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Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain

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ABSTRACT

Background: NMDA receptors are involved in the development and maintenance of neuropathic pain. We evaluated the efficacy and safety of intranasal (S)-ketamine, one of the most potent clinically available NMDA receptor antagonists.
Methods: Sixteen patients with neuropathic pain of various origins were randomized into two treatment groups: (S)-ketamine 0.2 mg/kg (group 1); (S)-ketamine 0.4 mg/kg (group 2). Plasma concentrations of (S)-ketamine and (S)-norketamine were measured over 6 h by High Performance Liquid Chromatography combined with mass spectrometry. Quantitative sensory testing (QST) was conducted before, during and after treatment. Side effects and amount of pain reduction were recorded.
Results: Intranasal (S)-ketamine administration lead to peak plasma concentrations of 27.7 ± 5.9 ng/ml at 10 ± 6.3 min (group 1) and 34.3 ± 22.2 ng/ml at 13.8 ± 4.8 min after application (group 2). Maximal plasma concentrations of (S)-norketamine were 18.3 ± 14.9 ng/ml at 81 ± 59 min (group 1) and 34.3 ± 5.5 ng/ml at 75 ± 40 min (group 2). Pain scores decreased significantly in both groups with minimal pain at 60 min after drug administration (70 ± 10% and 61 ± 13% of initial pain in groups 1 and 2). The time course of pain decrease was significantly correlated with plasma concentrations of (S)-ketamine and (S)-norketamine (partial correlations: (S)-norketamine: −0.90 and −0.86; (S)-ketamine: −0.72 and −0.71 for group 1 and group 2, respectively). Higher dosing elicited significantly more side effects. Intranasal (S)-ketamine had no significant impact on thermal or mechanical detection and pain thresholds in normal or symptomatic skin areas.
Conclusions: Intranasal administration of low dose (S)-ketamine rapidly induces adequate plasma concentrations of (S)-ketamine and subsequently of its metabolite (S)-norketamine. The time course of analgesia correlated with plasma concentrations.

1. Introduction

Hypersensitivity in either inflammatory or neuropathic pain is predominantly mediated by *N*-methyl-D-aspartate receptors (NMDARs) (Liu et al., 2008; Woolf and Salter, 2000). Therefore, several clinical trials addressed the therapeutic usefulness of NMDAR antagonists in perioperative as well as chronic pain management, or examined the potential effects of NMDAR antagonists on mechanical or thermal quantitative sensory testing (QST) (Muir, 2006; Lavand'homme et al., 2005; De Kock and Lavand'homme, 2007; Baad-Hansen et al., 2007; Elia and Tramèr, 2005). Although widely considered as a very promising class of drugs, the use of NMDAR antagonists is currently classified as a third line medication in the pharmacologic management of neuropathic pain (Dworkin et al., 2007, Chizh and Headley, 2005; Parsons, 2001). Racemic ketamine, clinically characterised as a dissociative anaesthetić, and a non-competitive NMDAR antagonist with a relatively low affinity to the NMDAR, is widely used in those studies. Whilst in perioperative pain management, a temporary intravenous or epidural route of administration is frequently chosen, this approach is considerably less feasible for prolonged treatment of chronic pain from neuropathic origin. Therefore, alternative, particularly oral or subcutaneous routes of administration, have been tested (Eide et al., 1995; Rabben et al., 1999). However, the bioavailability of oral ketamine preparations is known to be relatively poor (Yanagihara et al., 2003). Moreover, after oral administration, ketamine undergoes extensive first pass metabolism in the liver, resulting in high levels of norketamine. Interestingly, norketamine itself has displayed antinociceptive properties via non-competitive

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NMDAR antagonism in animal models of neuropathic pain (Ebert et al., 1997).

