The absolute bioavailability of racemic ketamine from a novel sublingual formulation

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AIM
The principal study objective was to investigate the pharmacokinetic characteristics of a new sublingual ketamine wafer and to establish its absolute bioavailability and local tolerability.

METHODS
The study was of open label, two way randomized crossover design in eight healthy male volunteers. Each participant received either a single 10 mg intravenous dose as a constant rate 30 min infusion or a 25 mg sublingual dose of ketamine wafer in two treatment periods with a 7 day wash out. Pharmacokinetic blood sampling and local tolerability and safety assessments were carried out during 24 h following both dosing occasions. Plasma concentrations were analyzed by non-compartmental methods and local tolerability was assessed using modified Likert scales.

RESULTS
The median (90% CI lower, upper limit) absolute bioavailability of sublingual ketamine was 29% (27, 31%). The first quantifiable plasma ketamine concentration was observed within 5 min for all eight participants for both routes of administration and the median (min–max) time of the peak plasma concentration was 0.75 h (0.25–1.0 h) after sublingual administration. The ketamine wafer had very good local tolerability.

CONCLUSION
Sublingual administration of the ketamine wafer resulted in rapid absorption. The ketamine wafer has comparable bioavailability with other oral transmucosal formulations of ketamine but with markedly reduced inter-subject variability, warranting further evaluation as an analgesic adjunct.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Ketamine is used as an analgesic adjuvant. Non-injected formulations such as via the oral or sublingual routes have low and variable bioavailability which require care and titration in use.

WHAT THIS STUDY ADDS
• A novel formulation of sublingual ketamine has been developed, which applies the drug in the sublingual space for a few minutes. Bioavailability was comparable with other non-injected formulations but with considerably lower inter-subject variability which makes it attractive for further clinical development.
Introduction

Ketamine is a general anaesthetic licensed for use by the intravenous (i.v.) route and has been in clinical practice for over four decades. In recent years there has been increasing interest in its use at non-anaesthetic low doses as an adjunct in acute and chronic pain management [1–5]. Its pain modifying properties are attributed to its antagonism at N-methyl-D-aspartate (NMDA) receptors, binding non-competitively to the phencyclidine binding site [6, 7]. When administered at sub-anaesthetic doses ketamine is effective at producing analgesia and also demonstrates some opioid sparing activity, although the mechanisms behind this remain poorly understood [8]. Ketamine’s analgesic efficacy correlates well with its inhibition of NMDA receptor-mediated pain facilitation and a decrease in activity of brain structures that respond to noxious stimuli [9]. Therefore its utility in the management of acute pain is of interest [10–12].

The licensed formulation of ketamine is a racemic mixture of two enantiomers R-(–) and S-(+) of which the S-(+) enantiomer is four times more potent than the R-(–) enantiomer in humans when administered via the parenteral route [13–16]. Metabolism after parenteral administration is extensive and rapid, and is mediated by various isoforms of cytochrome P450, specifically CYP3A4 and CYP2B6 [17, 18]. Norketamine, a major metabolite, also has NMDA antagonist properties, although due to differences in potency and pharmacokinetics, it plays a minor role in overall drug action when ketamine is administered by the i.v. route but not necessarily by the oral route [19, 20].

Because of high hepatic first pass metabolism, oral formulations of ketamine have low bioavailability with higher norketamine/ketamine plasma area under the curve (AUC) ratios than after i.v. administration [20, 21]. When administered sublingually (SL) as a liquid formulation or as a tablet, the AUCs were comparable [21] or about 50% higher [20] than after oral administration, suggesting that the SL formulations were largely swallowed. Recently, a novel rapidly dissolving SL wafer formulation has been developed. By releasing the drug in a small volume immediately adjacent to the mucosal membranes, there is the possibility of significant direct SL absorption with higher bioavailability than other oral formulations. The primary aim of this study was to assess the absolute bioavailability of a single 25 mg SL dose of racemic ketamine administered as a wafer formulation to healthy male volunteers. A formulation that does not require i.v. administration may be of use as an adjunct in both acute and chronic pain management. The pharmacokinetic characteristics and local tolerability of the novel wafer formulation were also assessed.

