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Phase 1A safety assessment of intravenous amitriptyline

Peter Fridrich, M.D.^{*}, Hans Peter Colvin[&], Anthony Zizza⁺⁺, Ajay D. Wasan, M.D., M.Sc.[§], Jean Lukanich, M.D.[^], Philipp Lirk, M.D., M.Sc.[§], Alois Saria, Ph.D.[°], Gerald Zernig, M.D.⁺, Thomas Hamp[#], and Peter Gerner, M.D.[¶]

^{*}Attending Anesthesiologist, Trauma Hospital Lorenz Boehler, Vienna, Austria.

[#]Research Assistant and Medical Student, Trauma Hospital Lorenz Boehler, Vienna, Austria.

[§]Resident, Department of Anesthesiology and Critical Care Medicine, Division of Neurochemistry, Medical University Innsbruck, Austria.

[&]Research Assistant and Medical Student, Department of Anesthesiology and Critical Care Medicine, Division of Neurochemistry, Medical University Innsbruck, Austria.

[•]Professor, Department of Psychiatry, Division of Neurochemistry, Medical University Innsbruck, Austria.

⁺Associate Professor, Department of Psychiatry, Division of Neurochemistry, Medical University Innsbruck, Austria.

[§]Instructor, Department of Anesthesiology, Perioperative and Pain Medicine and Department of Psychiatry, Perioperative, and Pain Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[^]Assistant Professor, Department of Thoracic Surgery, Perioperative, and Pain Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[¶]Assistant Professor, Perioperative, and Pain Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁺⁺Research Assistant and Medical Student, Department of Anesthesiology, Perioperative, and Pain Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

The antidepressant amitriptyline is used as an adjuvant in the treatment of chronic pain. Among its many actions, amitriptyline blocks Na⁺ channels and nerves in several animal and human models. As perioperative intravenous lidocaine has been suggested to decrease post-operative pain, amitriptyline, because of its longer half-life time, might be more useful than lidocaine. However, the use of intravenous amitriptyline is not approved by the US Food and Drug Administration. We therefore investigated the adverse effects of preoperative intravenous amitriptyline in a typical phase 1A trial. After obtaining written Food and Drug Administration and institutional review board approval, we obtained written consent for preoperative infusion of amitriptyline in an open-label, dose-escalating design (25, 50, and 100 mg, n=5 per group). Plasma levels of amitriptyline/nortriptyline were determined, and adverse effects were recorded in a predetermined symptom list. Infusion of 25 and 50 mg amitriptyline appears to be well tolerated; however, the study was terminated when one subject in the 100-mg group developed severe bradycardia. Intravenous infusion of amitriptyline (25 - 50 mg over 1 hour) did not create side effects beyond dry mouth and drowsiness,

Address for correspondence: Peter Gerner, M.D., Department of Anesthesiology, Perioperative, and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, pgerner@partners.org, Tel: 617-732-6889, FAX: 617-582-6195

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Work was done at Brigham and Women's Hospital, Boston, MA, and at Trauma Hospital Lorenz Boehler, Vienna, Austria.

or dizziness, in 2 of our 10 otherwise healthy participants receiving the 25-50 mg dose. An appropriately powered future trial is necessary to determine a potential role of amitriptyline in decreasing postoperative pain.

Perspective—Amitriptyline potently blocks the persistently open Na⁺ channels, which are known to be instrumental in various pain states. As this occurs at very low plasma concentrations, a single preoperative intravenous infusion of amitriptyline could provide long-lasting pain relief and decrease the incidence of chronic pain.

Keywords

Amitriptyline; safety; pre-emptive analgesia; pain; phase I trial

Introduction

For decades, the tricyclic antidepressant (TCA) amitriptyline has been administered orally for the treatment of various chronic pain states. Its mechanism of action is unclear; besides inhibiting serotonin and norepinephrine re-uptake, amitriptyline interacts with opioid¹⁵ and adenosine receptors^{29;30} and blocks α_2 -adrenergic,¹⁴ N-methyl-D-aspartate,¹³ nicotinic,²⁸ muscarinic cholinergic,²¹ and histaminergic receptors.³³ Furthermore, amitriptyline blocks various voltage-gated ion channels, e.g., K⁺,⁸ Na⁺,²⁷ and Ca⁺⁺ channels;²⁰ and induces apoptosis⁴ as well as inhibiting the mitochondrial inner membrane anion uniporter.⁵