To overcome the disadvantages of oral ketamine application, particularly to achieve a faster onset of drug effect as well as a higher bioavailability, the intranasal route of administration has been suggested. Carr and colleagues were able to show the efficacy of intranasal ketamine for break through pain after single dose administration of 10–50 mg (Carr et al., 2004). Whilst ketamine plasma concentrations after intranasal administration for induction of anesthesia in children have been delineated (Malinovsky et al., 1996), no studies addressed the time course of ketamine and norketamine plasma concentrations after a single, low dose, weight adapted intranasal application. Furthermore, no data are available concerning the possible short or long term effects of intranasal ketamine on QST parameters, or potential correlations between ketamine or norketamine plasma concentrations and pain scores as effect site parameters. As (S)-ketamine, the (S)-enantiomer of ketamine, as well as its major metabolite (S)-norketamine display a 5–8 times higher affinity to the NMDAR receptor complex when compared to the respective (R)-enantiomer (Ebert et al., 1997), (S)-ketamine was used in the study at issue.

2. Methods

2.1. Patients and randomization

The study was approved by the local Institutional Review Board (IRB), the responsible regulatory agency (Federal Institute for Drugs and Medical Devices; BfArM, Bonn, Germany), and written informed consent was obtained by all subjects enrolled in the study according to the Declaration of Helsinki. Inclusion criteria comprised chronic neuropathic pain syndromes, written informed consent and ASA physical status classification I–III. Patients with a history of substance abuse, a known or supposed history of allergy or intolerance to (S)-ketamine, insufficient knowledge of written or verbal German language, psychological or neurological disorders other than neuropathic pain, psychosis, or patients suffering from nasal anomalies or disease (e.g. rhinitis) were excluded from the study. Additionally, patients displaying absolute or relative contraindications for the use of (S)-ketamine (i.e. severe or poorly controlled arterial hypertension, instable angina pectoris or coronary heart disease, increased intracerebral pressure, history of seizures) as well as patients suffering from severe liver or kidney disease or those who were taking thyroid hormones or sympathomimetic drugs were excluded from the study. The patients were advised not to drink alcohol for a period of 24 h before and after the study. Following enrolment in the study, patients were assigned in a double-blind randomized manner to one of the treatment groups. Patients in group 1 received 0.2 mg/kg (S)-ketamine, whereas patients in group 2 were treated with a single dose of 0.4 mg (S)-ketamine per kilogram body weight.

2.2. Preparation of (S)-ketamine and drug administration

A commercially available pharmaceutical preparation of (S)-ketamine (Ketanest® 25 mg/ml Esketaminhydrochlorid, Pfizer, Karlsruhe, Germany) was prepared in an aqueous solution. In order to ensure a double-blind study design, equal volumes of different concentrations adjusted to the patients' weight and study group were manufactured, and administered by a standard nasal spray vial and applicator. The spray was custom made in a fashion that each vial contained 3 ml, and the respective dosing was achieved by rapid administration of 2 times five sprays into each nostril.

2.3. Sampling and detection of (S)-ketamine and (S)-norketamine plasma concentrations

Thirteen 5 ml venous blood samples were drawn before and 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, and 360 min after drug administration. Plasma was immediately separated by centrifugation and stored at −20° C until analysis. Determination of (S)-ketamine plasma concentrations and its major metabolite (S)-norketamine was conducted by applying High Performance Liquid Chromatography (HPLC; column: Agilent Zorbax XDB-C8). As the anticipated plasma concentrations were much lower than in studies investigating the anaesthetic properties of ketamine (GEISSLINGER et al., 1993), HPLC was combined with tandem mass spectrometry for compound quantitation (liquid chromatography–mass spectrometry/mass spectrometry: LC–MS/MS) (API 4000, Applied Biosystems). Ketamine-d4 and norketamine-d4 (50 ng/ml, respectively) were used as internal standard (Cerilliant, USA). Levels of detection were ∼0.7 ng/ml for (S)-ketamine and ∼4 ng/ml for (S)-norketamine.

