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Development of a Sublingual/Oral Formulation of Ketamine for Use in Neuropathic Pain

Preliminary Findings from a Three-Way Randomized, Crossover Study

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Abstract

Background and objective: Enterally administered low-dose ketamine is being used increasingly to treat pain states. However, suitable oral or sublingual formulations are not available. The objective of the study was to develop a lozenge formulation of ketamine for use in patients with neuropathic pain, and to investigate its storage stability and bioavailability after oral or sublingual administration.

Methods: A lozenge containing 25 mg of ketamine was formulated and manufactured in a hospital pharmacy setting. Stability was assessed by high-performance liquid chromatography (HPLC) during storage at 25°C or 2–8°C for up to 14 weeks. Bioavailability after both oral and sublingual administration was evaluated in six patients with chronic neuropathic pain. Ketamine and its metabolite norketamine in plasma were measured by HPLC.

Results: The lozenge formulation was chemically stable for at least 14 weeks. Oral and sublingual bioavailabilities [median (interquartile range)] were 24% (17–27%) and 24% (19–49%), respectively. There was substantial metabolism to norketamine for both routes. The mean norketamine/ketamine area under the plasma concentration-time curve from baseline to 8 hours ratios were 5 and 2.1 after oral or sublingual administration, respectively.

Conclusion: The ketamine lozenge showed acceptable storage stability. Bioavailability was sufficiently high and reproducible to support its use in routine pain management. There was extensive first-pass conversion to norketamine. Efficacy studies are warranted to evaluate sublingual and oral administration of our new lozenge formulation of ketamine in patients with chronic pain states. Investigation of the role of the metabolite norketamine, which is also an

NMDA receptor antagonist, is particularly important because this may contribute significantly to clinical efficacy.

Background

Ketamine is an NMDA receptor antagonist with analgesic and dissociative anaesthetic properties that has been in use since 1965.[1] Low or subanaesthetic doses of ketamine have been used effectively as adjuvant analgesia, usually with an opioid.[2] Recent renewed interest in ketamine stems from reports of its efficacy in treatment of chronic pain states such as central pain, complex regional pain syndrome, fibromyalgia, and ischaemic and neuropathic pain.[3,4] Ketamine may also reduce opioid requirements in opioid-tolerant patients.[5-7] This opioid-sparing effect is observed in treatment of acute postoperative pain when ketamine is given intravenously or epidurally.[8]

Racemic ketamine is an equal mixture of two enantiomers, *R*-(−)-ketamine and *S*-(+)-ketamine, which have different anaesthetic and analgesic potencies. After administration of the racemate, the concentration-time profiles are similar. *S*-(+)-ketamine is four times more potent than *R*-(−)-ketamine in humans.[1] Its main mechanism of action is via blockade of NMDA receptors, although an agonist effect on opioid receptors may contribute.[1] The metabolism of ketamine is thought to be linear over dose ranges used for both analgesic and anaesthetic purposes.[9] Ketamine is rapidly metabolized by various cytochrome P450 isoforms,[10] and its main metabolite norketamine is formed primarily during first-pass metabolism.[9] Hence its concentrations (and effects) are dependent on the route of administration.

Previously, non-parenteral routes of administration of ketamine have not been favoured because of high first-pass metabolism. However, there are now reports of their use in treatment of chronic pain states.[11-13] The parenteral route of administration is also limited in its application because of the narrow therapeutic window of ketamine, and the expenses associated with preparation and administration. Given the expanding clinical applications of ketamine in acute and chronic pain states, more research into oral and transmucosal routes of applications is warranted.

The primary aims of the present study were to develop a simple lozenge formulation of ketamine that could be used in patients with neuropathic pain and to investigate its storage stability and bioavailability after oral or sublingual administration. Secondary aims were to examine the pharmacokinetics of ketamine and norketamine after oral or sublingual administration.

