Topical Amitriptyline and Ketamine in Neuropathic Pain Syndromes: An Open-Label Study

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Abstract: **Twenty eight subjects with refractory, moderate to severe peripheral neuropathic pain participated in an open label prospective trial examining perceived analgesic effect, patient satisfaction, and safety of topical amitriptyline 2%/ketamine 1% cream. Outcome measures included an 11-point numerical rating scale for pain intensity (NRS-PI), a 5-point satisfaction scale, blood chemistry screen, drug and metabolite levels, urinalyses, electrocardiogram (ECG), and physical examination. Adverse events were monitored. Twenty-one subjects completed the trial. At 6 months, subjects reported an average long-term reduction in pain of 34% (standard deviation [SD] = 37%); 5 subjects (25%) achieved 50% or greater reduction in pain and 1 subject (5%) achieved 100% reduction in pain. At 12 months, the average reduction in pain was 37% (SD = 40%); 7 subjects (40%) achieved 50% or greater pain reduction. At the end of the study, 89% of subjects rated their satisfaction as 3/5 or greater and 2 subjects (10%) were pain free. Minimal adverse events were reported and there were no serious medication related adverse events. Blood levels revealed minimal systemic absorption. In conclusion, topical 2% amitriptyline/ 1% ketamine cream was associated with long-term reduction (6-12 months) in perceived pain, moderate to complete satisfaction, and was well tolerated in treatment of neuropathic pain. There was no significant systemic absorption of amitriptyline or ketamine.**

Perspective: ***This study demonstrates that topical 2% amitriptyline/1% ketamine, given over 6-12 months, is associated with long-term perceived analgesic effectiveness in treatment of neuropathic pain. Antidepressants and ketamine both produce multiple pharmacologic effects that may contribute to peripheral analgesia; such actions include block of peripheral N-methyl-D-aspartate receptors, local anesthetic properties, and interactions with adenosine systems.***

Key words: *Neuropathic pain, topical amitriptyline and ketamine, clinical trial.*

The involvement of peripheral mechanisms in the generation of neuropathic pain suggests that the use of topical approaches may be a useful treatment strategy.[1,2] Controlled clinical trials have demonstrated efficacy for topical capsaicin,[10,15] local anaesthetics,[3,4,11] and doxepin[8,9] in the treatment of neuropathic pain. In a previous pilot trial, we examined the analgesic effects of a topical cream containing 1% amitriptyline/ 0.5% ketamine.[6] Although there was no acute treatment effect during the 2-day placebo controlled part of the trial, in 11 patients who took part in the 7-day open phase of the trial, there was a significant analgesic effect from day 3 to day 7 of treatment. The goal of this open-label prospective study was to assess perceived effectiveness, patient satisfaction, and tolerability of a higher-dose combination cream (2% amitriptyline/1% ketamine) over a longer period of time (6-12 months) in a mixed group of patients with neuropathic pain due to diabetic neuropathy, postherpetic neuralgia, or post-surgical/post-traumatic pain. A mixed group was chosen for study because this group most closely resembles the population we see in the pain clinic. In addition, this is the same group used in previous trials examining topical tricyclic antidepressants.[9,10]

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Materials and Methods

Participants

Study subjects were recruited from a tertiary care pain clinic (Pain Management Unit, Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia). Subjects had previously completed a randomized controlled trial with the same topical cream.[7] Subjects from that trial who were interested in participating in the current trial and who

had not experienced an adverse event were eligible for the current trial. Inclusion criteria were: 1) nonpregnant adults with a neuropathic pain diagnosis of postherpetic neuralgia, diabetic neuropathy, or postsurgical/posttraumatic neuropathic pain; 2) presence of moderate to severe pain all or most of the time despite other treatment modalities; 3) pain that has persisted for 3 months or longer; 4) presence of dynamic tactile allodynia or pinprick hyperalgesia in the area of pain; and 5) normal cognitive and communicative ability as judged by clinical assessment and completion of self-report questionnaires. Exclusion criteria were: 1) evidence of another type of pain as severe as the pain under study; 2) evidence of another type of neuropathic pain not included in this study; 3) a major depression requiring treatment; 4) an allergy to ketamine or amitriptyline; or 5) concomitant use of a monoamine oxidase inhibitor. Subjects were permitted to continue using previous oral analgesics including nonsteroidal antiinflammatory drugs, opioids, antidepressants (including amitriptyline and other tricyclics), and anticonvulsants.