2.4. Quantitative sensory testing (QST)

QST followed the standardized protocol, and used the instruments as described by the German Research Network on Neuropathic Pain (DFNS) (Rolke et al., 2006a,b). This protocol includes thermal testing of cold and warm detection thresholds (CDT, WDT), thermal pain thresholds (cold pain threshold CPT, heat pain threshold HPT) and the detection of paradoxical heat sensations (PHS) during administration of alternating cold and warm stimuli (Thermal sensory limen TSL). Furthermore, it comprises mechanical testing including determination of mechanical detection threshold (MDT), mechanical pain threshold (MPT), and pressure pain threshold (PPT). Unlike the DFNS protocol, the amount of mechanical pain sensitivity and the respective degree of mechanical allodynia as well as vibration detection threshold and wind-up ratio were not determined, as these tests were regarded being too time consuming considering the constantly declining (S)-ketamine plasma concentrations. QST testing commenced before administration of the study drug, second QST started 60 min after administration of (S)-ketamine, whereas the final QST proceeded 7 days after drug application. Thermal testing was performed using a Medoc Thermal Stimulus Analyser TSA-2001 device (Medoc, Ramat Yishai, Israel) using a computer-controlled Peltier-based probe. The basic principles of the Peltier stimulator are described in detail elsewhere (Verdugo and Ochoa, 1992). MDT was assessed with modified von Frey hairs which exert forces between 8 and 512 mN. For determination of MPT, pinprick stimulators (8–512 mN) were administered. Finally, PPT was calculated by means of a pressure gauge device (FDN200, Wagner Instruments, USA), which exerts pressure up to 20 kg/cm^2 (≈200 N/cm^2 ≈ 2000 kPa).

2.5. Test algorithm

The body area affected by the disease was termed "affected", while the other side was termed "contralateral". All testing commenced in the contralateral side. The course of assessments was explained to the subjects by written standard patient instructions. All tests were demonstrated in a remote test area not affected by the underlying disease. The standard order of tests for all patients was: CDT, WDT, TSL, CPT, HPT, MDT, MPT and PPT. Identification of a cold stimulus as either hot or burning pain during the TSL procedure was denoted as the occurrence of paradoxical heat sensation (PHS). For an elaborate discussion of the QST algorithm see Rolke and colleagues (Rolke et al., 2006b).

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2.6. Pain assessment, hemodynamic measurements and detection of side effects

In all groups, heart rate (HR) as well as estimation of arterial oxygen saturation by means of pulse oximetry (SpO_2) were monitored continuously, and recorded along with the parameters from non-invasive arterial pressure before and 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, and 360 min after drug administration. Additionally, patients rated the intensity of their chronic pain by means of an 11-point Likert scale ranging from 0 to 10 at the same time intervals as described above. Pain scores, as well as HR, and mean arterial pressure (MAP) were transformed into ratios (t_x/t_0) to obtain a better comparability of changes from baseline. Mini mental status test (MMS) was performed as a screening test of cognitive impairment. The test was performed after informed consent was given (at least one day prior to the study day) as well as 30 min after (S)-ketamine dosing. This design was chosen in order to control for possible learning effects. The maximum MMS is 30, with scores 23 or less indicating a cognitive impairment. A decrease of two or more points was considered as impairment of cognitive function.

For evaluation of side effects, patients were interviewed before beginning of the study as well as 360 min after administration of (S)-ketamine. Patients were asked to rate nausea, vomiting, confusion, noise intolerance, blurred vision, difficulty to concentrate, sedation and vertigo, on a five point scale (weighted score: 0 = no; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe).

2.6. Statistics

Kolmogorov–Smirnov's test was performed to assess deviations from normal distribution in the dataset. Pharmacokinetic variables were analysed using two-sided Student's t test for unpaired comparisons. QST differences between affected and control site at a given time were analysed using Student's t test for paired comparisons. Multiple time dependent observations were analysed using a general linear model for repeated measures with the between subject factor group, time as within subject factor, body side in QST data (ipsilateral vs. contralateral) and baseline values serving as covariate to control the effect of regression to the mean. Furthermore, within subjects contrasts were conducted by applying an orthogonal decomposition of the Type III sum of squares. Besides CPT and HPT, QST data were transformed into decadic logarithms to achieve secondary normal distributions of these data. For CPT and HPT, arithmetic means were used for analysis. Categorical data were analysed using Yates-corrected χ^2 or Fisher's exact test as appropriate. PHS data were analysed with Friedman two-way ANOVA for paired ranked data. Pain ratios were compared with a pair wise bivariate correlation with the respective plasma concentrations of (S)-ketamine as well as (S)-norketamine. Furthermore, S-(ketamine) and (S)-norketamine plasma concentrations were entered into a stepwise forward regression equitation, in order to determine their influence on pain ratings. Finally, the bivariate and partial correlations between the pain ratings and the respective plasma concentrations were calculated. A probability level of $p < 0.05$ was considered significant. Results display Mean ± SD; graphics use Mean ± SEM. All analysis was performed using the SPSS® software package (SPSS® 16.0, SPSS Inc., Chicago, USA).