Patients and Methods

Formulation of Ketamine Lozenges

Lozenges (1 g final weight), each containing 25 mg ketamine, were manufactured in the Pharmacy Department, Royal Perth Hospital, Perth, Australia, according to the following formula: ketamine hydrochloride BP (2.5 g) [Jiangsu Hengrui Medicine Co. Ltd, Lianyungang Jiangsu, Peoples Republic of China], gelatin powder (25 g), glycerol BP (40 g), artificial sweetener (1 g), amaranth solution BP (1 mL), raspberry essence HC417 (1 mL) and purified water BP to 100 g. The lozenges were formed in a suppository mould, rolled in lactose and stored in batches at 2–8°C or 25°C. A preliminary experiment showed that the mean (± SD) sublingual dissolution time for the product was 10.4 ± 3.3 min.

Patients and Drug Administration

A three-way randomized, crossover study design approved by the Human Ethics Committee of the Royal Perth Hospital was used. Ten patients with neuropathic pain were recruited and provided written informed consent. Study exclusion criteria were: severe cardiovascular disease, heart failure, poorly controlled hypertension, recent myocardial infarction, history of cerebrovascular accidents or recent cerebral trauma, known hypersensitivity to ketamine, and difficult intravenous

access. Four patients did not complete the trial. One was discharged from hospital earlier than expected, and three withdrew after completing only one arm of the trial (one due to unpleasant sedation after the intravenous dose, one because of poor pain control and one for unspecified personal reasons).

Ketamine was administered orally (1 × 25 mg lozenge swallowed), sublingually (1 × 25 mg lozenge dissolved slowly in the mouth over at least 10 minutes) or intravenously (10 mg in 10 mL of a 1 mg/mL solution in normal saline over 60 seconds) according to a predetermined randomization schedule and with at least 1–2 days between each administration. Venous blood samples (4 mL heparinized) were collected from a suitably placed intravenous cannula (separate to that used for intravenous administration). Samples were taken just before drug administration and at 5, 10, 20 and 30 minutes and 1, 2, 3, 4, 6 and 8 hours after intravenous administration or at 15, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hours after oral or sublingual administration. There were some deviations from the intended collection times because of patient commitments to routine diagnostic/therapeutic procedures. Additional ketamine was not allowed during or in the 1–2 days before the next study period and pain control was maintained with alternative analgesics as required.

Chemicals and Reagents

Authentic ketamine hydrochloride (Lot 121K1350) and ephedrine were purchased from Sigma-Aldrich Fine Chemicals, St Louis, MO, USA. Norketamine (Lot 34697-63C) was obtained from Cerilliant™ Austin, TX, USA. All other chemicals were of analytical or high-performance liquid chromatography (HPLC) grade.

Measurement of Ketamine and Norketamine in Plasma by High-Performance Liquid Chromatography (HPLC)

Plasma (1 mL) was spiked with 100 ng of ephedrine (internal standard), alkalinized with 200 μL of 5 mol/L NaOH and extracted into dichloromethane : ethyl acetate (80 : 20). After centrifugation, the organic phase was back-extracted into 3 mL 0.1 mol/L HCl. The HCl phase was then alkalinized with NaOH, re-extracted into dichloromethane : ethyl acetate, evaporated to dryness at 45°C under nitrogen, and residues reconstituted in 100 μL of HPLC mobile phase prior to injection of aliquots onto the column. HPLC separations were performed on a Lichrospher™ RP Select B column (5 μm, 250 mm × 4 mm internal diameter; E. Merck GmbH, Darmstadt, Germany), with a mobile phase of 12% v/v acetonitrile in 20 mmol/L K_2HPO_4, 0.05% v/v triethylamine (pH 3) that was pumped at 1.3 mL/min. Analytes were detected at 210 nm. Quantification of chromatograms (peak height) was undertaken using Chemstation Software (version 9, Agilent Technology, Waldbronn, Germany). Intra- (n = 5) and interday (n = 25) relative SDs (RSDs) for both ketamine and norketamine, measured at 5 μg/L, 50 μg/L and 200 μg/L, ranged between 14.3% and 4.2%. The limit of quantitation for the assay was 2 μg/L for both analytes. Stability of ketamine and norketamine in both analytical standards and plasma has been demonstrated previously.[14,15]