Amitriptyline has been shown to provide longer nerve blockade than does the classic local anesthetic lidocaine, at least in part due to the high potency of amitriptyline in blocking Na⁺ channels.^{3;17;26}

Perioperative intravenous administration of lidocaine has been postulated to decrease the incidence of chronic pain.^{9;23;34;36;37} Therefore, perioperative administration of the longer-acting amitriptyline may significantly decrease pain sensation after surgery and reduce the incidence of chronic, neuropathic pain syndromes, such as post-thoracotomy chest pain. In addition, amitriptyline is a much more potent blocker of the open Na⁺ channel state than is lidocaine, and this open state is known to be instrumental in pain states.³⁵ Open-channel block with amitriptyline occurs well below the plasma levels achieved with the usual dosages of amitriptyline for the treatment of various chronic pain conditions;³⁵ thus, amitriptyline could provide effective pain relief with a better therapeutic ratio than that achieved with lidocaine.

A variety of study designs have been used to determine the pharmacokinetics of amitriptyline.^{2;11} However, amitriptyline has traditionally been administered orally or infused intravenously over weeks, and plasma levels obtained therefore reflect steady-state values, whereas our design investigates the administration of one dose of amitriptyline infused over a relatively short time.

We chose to study the preoperative intravenous route of administration of amitriptyline for the following reasons: the plasma levels reached when amitriptyline is administered orally when patients usually come to the hospital—2 hours before surgery—are not sufficient when surgery is initiated, and having the patient take the medication before arrival at the hospital will most likely cause sedation and therefore not permit the patient to drive to the hospital. Similarly, intramuscular administration of amitriptyline also results in a relatively late onset of adequate plasma levels and great interindividual differences in plasma levels. However, because intravenous use of amitriptyline is not approved by the United States Food and Drug Administration (FDA), amitriptyline is not available in the US as an intravenous formulation. As an initial step for regulatory approval, the FDA mandated the investigation of the safety of intravenous amitriptyline in a study with an open-label dose-escalating design. For our

preliminary evaluation of the efficacy of amitriptyline in decreasing postoperative pain, we also compared visual analog pain scores (VASs) and piritramide (a synthetic opioid) usage with a placebo group. This additional pilot study was conducted for the purpose of power calculation for a potential phase IB trial.

Materials and Methods

Study Approach

This was a multicenter, single-blinded, dose-escalating safety study of intravenous amitriptyline. After receiving FDA (Investigational New Drug # 68,832) and Institutional Review Board approval from Brigham and Women's Hospital, Boston, MA, as well as approval from the investigational drug pharmacy of this institution to use a drug not commercially available in the US, we commenced the study of intravenous amitriptyline given as an infusion before surgery. We initially enrolled five subjects undergoing video-assisted thoracoscopic surgery (VATS) for wedge resection of a lung tumor, beginning at a dosage of amitriptyline of 25 mg administered pre-operatively over 2 hours. If the patients experienced no major adverse effects, the dose was to be escalated to 50 mg and then to 100 mg. However, after having completed the 25-mg amitriptyline group (five subjects, who provided informed consent), we abandoned the initial study design because we found the 2-hour infusion time to be impractical because of the arrival of patients less than 2 hours before surgery and the reassignment of some study patients to different operating rooms because of a great expansion in surgical volume at the hospital. We therefore stopped enrollment at Brigham and Women's Hospital and obtained new IRB approval for a revised protocol (shortening the time of infusion to 1 hour) at a different institution (Trauma Hospital Lorenz Boehler, Vienna, Austria) and enrolled otherwise healthy subjects undergoing shoulder arthroscopy. We followed a traditional open-label dose-escalating design, at dosages of 25, 50, and 100 mg of amitriptyline ($n = 5$ per group). For preliminary evaluation of a potential pain-decreasing and/or opioid-sparing effect, we included five subjects undergoing shoulder arthroscopy but receiving placebo, 250 ml of normal saline in an infusion over 1 hour, in a single-blinded (patient-blinded) manner.

Inclusion Criteria

Adults between the ages of 21 and 70 years with American Society of Anesthesiologists physical status I-III who were undergoing video-assisted thoracoscopic wedge resection of lung tissue or shoulder arthroscopy were included.