Methods

The study was approved by the Royal Adelaide Hospital Human Research Ethics Committee and was registered with the Australian Therapeutic Goods Administration under the Clinical Trial Notification scheme and with the Australian and New Zealand Clinical Trials Registry (Number: 2011/0292). The study was conducted in accordance with the principles of the Declaration of Helsinki [22] and Good Clinical Practice Guidelines [23].

Design

The study was of open label two way randomized, crossover design in eight healthy male volunteers who all gave written informed consent. Each participant received either a single 10 mg i.v. dose as a constant rate 30 min infusion or a 25 mg SL dose of ketamine in two treatment periods with a 7 day washout. Both the SL and i.v. doses, and the duration of the i.v. infusion were chosen to ensure adequate characterization of the plasma concentration–time profiles and good quality estimates of pharmacokinetic (PK) variables for both routes of administration. The i.v. dose of 10 mg has been used in similar studies and has been well tolerated. Bioavailability values of 24–32.2% have been reported in the literature for sublingually administered ketamine. Even if the bioavailability of the wafer formulation was higher, a 25 mg dose was not expected to show a systemic tolerability markedly different from that of the i.v. dose. The sequence of the two formulations was according to a computer-generated randomization code.

Clinical

The SL wafer formulation was a freeze dried solid dispersion of racemic ketamine hydrochloride in a porous matrix using lactose as a filling agent. Prior to administration of the wafer the sublingual space was rinsed with 3 ml of water after which the wafer was placed sublingually by a member of the study staff. The participants were instructed to avoid chewing or swallowing of the wafer within 5 min of its placement. For i.v. administration, commercially available ketamine (Ketalar®) was diluted to 30 ml in saline and administered over 30 min using a volumetrically controlled syringe driver. The infusion line was primed prior to start of the infusion.

Pharmacokinetic blood sampling and clinical assessment of local tolerability and safety were carried out for 24 h following both dosing occasions.

Key inclusion criteria were healthy adult males aged 18–65 years with a BMI 19–30 kg m⁻² in good general health including mental health as assessed by the Symptom Checklist-90-R (SCL-90-R®), a screening instrument which evaluates a broad range of psychological problems and symptoms of psychopathology. Pharmacokinetic blood samples (5 ml), were taken following both i.v. and SL administration at predose 5, 10, 15, 30, 35 and 45 min, and at 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12 and 24 h post-dose.

Whole blood was drawn into prechilled lithium heparin tubes and remained on ice post-sample collection until
centrifugation. Samples were centrifuged at 1800 g for 10 min in a refrigerated centrifuge at 4°C. Plasma was decanted and frozen at –80°C.

To assess the local tolerability profile of the SL formulation, modified Likert scales (0–10) were recorded at 5, 10, 15, 30 and 45 min and 1 h post-dose administration at various time points for both the SL and i.v. formulation:

- Mucosal irritation
- Burning sensation
- Bitterness
- Nausea
- Residual grittiness in the mouth

Safety assessments included scheduled adverse event probes, spontaneous adverse event (AE) reporting, physical examination, routine laboratory investigations, ECGs and vital sign evaluation.

Vital signs (including systolic and diastolic blood pressure, pulse, respiratory rate and body temperature) were performed predose and at hours 0.5, 1, 2, 4, 6, 8, 12 and 24 h post-dose. Pulse oximetry was recorded predose and continuously for the first 3 h post-dose administration.

**Laboratory**

Safety laboratory testing (biochemistry, haematology and urinalysis) was performed predose and at hour 24 post-dose administration in each period.

Quantification of the plasma concentrations of racemic ketamine was performed using a validated HPLC method with u.v. detection, a lower limit of quantification (LLOQ) of 2 ng ml\(^{-1}\) and <20% bias and imprecision [24].