3. Results

3.1. Demographic data

Sixteen patients suffering from chronic neuropathic pain conditions and ASA physical status classification I–III gave written informed consent to participate in the study. Demographic data are demonstrated in Table 1.

3.2. Plasma concentrations

The mean plasma concentration–time profiles for (S)-ketamine and (S)-norketamine are shown in Fig. 1 and are summarized in Table 2. Clinically relevant plasma concentrations were achieved in both groups ($n = 10$ for plasma samples). However, neither peak plasma levels of (S)-ketamine (C_{max} (S)-ketamine = 27.7 ± 5.9 ng/ml group 1 vs. 34.3 ± 22.2 ng/ml group 2; $p = 0.60$), nor time to maximal plasma concentration differed between groups (T_{max} = 10 ± 6 min group 1 vs. 14 ± 5 min group 2; $p = 0.35$). Furthermore, there was a strong trend towards a significant difference in (S)-norketamine plasma concentrations between both groups (C_{max} (S)-norketamine = 18.26 ± 14.93 ng/ml group 1 vs. 34.3 ± 5.53 ng/ml group 2, $p = 0.053$), while time to peak plasma concentration of (S)-norketamine was comparable (81 ± 59 min group 1 vs. 75 ± 40 min group 2; $p = 0.88$).

Comparison of (S)-ketamine plasma concentrations by repeated measures ANCOVA revealed a highly significant overall effect of time (ANCOVA within factor time: $F_{11,88} = 18.6$; $p \ll 0.001$), but no effect of group ($F_{1,8} = 1.3$; $p = 0.28$) nor group × time interaction ($F_{11,88} = 0.86$; $p = 0.59$). Likewise, ANCOVA of (S)-norketamine plasma concentrations displayed a highly significant effect of time ($F_{11,77} = 15.34$; $p \ll 0.001$) and no effect of group ($F_{1,7} = 1.2$; $p = 0.30$). However, there was a strong trend towards a group × time interaction ($F_{11,77} = 1.8$; $p = 0.07$). Furthermore, within subject contrasts with orthogonal decomposition (Type III sum of squares) yielded a significant fifth order group × time interaction ($F_{1,7} = 7.89$; $p = 0.026$), hence indicating an overall influence of time in the plasma concentration curves of (S)-norketamine, with a group interaction, signalling a difference in the slope of the curves between both groups.

3.3. Pain scores

Patients reported comparable levels of pain before initiation of the trial (group 1 = 6.4 ± 1.0 vs. group 2 = 6.6 ± 0.6; $p = 0.83$) as rated on 11-point Likert scales. Following (S)-ketamine application, pain ratings decreased rapidly in both groups, reaching a minimum at 60 min. Pain ratings declined to 4.4 ± 3 in group 1, i.e. to 70 ± 10% of initial pain and to 4.1 ± 3.1 in group 2, i.e. to 61 ± 13% of basic pain values (Fig. 2). Comparison of pain ratios with a general linear model for repeated measures, with time as within subject factor and group as between subject factor, displayed neither an overall effect of time ($F_{1,11} = 4.4$; $p = 0.36$), nor group ($F_{1,11} = 1.1$; $p = 0.32$) and no group × time interaction ($F_{1,11} = 11.2$; $p = 0.23$). However, pain scores (Fig. 2) exhibited a similar and significant time dependent curvature in both groups during the assessment period (highly significant quadratic effect of time – $F_{1,11} = 18.1$; $p < 0.001$) – in within subject contrasts with orthogonal decomposition of Type III sum of squares, but no group × time interaction ($F_{1,11} = 0.58$; $p = 0.46$).

Bivariate correlations suggested a meaningful relationship between the time courses of (S)-norketamine plasma concentrations and pain scores, which amounted to $r = -0.79$ for group 1 ($p < 0.001$) and $r = -0.71$ for group 2 ($p < 0.01$). In contrast, bivariate regression analysis revealed an apparent marginal correlation between time courses of (S)-ketamine plasma concentrations and pain scores of $r = -0.21$ for group 1 ($p = 0.25$) and $r = -0.27$ for group 2 ($p = 0.37$). However, entering (S)-ketamine plasma concentrations as a second predictor in a stepwise forward multiple regression to explain the residual variance left by respective (S)-norketamine plasma concentrations, revealed a highly significant dependency of pain on both (S)-ketamine and (S)-norketamine

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Table 1
Demographic data.