Exclusion Criteria

Those excluded were 1) women who were or might be pregnant, as determined by a urine dipstick test, or who were currently breast feeding; 2) patients weighing <50 kg; 3) patients with medical conditions that may increase the risk of arrhythmia (e.g., history of cardiovascular disorders, including coronary artery disease, sinus tachycardia or bradycardia, hypokalemia, other electrolyte imbalances, and prolonged, corrected QT (QTc) interval (>450 msec) at baseline; 4) patients receiving drugs concurrently that alter the QT interval, such as monoamine oxidase inhibitors, methadone, clarithromycin, droperidol, and chloroquine; 5) patients with TCA contraindications, including a history of hyperthyroidism, seizures, urinary retention, narrow-angle glaucoma, increased intraocular pressure, benign prostatic hypertrophy, and bipolar disorder; 6) patients with pre-existing chronic pain and/or habitual or recent use of opioid pain medication; 7) patients using medication known to interact with a TCA and that significantly inhibits the cytochrome P450 isoenzyme, 2D6, such as rifampin, cimetidine, methylphenidate, various antipsychotics, calcium-channel blockers, terbinafine, and fluconazole; 8) patients with renal insufficiency (serum creatinine >1.5 mg/dl); and 9) patients with hepatic dysfunction (serum ALT/AST >40 U/L).

Recruitment

After the surgeon and/or anesthesiologist examined the operating room schedule, he or she identified subjects who met the inclusion/exclusion criteria. An anesthesiologist or co-investigator on the study team initiated contact with the patient at least two days before the surgical procedure. After carefully explaining the study and its associated benefits and risks, the investigator obtained the patient's informed, written consent.

Study procedures

The appropriate dose of 25, 50, or 100 mg amitriptyline (Saroten 50 mg/2 ml, Bayer Vital, Leverkusen, Germany) was prepared in 250 ml NaCl 0.9% in the preoperative holding room and administered to the subject intravenously over 2 hours (Brigham and Women's Hospital, Boston, MA) or 1 hour (Trauma Hospital Lorenz Boehler, Vienna, Austria). Whole blood (5 ml) was obtained to assay plasma levels of amitriptyline and nortriptyline before infusion; at the end of the infusion; and at 20 minutes and 1, 3, and 5 hours after administration of the drug. During the entire pre-induction, induction, intraoperative, and post anesthesia care unit (PACU) phases, patients were monitored with ECG, pulse oximetry, and blood-pressure monitoring. Specifically, QT interval was monitored via continuous ECG until 3 hours after surgery. Any clinically significant changes in blood pressure or heart rate ($> 25\%$ increase or decrease from baseline) and SaO_2 ($< 92\%$) from baseline values were to be followed by immediate discontinuation of the amitriptyline infusion.

After the amitriptyline infusion was completed, anesthesia was induced with propofol at 1.5-2.5 mg/kg and fentanyl at 2-4 $\mu\text{g/kg}$ body weight. Anesthesia was maintained with inhalation of sevoflurane (1-2%) or infusion of propofol (6-8 mg/kg/h) and $\text{N}_2\text{O/O}_2$ at 70/30% (VATS patients received 100% O_2 during one-lung ventilation). If the patient showed signs of pain (heart rate or blood pressure $> 20\%$ above pre-induction value), additional fentanyl was administered at 0.5-1 $\mu\text{g/kg}$.

Patients undergoing shoulder arthroscopy received a diclofenac-sodium infusion (75 mg in 100 ml of NaCl 0.9%) at the end of surgery, piritramide (1.5-6 mg intravenous on demand) in the PACU, and diclofenac (100 mg peroral) upon discharge. VAS from 0 to 10 (0 = no pain, with a score of 10 as the worst possible pain) was obtained for all patients at the time of arrival at the PACU and upon discharge. In addition, the post-operative on-demand use of intravenous piritramide in the PACU was compared with that of the placebo group.

Adverse effects were evaluated during the infusion, after surgery, and the following day. Patients were also asked whether they had any of the following symptoms (upon arrival to and discharge from PACU): fast or slow heartbeat, facial flushing, eye irritation, dry mouth, abdominal pain, nausea, vomiting, diarrhea, forgetfulness, anxiety, difficulty balancing, confusion, headache, dizziness, depression or euphoria, difficulty speaking, abnormal thinking, ringing in the ears, drowsiness, upset stomach, abnormal sweating, heartburn, sneezing, itching, and weakness. Patients were encouraged to mention any other symptoms.