**Data analysis**

Standard non-compartmental methods using the PK Solver plug-in for Microsoft Excel were used to derive pharmacokinetic variables, except for \(C_{\text{max}}\), \(t_{\text{max}}\) and \(t_{\text{astr}}\), which were taken as observations from the plasma concentration–time profile of each participant. Actual times were used when reporting \(t_{\text{max}}\). The terminal rate constant (\(\lambda\)) was estimated by log-linear regression, of the slope of the natural log plasma concentration vs. time curve where \(\lambda = -1 \times \text{slope}\). The linear regression in the terminal phase used the last three to six data points. The terminal \(t_{1/2}\) was calculated as \(t_{1/2} = \ln(2)/\lambda\).

The area under the plasma concentration time curve from time zero to the last quantifiable concentration (AUC(0,\(t_{\text{astr}}\))) was obtained using the linear trapezoidal method and extrapolated to infinity to obtain the total area, AUC(0,\(\infty\)), with \(C_{\text{astr}}/\lambda\), where \(C_{\text{astr}}\) is the last quantifiable plasma concentration. The AUC\(_{\text{extr}}\) (extrapolated portion of AUC(0,\(\infty\))) was calculated as \((1 - \text{AUC}(0,t_{\text{astr}})/\text{AUC}(0,\infty)) \times 100\). For the i.v. dose, clearance (CL) was calculated as dose/AUC(0,\(\infty\)) and \(V_{z}\) was calculated as CL/\(\lambda\). The bioavailability (\(F\)) of ketamine was calculated as the ratio of the dose adjusted AUC(0,\(\infty\)) following i.v. and SL dosing according to AUC(0,\(\infty\))\(_{\text{SL}}\)/AUC(0,\(\infty\))\(_{\text{i.v.}}\) x dose\(_{\text{i.v.}}\)/dose\(_{\text{SL}}\).

**Results**

Eight healthy male volunteers of mean (SD) 25 (7.6) years and BMI 26.1 (2.83) kg m\(^{-2}\) took part in the study.

The individual and mean plasma concentration profiles are shown graphically for i.v. and SL administration in Figures 1 and 2, respectively. The mean profiles for i.v. and SL are shown in Figure 3. The pharmacokinetic results are provided in Table 1. In all participants and for both administration routes, the first quantifiable ketamine plasma concentrations were observed at the first post-dose sample at 5 min. The SL plasma concentration profiles showed minor fluctuations in a few participants. In one participant three comparable peaks were observed during the first 1.5 h following SL administration, although no noticable difference in PK characteristics could be observed in comparison with the other participants. Following the \(C_{\text{max}}\) concentrations declined biophysically for both i.v. and SL with the trend being more prominent for i.v. Peak plasma concentrations following the i.v. infusion occurred at the end of the infusion in all but one participant, where the peak occurred 5 min after the end of the infusion. For the SL formulation, peak plasma concentrations were observed between 0.25 and 1 h, with a median \(t_{\text{max}}\) of 0.75 h. In one participant the dissolution time of the wafer was noticably longer, 6 min, than the 30–60 s noted in all other participants. The same participant showed among the highest scores for ‘residual grittiness’ during the first 30 min after dosing, but scores had returned to 1 at 45 min and to baseline values at 60 min post-dose. The
longer dissolution time did not translate into generally differing PK or systemic tolerability characteristics of ketamine in this participant. The cause of the prolonged dissolution time is unknown. Plasma concentrations were below the LLOQ in six participants at 24 h and in one participant at 12 h following SL dosing. Following i.v. dosing, all participants had quantifiable levels at 12 h and four participants at 24 h. The median (min–max) terminal half-lives for i.v. and SL were comparable at 4.5 (2.5–7.0) h and 3.4 (1.8–5.5) h, respectively. The extrapolated portion of the AUC(0,∞) was very small for both routes of administration with min–max of 3–7% for i.v. and 2–9% for SL dosing. The median (lower, upper 90% CI limit) for the bioavailability of the wafer was 29 (27, 31)% showing very low inter-subject variability. The participant who had the highest bioavailability, 38%, also had the highest clearance, 59.8 l h⁻¹.