	Group 1–0.2 mg/kg (n = 8)	Group 2–0.4 mg/kg (n = 8)	p-Value
Age (years)	54.5 ± 21.4	57.1 ± 17.4	0.79[a]
Gender	Three female/five male	Five female/three male	0.32[b]
Bodyweight (kg)	78.4 ± 14.4	64.9 ± 7.7	<0.05[a]
Diagnosis (number of patients)	CRPS (2)	CRPS (3)	
	PHN (2)	PHN (1)	
	PNP (1)	PNP (1)	
	Peripheral nerve lesion (1)	Plexus damage (1)	
	Trigeminal neuralgia (2)	Trigeminal neuralgia (1)	
		Central pain (1)	
Pain rating (11-pt LS)	6.4 ± 2.8	6.6 ± 1.6	0.83[a]

Mean ± SD.
LS: Likert scale.
CRPS: complex regional pain syndrome.
PHN: postherpetic neuralgia.
PNP: polyneuropathy.
[a] Unpaired t-test.
[b] Yates-corrected chi-square.

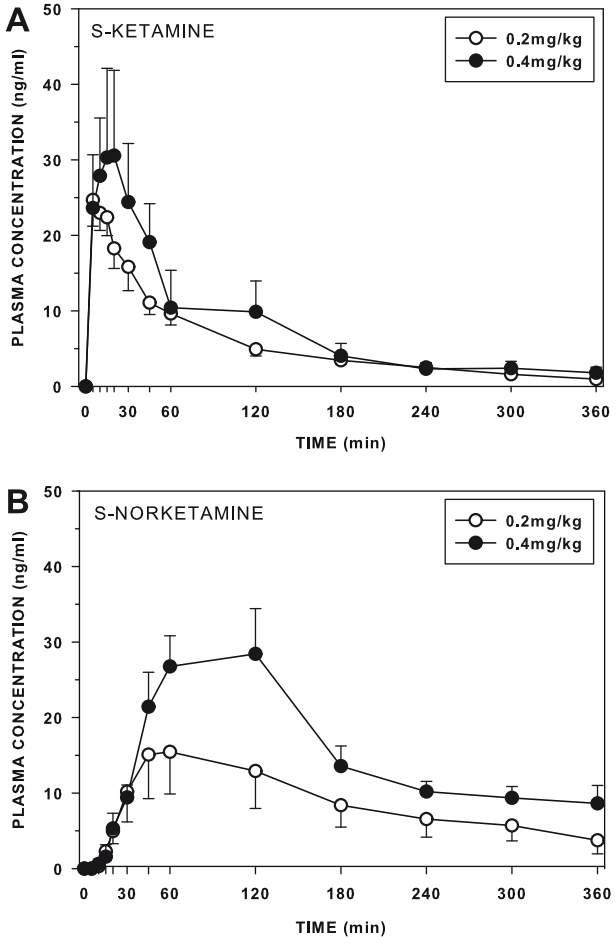

Fig. 1. Plasma concentration time profiles of (S)-ketamine (A) and (S)-norketamine (B) after intranasal application of 0.2 mg/kg or 0.4 mg/kg (S)-ketamine. (S)-ketamine as well (S)-norketamine profiles displayed a highly significant effect of time ($p < 0.01$), but no difference between different (S)-ketamine dosing regimes could be detected.

Table 2
Ketamine plasma concentrations.

	(S)-ketamine 0.2 mg/kg	(S)-ketamine 0.4 mg/kg
(S)-ketamine		
C_{max} (ng/ml)	27.7 ± 5.9	34.3 ± 22.2
T_{max} (min)	10.0 ± 6.3	14 ± 5
(S)-norketamine		
C_{max} (ng/ml)	18.3 ± 14.9	34.3 ± 5.5
T_{max} (min)	81 ± 59	75.0 ± 39.7

C_{max}: peak plasma concentration.
T_{max}: elapsed time at C_{max}.