Quality Control of Lozenges by HPLC

A single batch of lozenges was prepared for evaluation of product storage stability. Each lozenge containing 25 mg ketamine was diluted to 100 mL with the HPLC mobile phase. Two ketamine standards at 95% and 105% of assumed potency were prepared similarly. Aliquots (4 μL) of the test and standard solutions were assayed (in duplicate) by HPLC using the same column as for plasma, a mobile phase of 35% v/v methanol in 0.05 mol/L $NH_4H_2PO_4$ buffer containing 0.46% v/v triethylamine (pH 3) and pumped at 0.6 mL/min. Samples were quantified at 210 nm as above. Lozenges (two separate groups) were stored at monitored temperatures of 2–8°C or 25°C and, after dilution as above, assayed (in duplicate) for ketamine content on the day of preparation, and after 1, 2, 10 and 14 weeks (n = 7 at each time point). Both intra- and interday RSDs for the assay at the concentration of interest were <2.2% (n = 6).

Pharmacokinetic and Statistical Analysis

For the most part, plasma concentration-time data for ketamine and norketamine were analysed by non-compartmental methods to estimate terminal elimination rate constant (k_{el}), half-life ($t_{1/2}$), volume of distribution in the elimination phase ($V_z = CL/k_{el}$), where CL is clearance area under the plasma concentration-time curve from baseline to time x (AUC_8 or AUC_∞), and clearance ($CL = dose/AUC_\infty$).[16] For the oral and sublingual routes, the maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were calculated from the primary data where appropriate. The bioavailability of ketamine was calculated as:

$$AUC_8 \times dose_{intravenous}/AUC_{8intravenous} \times dose_{oral\ or\ sublingual}$$

Calculation of the extrapolated zero time concentration-axis intercept (C_0) for the intravenous ketamine dose was achieved by fitting a two-compartment model to the concentration-time data.[17] Unless otherwise specified, data are presented as mean (± SD or standard error [SE]) or median and interquartile range (IQR) as appropriate. Descriptive statistics including Kruskal-Wallis ANOVA or parametric ANOVA were used to examine pharmacokinetic and storage stability datasets, respectively (SigmaStat version 3.5, SPSS Inc., Chicago, IL, USA).

Results

The overall mean (± SD) content of the lozenges (N = 70) was 25.2 ± 0.8 mg. Repeated measures ANOVA showed that the ketamine content (mean ± SD for both temperatures combined, N = 14) did not change significantly during storage at either 2–8°C or 25°C for 1 (24.8 ± 1 mg), 2 (25.3 ± 0.5 mg), 10 (25.6 ± 0.9 mg) or 14 (25.2 ± 0.7 mg) weeks compared with the content on the day of preparation (25.3 ± 0.4 mg). The maximum SD variation of the mean content observed at either temperature was 4%.

The physical characteristics and the clinical and pathological descriptions of the patients are summarized in table I. The patients were also taking a range of other medications for pain relief and other conditions (details not shown). These co-therapies were kept as constant as possible across the period of study. The mean intravenous, oral and sublingual ketamine doses were 0.14 mg/kg, 0.34 mg/kg and 0.34 mg/kg, respectively. The plasma concentration-time profiles

Table I. Physical characteristics and clinical and pathological conditions of patients included in the study[a]

Patient no.	Age (y)	Weight (kg)	Sex	Hb (g/L)	WCC ($\times 10^6$/L)	Serum ALP (U/L)	Serum ALT (U/L)	Serum bilirubin (μmol/L)	Serum albumin (g/L)	CL_{CR} (mL/min)	Co-existing pathologies
1	40	73	F	110	2.2	75	47	6	47	115	SLE, Sjögren's syndrome, oesophageal dysmotility, recurrent DVT, hypercholesterolaemia, PVD
2	33	76	M	110	8.5	55	25	7	46	140	Chronic alcoholism, amputated arm
3	45	65	M	132	6.0	67	35	6	30	140	Chronic alcoholism, incomplete tetraplegia
4	66	85	M	113	8.5	110	11	4	31	140	Chronic alcoholism, anxiety, paraplegia
5	45	64	M	124	5.0	62	12	5	43	119	Chronic pancreatitis, chronic alcoholism
6	41	80	M	111	8.1	37	42	18	31	180	Multiple fractures