Study subjects were examined by physician specialists in pain management who confirmed the diagnostic subcategory of neuropathic pain and completed the physical and sensory examination. It was also ascertained that subjects did not have any other medical condition that would affect their ability to safely take part in the study. All those who met the criteria listed above, and who provided written informed consent, were included. The study was approved by the research ethics review committee at the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia.

Procedure

The study treatment consisted of a topical cream containing a combination of 2% amitriptyline/1% ketamine. The vehicle consisted of a moisturizing creamlike base, consisting of an oil water emulsion system containing standard compendial emollients. The cream base used to formulate the topical delivery formulation is proprietary and in development, and was formulated to enhance delivery of compounds. Subjects were instructed to clean the area and then apply 4 mL of cream to the site of maximum pain (size of the area of pain varied) 3 times per day. Subjects returned to the study site every 2 months subsequent to initiation of treatment, at which time pain levels and satisfaction were documented using the measures described below, vital signs were recorded, and blood and urine samples were done. A full physical examination was completed pretreatment and at the completion of the study.

Outcomes

Spontaneous Pain

The measure of spontaneous pain consisted of an 11-point numerical rating scale for pain intensity (NRS-PI) with the anchors "no pain" and "severe pain." Patients were asked by the nurse to grade the severity of their pain over the past 24 hours.

Subject Satisfaction

A 5-point numerical rating scale for satisfaction with the treatment was used to assess how satisfied subjects were with the cream. Subjects were asked by the study nurse to rate their satisfaction with the topical cream since the last visit on a 1 to 5 point scale: (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent).

Laboratory Measures and Physical Assessment

Routine blood screens for hematology (complete blood count [CBC] and differential) and blood chemistry (hepatic and renal function, glucose, electrolytes) were done at the start and end of the study and every 2 months during the study, along with vital signs and a urinalysis. A full physical examination and electrocardiogram (ECG) were performed at the start and finish of the study.

Measurement of Serum Levels

Amitriptyline was measured by reverse phase high-performance liquid chromatography with ultraviolet (UV) detection.[2] The lower limit of detection was 15.7 ng/mL for amitriptyline and nortriptyline. Ketamine and norketamine levels were determined by liquid chromatography/mass spectrometry; this method was validated in human serum for a range of 5 to 5000 ng/mL for ketamine and 2.5 to 2500 ng/mL for norketamine. (The ketamine analysis is an internally validated method at PPD Pharmaco Labs and was performed under GLP conditions.) Blood was collected for drug levels every 2 months during treatment and at the end of treatment. For subjects taking oral amitriptyline, pretreatment serum amitriptyline levels were performed prior to initiation of treatment.

Adverse Events

Adverse events were monitored, recorded, and reported according to ICH-GCP guidelines.

Results

Twenty-eight subjects participated in the study. During the study, 7 subjects withdrew. Reasons for withdrawal included: adverse events (4), lack of efficacy (2), and protocol violation (1). In total, 21 subjects completed the study (18 of whom used the cream for 12 months, 3 for 6 months). (The reason for the shorter duration in the last 3 patients is that the manufacturer stopped supplying this concentration of cream.) The characteristics of the study population are presented in Table 1. Details regarding the 7 subjects who did not complete the study are presented in Table 2.

Perceived Effectiveness and Patient Satisfaction With Treatment

At the end of 6 months, subjects reported average long-term reduction in pain of 34% (SD = 37%); 5 subjects (25%) achieved 50% or greater reduction in pain,

Table 1. Demographic Characteristics and Baseline Pain Scores of Subjects in the Different Diagnostic Categories Who Completed the Trial

	Diabetic Neuropathy	*Postherpetic Neuralgia*	*Postsurgical/ Posttraumatic*
n	3	2	16
Men	3	2	5
Women	0	0	11
Mean duration of pain (yrs)	6.8	11.7	7.2
Location of pain			
Face/head	0	1	4
Extremity	3	0	5
Trunk	0	1	7
Baseline* pain severity mean (SD)	7.3 (.57)	6.5 (2.12)	6.4 (2.02)

*There was no significant difference between groups in baseline pain.

and 1 subject (5%) achieved 100% reduction in pain (Table 3). At the end of 12 months the average pain reduction was 37% (SD = 40%); 7 subjects (40%) achieved 50% or greater reduction in pain and 2 (11%) achieved 100% reduction in pain, which they attributed to the cream, and were pain free by the end of the study. The majority of subjects (89%) rated their satisfaction as 3/5 or greater (good – excellent) (Table 3). Five subjects (24%) were able to decrease or discontinue oral analgesics (including opioids) due to the decreased pain they attributed to the use of the topical cream (Table 4).