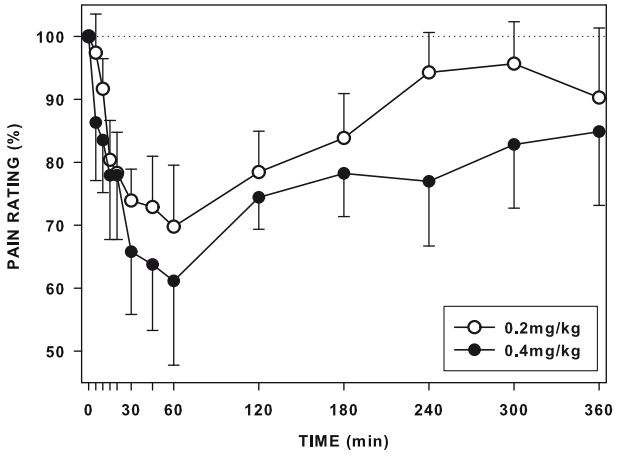

Fig. 2. Time profile of pain ratings after intranasal application of 0.2 mg/kg or 0.4 mg/kg (S)-ketamine. Pain ratings decreased significantly ($p < 0.05$) after study drug application, though no differences between both treatment groups occurred.

plasma concentrations. Accordingly, partial correlations between pain scores and (S)-ketamine concentrations controlling for the respective (S)-norketamine concentrations demonstrated the influence of (S)-ketamine concentrations on VAS-ratios (partial correlations for (S)-ketamine = −0.72 for group 1 ($p < 0.01$) and $r = -0.71$ for group 2 ($p < 0.01$). Moreover, entering (S)-ketamine plasma concentrations to the equation accentuated the impact of (S)-norketamine concentrations on pain scores (partial correlations (S)-norketamine increasing to $r = -0.90$ for group 1 ($p < 0.001$) and $r = -0.86$ for group 2 ($p < 0.001$). The two predictor multiple regression model explained 86% and 72% of total variance in groups 1 and 2, respectively ($p \ll 0.001$ each), suggesting that (S)-norketamine was ~2.3 times more effective than (S)-ketamine.

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3.4. Quantitative sensory testing

Quantitative sensory testing (QST) was performed to detect potential effects of (S)-ketamine on somatosensory sensitivity in areas affected as well as in contralateral skin areas. Since QST measurement did not differ between groups, data were pooled to enhance sensitivity of the statistical analysis.

The majority of sensory test parameters displayed sensory loss in the affected areas compared to mirror image control areas, e.g. average cold detection threshold (CDT) was approximately 5.5 °C compared to 3.5 °C in control areas, and average tactile detection thresholds (MDT) were approximately 4 mN compared to 1.3 mN (Fig. 3 and Table 3). Similar differences were shown for warm detection thresholds (WDT), thermal sensory limen (TSL, data not shown), vibration detection thresholds (VDT), and mechanical pain thresholds (MPT). However, due to the limited number of patients included, these differences failed to reach statistical significance. In contrast, significant differences in pressure pain thresholds (to blunt pressure; PPT) between the affected and the contralateral side occurred at all times of assessment, signalling significant hyperalgesia to blunt pressure at the site of neuropathic pain. Prior to drug application, PPT at the affected side was 70 kPa (lg = 1.84 ± 0.28) compared to 155 kPa (lg = 2.19 ± 0.33) at the control side ($p < 0.05$). These threshold were completely unmodified both at 60 min and one week after (S)-ketamine, therefore remaining significantly different ($p < 0.05$, each). For further details see Fig. 3 and Table 3. Paradoxical heat sensation, i.e. burning pain to mild cold stimuli (PHS) merely occurred in 5 of 14 patients (19/84 trials in both hands) prior to (S)-ketamine administration (22.6% of trials). Sixty minutes after administration of (S)-ketamine, PHS encountered in 14/84 trials (16.6%), and in 14/70 trials (20%) after 7 days. This marginal reduction did not reach statistical