a Normal reference ranges are: Hb female 115–160 g/L, male 135–180 g/L; WCC 4–11 $\times 10^6$/L; serum ALP 35–135 U/L; serum ALT <40 U/L; serum bilirubin <20 μmol/L; serum albumin 35–50 g/L.

ALP = alkaline phosphatase; **CL_{CR}** = creatinine clearance; **DVT** = deep vein thrombosis; **F** = female; **Hb** = haemoglobin; **M** = male; **PVD** = peripheral vascular disease; **SLE** = systemic lupus erythematosus; **WCC** = white cell count.

for ketamine and norketamine for the three different routes of administration are shown in figure 1, and the corresponding pharmacokinetic descriptors in table II. Data for patient 6 for the sublingual route were unavailable due to a contaminating peak that interfered in the assay. After the intravenous dose, the median extrapolated C_0 in plasma was 202 μg/L. This value is likely to be somewhat overestimated since the dose was administered slowly over 1 minute. For norketamine after intravenous ketamine, the median C_{max} of 26 μg/L occurred at a median t_{max} of 20 minutes. The median C_{max} for oral ketamine was 21 μg/L at a t_{max} of 2 hours, while for sublingual ketamine the median C_{max} was 30 μg/L at a t_{max} of 0.5 hours. The median norketamine C_{max} after oral ketamine was 86 μg/L at a t_{max} of 1.5 hours, while for sublingual ketamine the median norketamine C_{max} was 74 μg/L at a median t_{max} of 1.8 hours.

For all routes, the median $t_{1/2}$ ranged from 5.1 to 5.6 hours for ketamine and from 3.9 to 6.4 hours for norketamine, and was similar across routes for both ketamine and norketamine, respectively. The median V_z for ketamine was 5 L/kg after intravenous administration, which was significantly lower than that for oral (24.5 L/kg; $p = 0.017$) or sublingual administration (19.7 L/kg; $p = 0.025$). The median apparent CL of ketamine after oral (3 L/h/kg) or sublingual (4 L/h/kg) administration was significantly (both $p < 0.05$) higher than the total CL for the intravenous route (0.9 L/h/kg).

Using dose-normalized AUC_8 data, the median bioavailabilities of ketamine after oral and sublingual administration were similar at 24% (17–27%) and 24% (19–49%), respectively. Following intravenous administration, the median dose-corrected AUC_8 for norketamine was similar to that for ketamine, while after oral and sublingual administration, norketamine contributed AUC values that were 5 and 2.1 times greater, respectively, than the corresponding data for ketamine.