Amitriptyline assay

We analyzed the serum samples by high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) as described previously.²² To that end, plasma samples (190 μl) were spiked with 10 μl of d3-methadone internal standard (1 $\mu\text{g/ml}$ in methanol; mass transition 268 $>$ 265), and extracted with 500 μl of acetonitrile at -20°C . Supernatant (100 μl) was injected directly into the HPLC/MS/MS instrument. The analytes were separated chromatographically on a reverse-phase C18 column (Acquity BEH C18, 1.7 μm , 2.1 $\times$ 50 mm, Waters, Milford, MA) with a mobile-phase gradient starting at 50% acetonitrile and 50% 5 mM formic acid in water and proceeding to 100% acetonitrile over 3 min at a flow rate of

0.25 ml/min. Chromatographic peaks were quantified by MS/MS on a Micromass Quattro Ultima (Waters., Milford, MA) using the mass transitions 278 > 117 m/z for amitriptyline and 310 > 265 m/z for nortriptyline.

The standard curve (internal standard, 50 ng/ml d3-methadone) was essentially linear up to the highest concentration tested, i.e., 250 ng/ml (quadratic equation fit, weighting 1/x, $r > 0.99$).

The level of detection was 0.1 ng/ml (at a signal/noise ratio of 3/1); the level of quantification was 0.5 ng/ml. Interday precision (expressed as the coefficient of variation, i.e., the standard deviation as percent of mean) obtained under real-life routine conditions (i.e., obtained each day from the quality-control sample (blank plasma spiked with 30 ng/ml of the drug) located in the middle of the routine run of the day, which typically consisted of at least 30 samples plus four calibration samples, was 30% for amitriptyline and 22% for nortriptyline (n=102).

Statistics

For the purposes of serum analysis, all subjects receiving 25-mg doses were pooled regardless of the duration of their infusion. Plasma levels of amitriptyline and nortriptyline were compared between dose arms over time, assuming compound symmetry covariance structure. Post hoc comparisons were performed with a Tukey-Kramer adjustment. QTc differences from baseline to 1 hour were compared with paired t tests. VASs at admission to and discharge from the PACU and the difference between the total use of intravenous diclofenac between treatment arms were compared with use of Kruskal-Wallis tests.

Results

Eight women and 15 men were studied, all of them white (total N=23, placebo=5, 25 mg=10, 50 mg=5, 100 mg=3). Their mean age was 53 ± 14.6 years and weight was 68 ± 7 kg. The mean age and weight of subjects in the different drug arms did not differ when tested with ANOVA. The intraoperative use of fentanyl was comparable among all groups analyzed, i.e., 405.0 ± 195.0 μ g, 337.5 ± 42.7 μ g, 410.0 ± 48.5 μ g, and 333.3 ± 88.2 μ g for the placebo, 25 mg, 50 mg, and 100 mg amitriptyline groups, respectively.

Adverse effects were dose-dependent (Table 1): one patient in the 25-mg group reported dry mouth and drowsiness. In the 50-mg group, the only adverse effect mentioned by one patient was dizziness. In the group that received a 100-mg infusion of amitriptyline, the first patient showed agitation and the second patient reported dry mouth, drowsiness, and difficulty speaking. The third patient in this group developed severe bradycardia (heart rate 30/min). Because of these safety concerns, we abandoned the 100-mg dosage and terminated this arm of the study.

Serum levels of amitriptyline at predetermined time points before and after the infusion are shown in fig. 1. The toxic range of amitriptyline commences at 500 ng/ml.²⁵ serum levels never came close to that value. The mean concentration of amitriptyline decreased steadily over 5 hours except for a slight increase from 20 min to 1 hour in the group that received the 100-mg infusion.

As expected, the serum levels of nortriptyline, the metabolite of amitriptyline, increased in the reverse order of those of amitriptyline (fig. 2) but were well below the published toxic levels (> 500 ng/ml).²⁵

ECG monitoring revealed a minimal decrease from baseline of QTc in the 25- and 50-mg groups and a moderate increase (~6%) in the 100-mg group at 1 hour after the start of the

infusion (fig. 3). This time point was chosen because it coincided with the end of infusion and showed the greatest changes, albeit not clinically significant, from the baseline value.