Nineteen adverse events thought to be related to treatment were reported. Most were expected CNS-type effects typical of ketamine: light headed (n = 1 for i.v. and n = 3 for SL), hazy (i.v. n = 2), numbness in mouth and/or face (i.v. n = 5, SL n = 1), and one each of body feels heavy, dry mouth and visual disturbance for i.v., and for SL one each of terrible taste in mouth, blurred vision, decreased sensation in arm and dizziness, respectively. The onset was comparable.

Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cmax,i.v. (ng ml⁻¹)</th>
<th>Cmax,SL (ng ml⁻¹)</th>
<th>Tmax,SL (h)</th>
<th>AUC(0,∞) i.v. (ng ml⁻¹ h)</th>
<th>AUC(0,∞) SL (ng ml⁻¹ h)</th>
<th>CL (l h⁻¹)</th>
<th>Vz (l)</th>
<th>t1/2,i.v. (h)</th>
<th>t1/2,SL (h)</th>
<th>F (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>226.7</td>
<td>88.8</td>
<td>0.58</td>
<td>282.7</td>
<td>202.9</td>
<td>35.4</td>
<td>126</td>
<td>2.5</td>
<td>2.9</td>
<td>28</td>
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<td>2</td>
<td>163.3</td>
<td>128.3</td>
<td>0.25</td>
<td>243.2</td>
<td>162.5</td>
<td>41.1</td>
<td>158</td>
<td>2.7</td>
<td>1.8</td>
<td>27</td>
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<tr>
<td>3</td>
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<td>78.7</td>
<td>0.75</td>
<td>254.6</td>
<td>184.3</td>
<td>39.3</td>
<td>283</td>
<td>5.0</td>
<td>3.2</td>
<td>29</td>
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<tr>
<td>4</td>
<td>124.2</td>
<td>60.2</td>
<td>1</td>
<td>270.0</td>
<td>203.5</td>
<td>37.0</td>
<td>253</td>
<td>4.7</td>
<td>5.5</td>
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<tr>
<td>5</td>
<td>120.4</td>
<td>50.0</td>
<td>0.75</td>
<td>289.2</td>
<td>211.3</td>
<td>33.4</td>
<td>164</td>
<td>3.4</td>
<td>2.3</td>
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<tr>
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<td>7</td>
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<td>261.0</td>
<td>186.1</td>
<td>38.3</td>
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<td>4.6</td>
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<tr>
<td>8</td>
<td>81.1</td>
<td>61.2</td>
<td>0.5</td>
<td>167.2</td>
<td>161.6</td>
<td>59.8</td>
<td>375</td>
<td>4.3</td>
<td>5.1</td>
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</tr>
<tr>
<td>Gmean*</td>
<td>128.1</td>
<td>71.1</td>
<td>0.75</td>
<td>255.0</td>
<td>184.6</td>
<td>39.2</td>
<td>237</td>
<td>4.5</td>
<td>3.4</td>
<td>29</td>
</tr>
<tr>
<td>Min–max</td>
<td>81.1–226.7</td>
<td>50.0–128.3</td>
<td>0.25–1</td>
<td>167.2–299.4</td>
<td>161.6–211.3</td>
<td>33.4–59.8</td>
<td>126–385</td>
<td>2.5–7.0</td>
<td>1.8–5.5</td>
<td>23–38</td>
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<tr>
<td>CV (%)</td>
<td>16</td>
<td>14</td>
<td>21</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>18</td>
<td>16</td>
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<td>6</td>
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<tr>
<td>90% CI†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Cmax, peak plasma concentration; Tmax, time of Cmax; AUC(0,∞), area under the plasma concentration–time curve from time zero to infinity; CL, clearance following i.v. administration; Vz, apparent volume of distribution following i.v. administration; t1/2, terminal half-life; F, bioavailability; NA, Not applicable; SL, sublingual. *Gmean is provided for all variables except for bioavailability, Tmax and t1/2 where medians are shown. 90% confidence interval (lower, upper).

Figure 2

Individual racemic ketamine plasma concentration–time profiles and geometric mean (bold line) during the first 12 h following a 25 mg sublingual dose to eight healthy volunteers.

