroxide) by the Investigational Drug Service of Brigham and Women's Hospital. The vehicle used here is based on one used by Kissin et al.²¹ in similar studies involving lidocaine. Each subject (randomized and blinded) received 0.3 mL of 4 solutions—placebo (vehicle only) and 10 mmol/L, 50 mmol/L, and 100 mmol/L amitriptyline in vehicle—resulting in a total dose of 15 mg of amitriptyline. These concentrations were chosen because the total dose per subject

appeared very safe. Furthermore, these concentrations provided an acceptable duration for volunteers in pilot studies.

Four areas, 2 on each arm, of approximately 1 cm² each were marked on the ventral aspect of the upper arm. A 1-cm² piece of sterile gauze was then placed on each of the marked areas and affixed to the arm with an occlusive dressing (Tegaderm, 6 × 7 cm, 3M HealthCare, St. Paul, MN). The gauze on the 4 test areas was saturated via syringe with 0.3 mL of placebo solution and amitriptyline solutions of 10, 50, and 100 mmol/L concentrations. At the end of 1 hour, the dressings and gauze were removed. A 16-G blunt needle was used to grade the pain (visual analog scale, 1 = complete analgesia, 10 = normal pain sensation) at the marked area immediately after removal of the dressing and then once per hour subsequently. Testing was done by the same investigator who was trained to apply a reproducible force on the skin with the blunt needle tip and was also blinded to the drug as well as to the test results obtained during earlier time points.

The safety of amitriptyline was assessed by asking subjects to rate the redness, itching, burning, paleness, and/or swelling of their skin throughout the study as mild, moderate, or severe (at time points immediately after removal of the dressing, after 3 hours, after 6 hours, and after 1 day). Subjects also were asked to complete a symptom checklist at the end of the first day of the study and again on the following day. They were given a brief physical examination at the beginning of the study, at the end of the first day, and again on the next day to further assess the safety of amitriptyline.

Power analysis (α 0.05, β 0.20) was used to calculate the sample size. Fifteen subjects were enrolled, with 14 subjects actually participating; all of them completed the study (1 subject missed the appointment for patch application). The overall significance of the analgesic effects of amitriptyline and/or placebo was determined by analysis of variance for repeated measurements. Post-hoc analysis (pairwise comparison of different concentrations and/or placebo at each time point) was done by Scheffe's method. Correlation between drug concentration and redness was assessed by 1-way analysis of variance and post-hoc analysis by Tukey test.

Results

The analgesic effects of amitriptyline are significant ($P < .05$) at concentrations of both 50 and 100 mmol/L when compared with the effects of placebo and 10 mmol/L amitriptyline (Fig 1). No significant

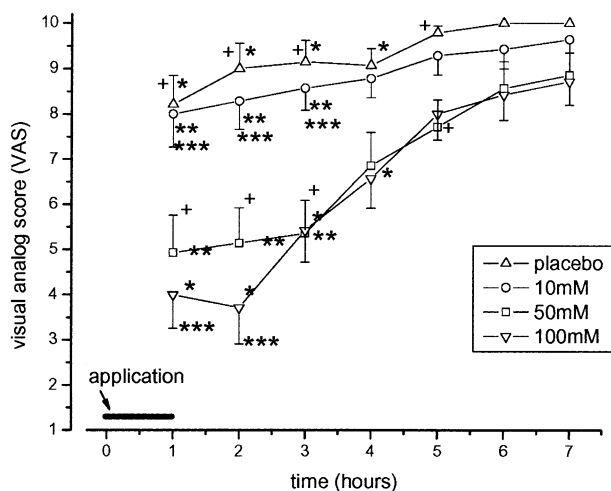


Fig 1. Analgesia after patch removal for placebo (vehicle only) and amitriptyline at various concentrations. Application time was 1 hour (arrow). After removal of the patch, blinded subjects were “poked” each hour with a blunt needle at a designated test area versus a control area and the respective visual analog score reported to the blinded experimenter. Data are presented as mean \pm standard error of the mean. Overall significance was determined by analysis of variance for repeated measurements. Post-hoc analysis (pairwise comparison of different concentrations and/or placebo at each time point) was done by Scheffe’s method. $P < .05$ for *(placebo vs. 100 mmol/L), **(10 vs. 50 mm), *** (10 vs. 100 mmol/L), and + (placebo vs. 50 mmol/L amitriptyline).

difference was found between the placebo and the 10-mmol/L groups and between the 50- and 100-mmol/L groups. Two of 14 subjects reported complete analgesia with the 100-mmol/L concentration but only at the earliest time point (immediately after patch removal). Most subjects experienced some mild redness of the skin at the application site; the incidence of this redness was statistically significant in the 50- and 100-mmol/L groups compared with the placebo and 10-mmol/L groups (Table 1). The degree of redness was fairly consistent during the first day of testing but disappeared completely overnight (except in 1 subject who had residual redness the next morning at the 50- and 100-mmol/L application sites, which disappeared completely within a few hours). One subject reported additional side effects consisting of a mild itching and burning sensation at the site of application of the drug but only immediately after removal of the patch, and these symptoms disappeared completely within 3 hours. Subjects also were given a symptom checklist including potential side effects such as drowsiness, nausea, and dry mouth; no subjects reported any of these symptoms at any time.