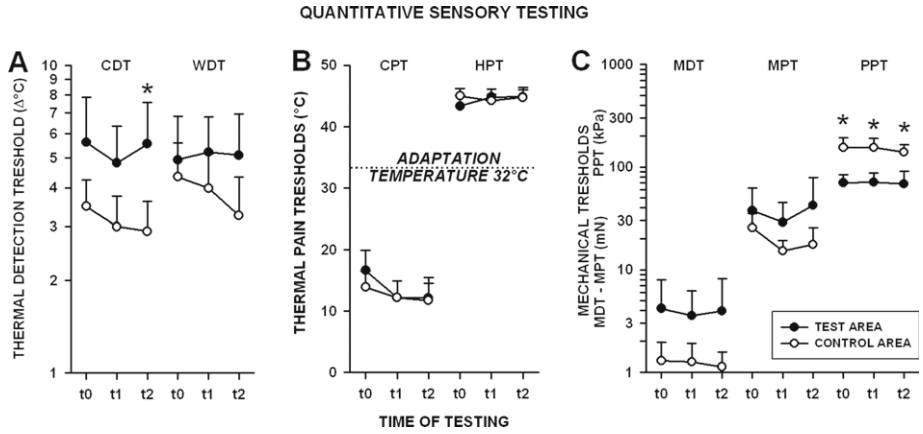

Fig. 3. Changes in quantitative sensory testing (QST) after intranasal (S)-ketamine application. QST displayed a significant hyperalgesia for blunt pressure, signalled by the decreased PPT thresholds. No effects of (S)-ketamine on QST parameters were observed. T_0: Before (S)-ketamine application; T_1: 60 min after (S)-ketamine; T_2: one week after (S)-ketamine application.

Table 3
Quantitative sensory testing (QST).

Test	Test area	T_0	T_1	T_2
Thermal testing				
CDT mean (mean log ± SD)	Affected	5.62 °C (0.75 ± 0.55)	4.81 °C (0.68 ± 0.45)	5.56 °C (0.74 ± 0.51)[a]
	Contralateral	3.48 °C (0.54 ± 0.33)	2.99 °C (0.48 ± 0.37)	2.89 °C (0.46 ± 0.36)[a]
WDT mean (mean log ± SD)	Affected	4.93 °C (0.69 ± 0.53)	5.22 °C (0.72 ± 0.43)	5.1 °C (0.71 ± 0.51)
	Contralateral	4.09 °C (0.64 ± 0.43)	3.98 °C (0.6 ± 0.42)	3.24 °C (0.51 ± 0.47)
CPT (mean ± SD)	Affected	17.37 ± 11.95 °C	13.81 ± 10.37 °C	13.83 ± 11.95 °C
	Contralateral	13.89 ± 9.69 °C	13.77 ± 9.95 °C	12.24 ± 10.1 °C
HPT (mean ± SD)	Affected	43.33 ± 6.17 °C	44.78 ± 4.85 °C	44.85 ± 5.56 °C
	Contralateral	44.41 ± 4.8 °C	44.2 ± 4.1 °C	44.75 ± 4.5 °C
Mechanical testing				
MDT mean (mean log ± SD)	Affected	4.18 mN (0.62 ± 1.1)	3.55 mN (0.55 ± 0.94)	3.95 mN (0.6 ± 1.22)
	Contralateral	1.28 mN (0.11 ± 0.7)	1.26 mN (0.1 ± 0.69)	1.13 mN (0.05 ± 0.56)
MPT mean (mean log ± SD)	Affected	37.32 mN (1.57 ± 0.83)	28.93 mN (1.46 ± 0.71)	41.97 mN (1.62 ± 0.95)
	Contralateral	25.61 mN (1.4 ± 0.52)	15.3 mN (1.19 ± 0.37)	17.64 mN (1.25 ± 0.57)
PPT mean (mean log ± SD)	Affected	69.79 kPa (1.84 ± 0.28) [a]	70.78 kPa (1.85 ± 0.31)[a]	68.31 kPa (1.83 ± 0.43)[a]
	Contralateral	154.63 kPa (2.2 ± 0.33)[a]	154.42 kPa (2.19 ± 0.3)[a]	138.55 kPa (2.14 ± 0.27)[a]

CDT: cold detection threshold.
WDT: warm detection threshold.
CPT: cold pain threshold.
HPT: heat pain threshold.
MDT: mechanical detection threshold.
MPT: mechanical pain threshold.
PPT: pressure pain threshold.
T_0: before drug application.
T_1: 60 min after (S)-ketamine dose application.
T_2: 7 days after (S)-ketamine dose application.
[a] $p < 0.05$ vs. contralateral side.