VASs at PACU admission and discharge were assessed with Kruskal-Wallis tests. An overall difference in pain at admittance was observed between groups ($p=0.015$), while no difference in pain at discharge was found. Bonferroni-adjusted pair-wise Wilcoxon rank sum post hoc comparisons showed that patients receiving 50 mg of amitriptyline reported significantly lower mean VAS pain scores at admittance (4.1) than did patients receiving 25 mg (8.7) (adjusted p -value=0.047) but not placebo (6.6). No significant differences in usage of intravenous piritramide during the time in the PACU were found between drug arms, although there was a trend for the 50-mg group to require less opioid (19.0 ± 5.7 mg, 16.2 ± 2.0 mg, and 7.5 ± 3.0 mg for the placebo, 25-mg, and 50-mg groups, respectively, $p=0.125$ for 50 mg amitriptyline vs. placebo).

Discussion

In this small sample, preoperative intravenous infusion of amitriptyline did not create major side effects at a dose of 25 and 50 mg as assessed by QTc interval, adverse-effects monitoring, and measurements of plasma levels of amitriptyline and nortriptyline. The 100-mg dose of amitriptyline had to be discontinued because of one serious cardiac event (bradycardia). As subjects in the 25-50 mg group did not have any significant adverse outcomes beyond dry mouth and drowsiness, or dizziness, this dosage appears to be safe for performing a phase IB clinical trial in a rigorous safety/research environment.

Intravenous administration of amitriptyline has been used widely for decades in Europe for depression and given in relatively high dosages (75 mg as an infusion twice a day for 14 days) without major incidents.¹¹ However, no phase IA study, the obligatory first step for FDA approval of an intravenous application, has ever been published.

In general, arrhythmia is the most feared side effect of amitriptyline overdose. However, arrhythmia appears to be a relatively late symptom, and the level of consciousness appears to be the most sensitive clinical predictor of serious complications, as published in case reports of amitriptyline poisoning.³² In our study, the QTc interval was not significantly prolonged even in the cohort that received the 100-mg amitriptyline infusion, suggesting that other adverse cardiac reactions (such as the bradycardia in our patient) could also be indicators of pending cardiac arrest. This finding is in agreement with an informational database (<http://www.torsades.org>) stating that amitriptyline belongs to a group of “drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QT prolonging drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).”

Similarly, the plasma concentration of tricyclic drugs had, at best, moderate sensitivity and specificity for predicting complications.³² This result is in agreement with the mean amitriptyline plasma level of the 100-mg cohort, which, despite being clearly in the nontoxic range, produced one severe adverse effect. The impact of preoperative amitriptyline infusion on postoperative pain scores and the need for pain medications was inconclusive. Even though we found significantly less pain in the 50-mg group at admission to the PACU, this finding did not persist during their stay. We were unable to detect a significant difference in improvements in pain measurements during their time in the PACU in any of the amitriptyline groups; no differences were found in VAS scores over time ($p > 0.05$ with Dunnett's adjustment). Similarly, no significant difference was found in piritramide usage, but the trend

was positive, toward the use of less piritramide in the 50-mg group. This may be due to the low power of the study and the change in protocol, which effectively reduced the sample size even further. Nevertheless, the difference in pain scores at admittance in the 50-mg group and the positive trend in opioid usage suggest that there is a signal present worth further investigation. Clearly, a larger-scale study focusing on a more rigorous evaluation of pain is needed before we can draw any conclusions. The intravenous perioperative application of lidocaine has been shown to decrease postoperative pain. For example, in patients undergoing prostatectomy, intraoperative systemic administration of lidocaine (bolus 1.5 mg/kg/h followed by an intravenous infusion of 3 mg/min) has been shown to reduce pain scores postoperatively by more than 50% for several days.¹⁶ Similarly, lidocaine (bolus injection of 1.5 mg/kg in 10 min followed by an infusion of 1.5 mg/kg/h) decreased postoperative pain and morphine consumption after major abdominal surgery.²³ In a randomized double-blind, active-placebo-controlled, crossover trial, an intravenous bolus of lidocaine (1 mg/kg) followed by an intravenous infusion (4 mg/kg/h) also demonstrated an analgesic effect of intravenous lidocaine on postamputation stump pain.³⁶