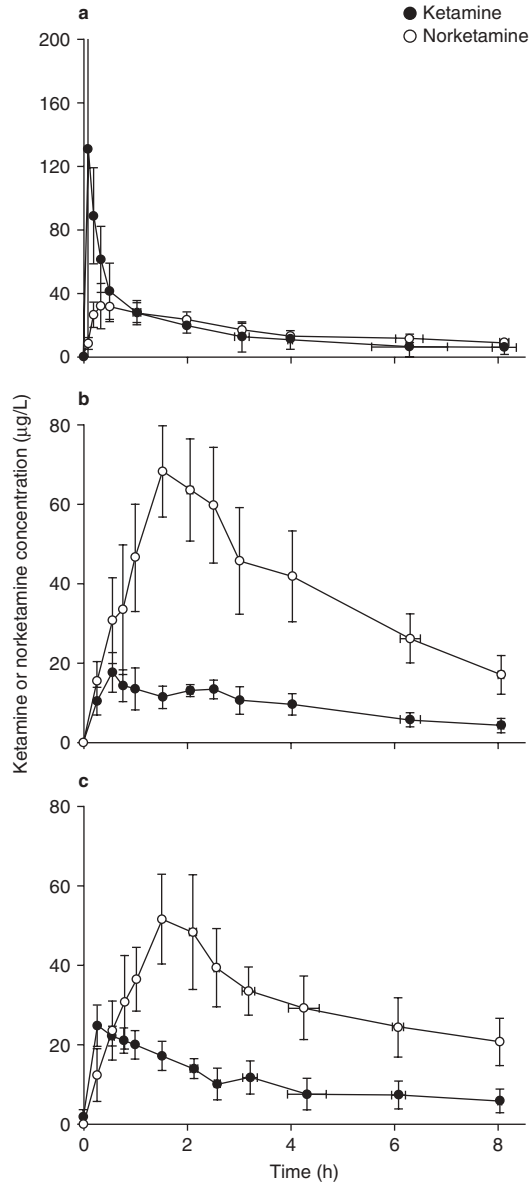

Fig. 1. Concentration-time plots (mean ± SE) for ketamine and norketamine after administration of ketamine to patients with chronic neuropathic pain: (**a**) 10 mg intravenously (n = 6); (**b**) 25 mg orally (n = 6); and (**c**) 25 mg sublingually (n = 5).

Discussion

The lozenges used in this study were developed for routine treatment in patients with severe neuropathic pain. The within-batch variation in active drug content was small and remained within 4% of stated and measured mean content

Table II. Pharmacokinetic parameters for ketamine and norketamine [data given as median (interquartile range)]

Parameter	Ketamine			Norketamine		
	intravenous	sublingual	oral	intravenous	sublingual	oral
$t_{1/2}$ (h)	5.2 (3.4–6.4)	5.1 (4.1–8.2)	5.6 (3.6–7.1)	5.5 (4.3–7.9)	6.4 (5.1–7.1)	3.9 (3.1–5.8)
V_z (L/kg)	5 (4–6)	19.7 (9.9–26.4)	24.5 (19–26)	NC	NC	NC
CL (L/h/kg)	0.9 (0.7–0.9)	4 (1–4.25)	3 (3–5)	NC	NC	NC
C_{max} (μg/L)	202 (123–344)[a]	30 (24–32)	21 (12–35)	26 (20–48)	74 (41–85)	86 (69–107)
t_{max} (h)	NA	0.5 (0.3–0.8)	2 (1.2–2.5)	0.33 (0.33–0.46)	1.8 (1.5–2)	1.5 (0.9–2.3)
AUC_8/dose (μg • h/L/mg)	13.3 (11–16)	4.2 (2.6–6.5)	2.5 (2.1–3.7)	11.2 (9.4–14)	8.8 (6.7–12.9)	12.7 (8.6–16)
Bioavailability (%)[b]	NA	24 (19–49)	24 (17–27)	NA	NA	NA

a Estimated C_0.

b From AUC_8 data.

AUC_8 = area under the plasma concentration-time curve from baseline to 8 hours; **C_0** = extrapolated zero time concentration-axis intercept; **CL** = clearance; **C_{max}** = maximum plasma concentration; **NA** = not applicable; **NC** = not calculated; **$t_{1/2}$** = half-life; **t_{max}** = time to reach C_{max}; **V_z** = volume of distribution in the elimination phase.

during up to 14 weeks' storage at either 2–8°C or 25°C.

The concentration-time profile for ketamine and its metabolite after sublingual and oral administration (figure 1) is also of interest in understanding the duration of analgesia. At our dose of 25 mg, C_{max} for ketamine was similar for both routes but t_{max} occurred earlier with sublingual administration (0.5 hours vs 2 hours for oral administration). The C_{max} of norketamine was higher but similar for both routes with a t_{max} of 1.8 hours for sublingual and 1.5 hours for oral administration. These profiles are generally consistent with data for a tablet formulation given by the same routes.[18]