Dose of Cream

Subjects were instructed to use the cream at a dose of 4 mL 3 times per day (tid); however, there was flexibility in that they were permitted to use less. The details of doses used were as follows: 6 subjects continued to use the cream 3 times a day throughout the study, 5 used 3 mL tid, 2 used 2.5 mL tid, 6 used 2 mL tid, 2 used 1.5 mL tid, 3 used 1 mL tid, and 1 used less than 1 mL tid; 2 patients changed their dose during the study, 1 from 4

Table 2. Data Regarding the 7 subjects Who Did Not Complete the Trial, Reasons for Noncompletion and Bloodwork

Subject No.	*Weeks to Exit*	*Reason*	*Amitriptyline ng/mL (Nortriptyline) Pretreatment/ Subsequent Visits*	*Ketamine ng/mL (Norketamine) Pretreatment/ Subsequent Visits*
001*	36	Lack of effect	**24**/17/45/11/0/0 (**20**/0/41/0/0/0)	**0**/0/0/0/360/0 (0/0/0/0/0/0)
003*	1	Itchy rash	**0** **(78)**	**0** **(0)**
011	31	Alcoholic relapse	**0**/23/13/17/0 (**0**/0/0/0/0)	**0**/33/0/26/0 (**0**/0/0/0/0)
013*	18	Lack of effect	**16**/15/19 (**11**/14/15)	**0**/0/0 (**0**/0/0)
017	0	Never started treatment, cream inconvenient with outdoor clothing	**0** **(0)**	**0** **(0)**
024	3	Drowsy	**16**/0† (**0**/0)	**0** **(0)**
028	16	Weight gain fatigue dry mouth	**0**/0/0 (**0**/0/0)	**0**/0/0 (**0**/0/0)

NOTE: 0 = none detected.

*Patients on oral amitriptyline concurrently.

†Patient not on oral amitriptyline, appears to be a false positive value.

Table 3. NRS-PI and Satisfaction Scores for Subjects Who Completed the Study

	n	*NRS-PI Mean (SD)*	*Percentage Reduction in Pain*	*Satisfaction Mean (SD)*	*Percentage Reporting Satisfaction 3/5 or Greater*
Pretreatment	21	6.57 (1.8)			
2 mos	21	4.09 (2.46)	38%	3.33 (.85)	86%
4 mos	21	4.42 (2.46)	35%	3.61 (.92)	77%
6 mos	21	4.33 (2.35)	34%	3.61 (.92)	91%
8 mos	18	3.83 (2.28)	43%	3.61 (.97)	84%
10 mos	18	3.94 (2.90)	46%	3.50 (.98)	89%
12 mos	18	4.33 (2.89)	37%	3.61 (.91)	89%

Abbreviation: NRS-PI, numerical pain rating scale-pain intensity.

NOTE: Satisfaction scale; 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent.

Table 4. Subject Characteristics and Case Comments Regarding All Subjects Who Entered the Trial