The mechanism underlying this prolonged analgesic action may be related to the inflammation-modulating properties of local anesthetics (LAs); similarly, high-dose steroids can contribute to analgesia.^{7;12} Systemic LAs prevent the development of inflammation-mediated hyperalgesia, which may be explained in part by the action of LAs on neutrophils. It has been shown that LAs at very low concentrations inhibit neutrophil priming without interfering with their activation, thereby preventing their hyperactivation.¹⁹ Hence, intravenous administration of LAs provides pain relief that greatly exceeds the duration of action of the drug itself, possibly by preventing inflammatory responses to tissue injury. In addition, LAs prevent the release of cytokines.^{6;10} As amitriptyline at extremely low concentrations is ~10 times more potent as a blocker of Na⁺ channels in the open-channel state than is lidocaine and has anti-inflammatory properties,^{1;18;19;31;35} a one-time infusion of amitriptyline before surgery might be more useful than a perioperative infusion of lidocaine for both pre-emptive analgesia and prevention of neuropathic pain. Nevertheless, a randomized controlled trial of TCAs and morphine found that desipramine (but not amitriptyline), given for 1 week prior to surgery, followed by a single postoperative dose of morphine, increased and prolonged morphine analgesia alone.²⁴ However, the lack of efficacy in the amitriptyline group may have been due to the overall relatively low amitriptyline dosages used.

One limitation of this trial was that it was not randomized, and the use of escalating doses may lead to skewed baseline pain effects in the various groups; on the other hand, the focus of this study was on safety. Similarly, the small size of the placebo and 50-mg groups (n=5) does not allow any conclusion regarding a potential decrease in pain. However, the secondary goal was to screen for a potential decrease in postoperative pain in order to perform a power calculation for a future phase IB trial.

In summary, a single preoperative infusion of amitriptyline at dosages of 25 and 50 mg over 1 hour appeared to be safe in this small cohort of subjects. However, since one patient in the 100-mg amitriptyline group had a severe cardiac event, we conclude that a phase IB trial comparing the efficacy of placebo versus amitriptyline should be performed with a dosage of amitriptyline no greater than 50 mg when infused over 1 hour and only under stringent safety monitoring.

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Fig 1.

Plasma levels of amitriptyline after 1-hour infusions of 25, 50, and 100 mg (n=5 per group) or 2-hour infusion of 25 mg (n=5). Even after infusion of the high 100-mg dose and with the relatively rapid infusion over 1 hour, serum levels were well below toxic levels (the toxic range of amitriptyline commences at 500 ng/ml). Significant differences ($p < 0.05$) in plasma amitriptyline levels were seen at all time points. Dunn's post hoc comparison was used to identify which doses resulted in serum levels of amitriptyline different from the control condition; at baseline, 20 minutes, 1 hour, and 3 hours, 50-mg and 100-mg dose groups differed from controls; at 5 hours, only the 100-mg group differed from controls ($p < 0.05$).

Fig 2.

Plasma levels of nortriptyline, the metabolite of amitriptyline. As with amitriptyline, nortriptyline did not reach toxic levels (the toxic range of nortriptyline commences at 500 ng/ml). Levels of nortriptyline showed significant differences from baseline at 1, 3, and 5 hours ($p < 0.05$).

Fig 3.
Percentage change in QTc, the corrected QT interval, at the end of the 1-hour infusion, compared with baseline (immediately before start of the infusion).

Table 1**Symptom checklist and reported side effects**

Side Effect	Number of patients (group)*
fast or slow heartbeat	
facial flushing	
eye irritation	
dry mouth	One (25 mg), one (100 mg)
abdominal pain	
nausea	
vomiting	
diarrhea	
forgetfulness	
anxiety	
difficulty balancing	
confusion	
headache	
dizziness	One (50 mg)
depression or euphoria	
difficulty speaking	One (100 mg)
abnormal thinking	
ringing in the ears	
drowsiness	One (25 mg), one (100 mg)
upset stomach	
abnormal sweating	
heartburn	
sneezing	
itching	
weakness	

* Not included in the checklist are one patient in the 100-mg amitriptyline group who showed agitation and one patient in the same group with severe bradycardia (heart rate 30/min), leading to termination of this study arm.