Discussion

To our knowledge, this is the first report of the delivery of amitriptyline by transdermal patch providing cutaneous analgesia in humans. As mentioned earlier, 1 case report¹⁶ describes the transdermal delivery of amitriptyline in a severely depressed patient in whom neither oral nor intravenous administration was possible. The drug was successful in treating depression in this patient. However, no statement was found regarding local analgesia at the site of application.

We assessed the effect of placebo/amitriptyline by pinprick test and visual analog 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 cutaneous analgesia as reported in previous studies,^{22,23} we concluded that the above-mentioned technique yields the most reproducible results, thus producing the least variability.

In this study, 100 mmol/L amitriptyline and 50 mmol/L amitriptyline had similar analgesic effects. Several explanations for this phenomenon can be found. The most likely possibility involves the limited solubility of amitriptyline hydrochloride in the vehicle at pH 8.5. In pilot experiments, it has been observed that solutions of 100 mmol/L amitriptyline are extremely sensitive to the water content of the vehicle; the addition of just 1% water (by volume) changes the clarity of the solution from transparent to translucent, and the addition of another 1% water results in a mixture that is nearly opaque. This suggests that 100 mmol/L amitriptyline has a limited solubility in the vehicle and that the water content of the vehicle is critical. The preparation of solutions of pH 8.5 requires titration with sodium hydroxide, a procedure that could easily result in a 1% or greater excess of water. Previous studies with rats have shown that solutions in which amitriptyline was not completely dissolved had reduced ef-

Table 1. Number of Subjects Who Experienced Redness at the Application Site at Different Time Intervals and Concentrations

| Time (h) | Placebo | 10 mmol/L | 50 mmol/L | 100 mmol/L |
|----------|---------|-----------|-----------|------------|
| 0 | 0 | 1 | 9 | 12 |
| 3 | 0 | 1 | 9 | 11 |
| 6 | 1 | 1 | 10 | 12 |
| 24 | 0 | 0 | 1 | 1 |

NOTE. Total number of subjects is 14. Subjects in the 50 and 100 mmol/L amitriptyline groups had a significantly higher incidence of redness than did subjects in the 10 mmol/L or placebo group ($P < .05$ 1-way ANOVA and post-hoc analysis by Tukey test).

ficacy. For instance, at pH 13, a solution of 500 mmol/L amitriptyline was significantly less effective than one of 100 mmol/L amitriptyline. In addition, a solution of 100 mmol/L amitriptyline at pH 8.5 was more effective than a solution of the same concentration at pH 13, despite the fact that at the higher pH a greater ratio of the drug is in the base form, which is better able to penetrate the stratum corneum than the hydrochloride form. In visually evaluating the solutions, it was apparent that the 100 mmol/L, pH 13 solution was cloudier than the 100 mmol/L, pH 8.5 solution. We believe that the phenomenon observed in the current human study is analogous to that seen in this earlier rat study.

Another possible factor contributing to the observed phenomenon is vasodilatation caused by amitriptyline. There appears to be a strong correlation between redness of the skin and the efficacy of the drug. Whereas most subjects experienced consistent redness at the 50-mmol/L and 100-mmol/L patches throughout all time points, only 1 subject reported redness at the 10-mmol/L patch, and redness at the placebo patch was reported intermittently. It is possible that increased systemic resorption due to vasodilation could decrease the active concentration of amitriptyline before it reaches the nerve endings.

A further possibility is that the similar effectiveness of 50 and 100 mmol/L amitriptyline could represent a ceiling effect because of the short (1 hour) application time. It is feasible that a longer application time could reveal a higher grade and longer duration of analgesia in the 100-mmol/L group because our relatively short application time might not allow sufficient drug transfer.

Another goal of this trial was to preliminarily assess the safety of transdermally applied amitriptyline. Although nearly all subjects reported redness from the 50-mmol/L and 100-mmol/L patches, the redness was not severe and in most subjects had completely disappeared by the next day. In addition, itching and burning sensations were present only in the period that immediately followed removal of the patch. The mildness and reversibility of these effects seem to support the safety of the transdermal application of amitriptyline, but this needs to be confirmed in an adequately powered study.

In summary, topical amitriptyline applied as a patch appears effective in humans. Future studies testing different formulations and application times will be required to optimize drug delivery through the skin and determine skin tolerance. Studies involving an active control group, such as a group given lidocaine, will also be necessary to address the

relative efficacy of topical amitriptyline in comparison to other drugs.

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