Subject No.	Age	Sex	Diagnosis	Evoked Sensory Findings	Number of Concurrent Medications*	Comments from Case Notes
001 (NC)	59	M	DN	O	4	Reported decreased pain at first, but by 8 mos lost effect and patient withdrew
002	56	F	PSTN	A, H, O	2	Pain, stamina, activity all improved, able to wear dress shoes, able to get back to work part time, allodynia resolved
003 (NC)	47	M	PSTN	O	2	Developed rash and withdrew after 1 wk
004	60	M	PSTN	A, H, O	0	Excellent pain relief, able to do physical activities had not been able to do "for years"
005	56	F	PSTN	H, O	3	Overall benefit, able to discontinue muscle relaxant
006	51	M	PSTN	H, O	3	Pain improved with the cream, patient was able to return to work
007	58	M	DN	A, H, O	1	Pain improved, able to walk and stand for longer, able to discontinue Tylenol #3, decrease in severity of allodynia
008	67	M	PSTN	A, H	4	Improvement in surface pain and sensitivity, able to shave again, decrease in allodynia and hyperalgesia
009	33	F	PSTN	A, H, O	2	Decrease in pain and decrease in severity of allodynia
010	76	M	DN	A, H, O	2	Pain improved, able to pursue outdoor activities with greater ease, states "I don't know what I will do without it" (the cream), able to decrease hydromorphone
011 (NC)	52	M	PSTN	H	1	Pain improved with cream but patient had to be withdrawn from study due to alcoholic relapse with elevated liver enzymes resolving rash as well.
012	53	F	PSTN	H	4	Pain much improved, down to 2/10, hyperalgesia also improved, able to do more without worrying about feet, able to discontinue NSAID and Tylenol #3, decreased Tylenol #1 and Tylenol
013 (NC)	56	F	PSTN	A, H	3	Patient withdrew at 18 weeks due to lack of effectiveness
014	47	M	PHN	A, O	1	Dramatic decrease in pain 9/10 down to 2/10, resolution of allodynia
015	84	M	PHN	A, H	3	Much improved, able to discontinue gabapentin
016	54	F	PSTN	A, H	2	Temporary improvement
017 (NC)	46	M	PSTN	A, H	0	Patient never ended up using the cream, said inconvenient with outdoor clothing, withdrew
018	25	F	PSTN	A, H	1	Pain decreased "a lot," allodynia and hyperalgesia also decreased, now able to wear flip-flops, unable to tolerate these before cream
019	45	F	PSTN	A, H, O	0	Patient reports pain as much better, especially appreciates no side effects
020	40	F	PSTN	A, H	0	Pain and allodynia resolved, patient reported no pain
021	47	F	PSTN	A, H	0	Surface pain and sensitivity improved, clothing more tolerable
022	48	F	PSTN	A, H, O	2	Patient reported cream helped, also had DCSI inserted during the trial which brought significant benefit, but wanted to continue cream, returned to work, discontinued hydromorphone
023	39	M	PSTN	A, O	1	Cream most helpful with surface pain and sensitivity, able to shave more easily
024 (NC)	48	F	PSTN	H	1	Patient reported fatigue and decided to withdraw from the study at 3 weeks, no amitriptyline, ketamine, or metabolites detected on bloodwork
025	54	M	DN	O	1	Helped "a little"
026	34	F	PSTN	A, H	1	Patient noted significant decrease in dysesthetic pruritic foot pain (a part of her pain) that gave her an overall feeling of better pain control
027	35	M	PSTN	A, H, O	2	Patient reports cream helps with his facial pain
028 (NC)	31	F	PSTN	A, H	2	Cream helped with sensitivity at first but then noted fatigue, dry mouth, and weight gain so withdrew at 16 weeks, no amitriptyline or ketamine detected on bloodwork

Abbreviations: A, allodynia; H, hyperalgesia; O, hypoesthesia.

NOTE: NC indicates noncompleter for reasons indicated in Table 2.

*Concurrent medications included oral antidepressants, anticonvulsants, nonsteroidal anti- inflammatories and opioids.

Table 5. Drug Levels in 7 Completers with Detectable Amitriptyline or Nortriptyline levels

Subject No.	Dose of Oral Amitriptyline (AMI) or Nortriptyline (NTI) mg/day	AMI Level ng/mL (NTI Level ng/mL) Pretreatment/Subsequent Levels	Possible Treatment Related Adverse Event
002	10 AMI/10 NTI	**15**/0/14/0/0/15/0 (**0**/0/0/0/0/0/0)	None
004	None	**0**/13*/0/0/0/0/0 (**0**/0/0/0/0/0/0)	Occasional drowsiness and dry mouth
006	50–75 NTI	**0**/0/0/0/0/0/0 (**29**/64/57/70/97/56/130)	None
009	50–125 AMI	**26**/19/22/28/15/39/35 (**45**/31/28/39/30/60/67)	Occasional sensation of increased heart rate
015	25 AMI	**22**/40/58/56/27/0 (**19**/32/47/34/18/0)	Occasional heart papitations
022	None	**0**/12/11/0/23/14/13* (**0**/0/0/0/0/0/0)	None
025	75–175	**63**/120/98/0 (**18**/38/45/0)	None

mL tid to 6 mL twice daily (bid) at 17 weeks, the other from 3 mL tid to 3 mL tid at 30 weeks.