The median $t_{1/2}$ of ketamine after intravenous administration in our study was 5.2 hours, with similar values for the oral and sublingual routes. This is somewhat longer than previous estimates of 2.1 hours[18] and 3.1 hours[9] in healthy volunteers, but close to that of 4.9 hours in intensive care patients.[19] This finding was unexpected as we anticipated that disposition in our patients with chronic neuropathic pain might be similar to that in healthy volunteers. Hence in planning our study, we decided to collect blood samples over an 8-hour period after drug administration, which would have allowed sampling over approximately $2–2.5 \times t_{1/2}$ in the elimination phase. In the final data analysis, $t_{1/2}$ values were generally calculated from the data collected between 3 and 8 hours after drug administration and hence these estimates, and the derived values for V_z and CL, may not be particularly robust. Despite this important limitation, median ketamine CL after intravenous administration (0.9 L/h/kg) was similar to that previously reported (1.1–1.2 L/h/kg) in healthy volunteers,[18] but lower than that for intensive care patients (2.2 L/h/kg).[19] As would be expected, we found that both apparent CL and V_z after oral or sublingual administration were markedly higher than the corresponding values after intravenous administration.

The primary aim of our study was to estimate the bioavailability of our ketamine lozenge formulation when administered orally or sublingually. In estimating bioavailability, we chose to use AUC_8 data as the mean percent extrapolated AUC after 8 hours was large (22% for intravenous, 30% for sublingual and 34% for oral administration). In addition, in our subjective clinical experience, 8 hours is also the maximum time for which patients seem to derive analgesic benefit after sublingual administration of ketamine. The mean bioavailability after sublingual administration was 24% but interpatient variability was high, whereas when the same lozenge formulation was given orally, the median bioavailability was also 24% but with lower interpatient variability. Yanagihara et al.[18] previously reported that the bioavailability of a 50 mg tablet

formulation of ketamine[20] in volunteers was 18% after oral and 30% after sublingual administration, while others have estimated a bioavailability of 17% for an oral solution of ketamine.[9] The lower bioavailability of ketamine after oral administration suggests increased first-pass metabolism compared with the sublingual route, as demonstrated by the mean norketamine/ketamine AUC_8 ratios of 5 and 2.1, respectively.

Previous human and animal studies have suggested that norketamine has important analgesic properties,[9,21-23] with about one-third of the anaesthetic potency of ketamine.[1] In phase 2 of a rat formalin test, spinal norketamine was approximately equipotent to ketamine in producing antinociceptive effects.[23] Norketamine has been shown to be a non-competitive NMDA receptor antagonist in the forebrain and spinal cord,[22,23] with the *S*-(+)-enantiomer having approximately eight times higher affinity than *R*-(−)-enantiomer in the forebrain.[22] In addition, *S*-(+)-norketamine was approximately four times more potent in the cortex than in the spinal cord, whilst *R*-(−)-norketamine was only twice as potent.[23] In the rat, *R*-(−) and *S*-(+)-norketamine metabolically formed from ketamine also distribute significantly into the CNS.[24] Hence it has been suggested that norketamine is an important contributor to the overall analgesic effect after administration of the racemate.[25] In our study, we analysed the racemate because we had limited analytical sensitivity as a result of the clinically effective analgesic doses that were chosen.

Conclusion

In the present study we have developed a stable lozenge formulation of ketamine that can be administered either sublingually or orally to patients. The bioavailability was similar to that previously reported for a tablet formulation. For both routes, norketamine accounted for a greater proportion (two to five times) of the AUC than ketamine, and given its pharmacological activity profile, is therefore likely to be a major contributor to the overall analgesic effect.

We conclude that formal studies of the analgesic efficacy of oral and/or sublingual ketamine in patients with neuropathic or other severe pain are required. If possible, it would also be of interest to investigate the analgesic activity of norketamine alone. With regard to the formulation, a formal study of the stability of the ketamine lozenges will also be required, involving storage of the lozenges under accelerated conditions (80% relative humidity and 40°C). Moreover, a validated stability-indicating assay should be used in which potential degradation products are quantified in addition to ketamine.

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