Figure 3

Geometric mean racemic ketamine plasma concentration–time profiles during the first 6 h following sublingual administration of 25 mg (continuous line) and 10 mg as a 30 min i.v. infusion (dashed line) to eight healthy volunteers.
for the two routes of administration, being 6–22 min for i.v.
and 5–18 min for SL dosing. All AEs were mild and had a
short duration of less than 1 h with only three AEs ‘possibly’
or ‘probably’ related to treatment lasting over 30 min.
There were no serious adverse events. Local tolerability of
the SL formulation was excellent with transient bitterness
the only effect of note.

Discussion

In this study the pharmacokinetic characteristics and abso-
lute bioavailability of a novel SL wafer formulation of
racemic ketamine were determined, and the local toler-
ability was assessed. A majority of the adverse events were
typical CNS effects of ketamine, and were more frequently
observed for the i.v. dose, which is likely due to the higher
plasma concentrations achieved in comparison with the SL
dose. However, all AEs were mild, resolved within 1 h and
both the local and systemic tolerability was very good for
both routes of administration. The extrapolated portion of
the AUC(0,∞) was very small in all participants, indicating
high quality in the estimates of AUC and hence bioavailability.
The dissolution and subsequent absorption following SL administration was rapid, as shown by the
early quantifiable plasma concentrations. The similar ter-
minal half-lives across dosing routes confirmed that
absorption was rapid and not rate limiting for the elimina-
tion. The early t\textsubscript{max} was also indicative of fast absorption, in
the light of the similar terminal half-life values across
dosing routes. The t\textsubscript{max} was comparable with previously
reported values for SL administration of ketamine, with a
median (min–max) t\textsubscript{max} of 0.75 h (0.25–1 h) in the present
study, a median (interquartile range) of 0.5 h (0.3–0.8 h) for
a lozenge [21] and a mean (SD) of 40 (20) min for a tablet
formulation [20]. The median bioavailability at 29% was
also very similar to that observed for the lozenge formula-
tion, median of 24% [21] and tablet, mean of 32.2% [20].
However what differed markedly with the novel wafer for-
mulation compared with formulations presented in previ-
ous studies was that the between subject variability in
bioavailability was noticeably lower. The 90% CI was over a
very narrow range of 27–31%, in comparison with an
interquartile range of 19–49% for the lozenge [21] and a
standard deviation of 8.2% for the SL tablet [20]. It should
be noted that the variability estimates for all three formu-
lations have been derived from a small number of subjects
with three healthy volunteers for the SL tablet [20], 10
patients for the lozenge [21] and eight volunteers in
the present trial. The low inter-subject variability in
bioavailability of the novel wafer might be due to the for-
mulation delivering a more controlled release of drug into
the sublingual space than a SL lozenge [21] or tablet [20].
The inter-variability estimate for the novel wafer formula-
tion will require confirmation in future trials in a larger
number of subjects. In the context of a narrow therapeutic

index drug such as ketamine, reliable and consistent deliv-
ery is particularly important and hence the low variability
in bioavailability makes the new wafer formulation espe-
cially attractive for further evaluation as an analgesic
adjunct.

In conclusion the clinical safety and tolerability of
ketamine and the adverse event profile was as expected
for the dose levels used and prevailing clinical experience
and mild and transient local effects were seen. The
bioavailability of ketamine in the novel SL wafer formula-
tion was comparable with previously reported SL formula-
tions and in addition promises a very low inter-subject
variability. In view of ketamine’s relatively narrow therape-
utic index, low variability is appealing as it signifies
reproducible exposure and consequently clinical effect.

Competing Interests

All authors have completed the Unified Competing Inter-
est form at http://www.icmje.org/coi_disclosure.pdf (avail-
able on request from the corresponding author) and
declare PR, SL, VS, YL and VM had support from iX
Biopharma for the submitted work, PR and VS are directors
of iX Biopharma in the previous 3 years and there are no
other relationships or activities that could appear to have
influenced the submitted work.

We would like to thank the staff of the Pain and Anaesthe-
sia Research Clinic, University of Adelaide, for conducting the
study.

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