Adverse Events

Of 21 subjects who completed the study, 3 experienced adverse events judged to be possibly related to the study drug. One subject reported intermittent drowsiness and dry mouth but wanted to continue on the cream (blood levels revealed detectable amitriptyline 30 ng/mL at visit 2, but none was detectable at other visits), 1 further subject reported intermittent sensations of rapid heart rate, and another reported intermittent palpitations (both of these patients were also taking oral amitriptyline and blood levels taken throughout the study revealed minimal changes) (Table 5). There were no clinically significant abnormalities on patient ECG or vital signs. Physical examination at the exit visit revealed no medication-related adverse events. Two subjects exhibited abnormalities on laboratory studies; 1 exhibited transient elevation in total bilirubin and lactate dehydrogenase (LDH) at visit 4 that resolved and did not recur, and 1 exhibited a low blood sugar on 2 occasions. None of these events was judged to be related to the study drug. It should be noted, however, that only subjects who had not developed adverse events in a previous randomized controlled trial were included in the current trial and there were still 4 withdrawals due to adverse events.

Serum Drug Levels

In the 21 subjects who completed the trial, there was no detectable ketamine or norketamine. In 14 subjects, there was no amitriptyline or nortriptyline detected. Five of the 7 subjects exhibiting detectable blood amitriptyline or nortriptyline were taking oral amitriptyline concurrently; details appear in Table 5. Overall, there was no significant systemic absorption of amitriptyline or ketamine.

Discussion

Randomized controlled trials have demonstrated that topical doxepin produces analgesia in a mixed group of patients with neuropathic pain[8,9] and that topical amitriptyline 4% in combination with ketamine 2% exhibits a significant analgesic effect in patients with postherpetic neuralgia.[5] A lower-dose cream containing 2% amitriptyline and 1% ketamine did not exhibit a statistically significant analgesic effect in a randomized controlled trial of patients with mixed diagnoses of neuropathic pain[7]; however, post hoc analyses identified that the lower dose amitriptyline/ketamine cream may be analgesic in a subgroup of subjects with mixed neuropathic pain.[14] There are also case reports that topical ketamine provides analgesia in certain instances of neuropathic pain.[1,16]

The present open-label study extends previous literature by demonstrating that the long-term use (ie, up to 12 months) of topical 2% amitriptyline/1% ketamine is associated with long-term perceived analgesic effectiveness and satisfaction for treatment of a mixed group of patients with neuropathic pain, with no significant systemic absorption and minimal adverse events. Prior to treatment, subjects reported moderate to severe pain that persisted in spite of previous or ongoing use of analgesics and were thus refractory to other treatments. The lack of significant systemic absorption supports a topical rather than a systemic effect. This study also indicates that topical delivery is associated with minimal side effects.

The mechanisms involved in peripheral analgesia in instances of neuropathic pain are unclear. Although the neurobiology of pain is altered in neuropathic pain conditions (and this leads to an altered systemic pharmacology), topical approaches have been shown to be of use in neuropathic pain.[13] Antidepressants and ketamine both exhibit peripheral analgesic properties in various preclinical models of pain, and produce multiple pharmacolog-

ical effects that may contribute to peripheral analgesia; such actions include block of peripheral N-methyl-D-aspartate receptors, local anesthetic properties, and interactions with adenosine systems.[12,13]

As with all open-label studies, the results of this study should be interpreted cautiously. While further randomized controlled trials are necessary to clearly identify analgesic efficacy of the low-dose amitriptyline/ketamine cream, the current trial along with the randomized placebo controlled trial regarding the higher-dose amitriptyline/ketamine cream[5] support the notion that topical amitriptyline/ketamine cream appears to be a reasonable treatment option in the treatment of neuropathic pain due to diabetic neuropathy, postherpetic neuralgia, and postsurgical/posttraumatic pain.

Conclusions

Topical 2% amitriptyline/ 1% ketamine cream was associated with long-term patient satisfaction and was well tolerated with minimal side effects in the treatment of chronic moderate to severe neuropathic pain in a group of 21 subjects in an open-label trial. Future controlled trials should be performed to further evaluate the role of topical amitriptyline and ketamine in the treatment of neuropathic pain.

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