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significance ($p = 0.64$). No medication related changes were found, concerning neither mechanical nor thermal QST parameters.

3.5. Cardiovascular effects

Cardiovascular parameters differed inconsiderably between the treatment groups (MAP: 97.5 ± 10.7 vs. 93.2 ± 15.8 mmHg, $p = 0.54$; HR 77 ± 17 vs. 66 ± 10 bpm, $p = 0.13$). MAP remained stable during the initial 120 min after administration of (S)-ketamine. Subsequently, there was a slight decrease of MAP by about 5–15%, approaching a minimum after 180 min in both groups (Fig. 4). This subtle post-treatment drop of MAP between 180 and 360 min reached statistical significance (quadratic effect of time – $F_{1,11} = 20.6$; $p < 0.001$) by within subject contrasts with orthogonal decomposition of Type III sum of squares. No significant changes occurred in HR (ANCOVA time: $F_{1,11} = 2.8$; $p = 0.44$).

3.6. Side effects

Oxygen saturation (SpO_2) measured prior to administration of the study drug was comparable between both groups (group 1: 96.1 ± 0.6% vs. group 2: 96.9 ± 0.6%; $p = 0.42$). No significant decreases in SpO_2 ratios were detected, neither in terms of an effect of time ($F_{1,11} = 0.31$; $p = 0.90$) nor treatment group ($F_{1,11} = 0.23$; p:0.64), nor group × time interaction ($F_{1,11} = 0.97$; $p = 0.67$).

A considerable amount of psychotropic side effects was registered, particularly in the group receiving 0.4 mg/kg (S)-ketamine. A noteworthy frequency of side effects was encountered for vertigo, sedation and difficulties to concentrate (Fig. 5). Overall, side effects were approximately doubled in the higher dose group (weighted scores: 14 vs. 32 for groups 1 and 2, respectively; $p < 0.05$).

No impairment of cognitive functioning was found after administration of intranasal (S)-ketamine (MMS before (S)-ketamine: 28.6 ± 0.5 for group 1 vs. 27.9 ± 1.9 for group 2; MMS 30 min after (S)-ketamine: 27.9 ± 3.1 for group 1 vs. 28.4 ± 1.3 group 2). No differences between the study groups could be detected ($p > 0.80$).

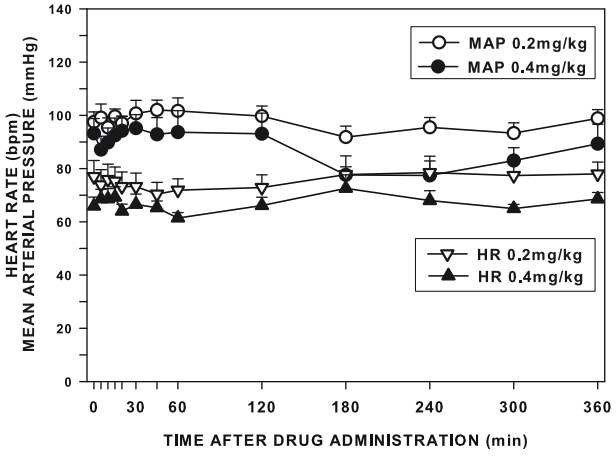

Fig. 4. Profile of hemodynamic changes after intranasal (S)-ketamine application. MAP decreased 5–15% 180 min after drug application ($p < 0.05$). No initial increase of heart rate (HR) or mean arterial pressure (MAP) was observed.

4. Discussion

Low-dose intranasal administration of (S)-ketamine rapidly produces adequate plasma concentrations of (S)-ketamine and consecutively sustained concentrations of (S)-norketamine without induction of major remarkable side effects. Ongoing neuropathic pain was significantly and dose-dependently reduced for about 2–3 h. The maximal pain reduction of approximately 30% and 40% was reached 60 min after nasal (S)-ketamine application, and the time course of pain reduction highly correlated with the respective combined plasma concentrations of (S)-norketamine and (S)-ketamine. In contrast, QST revealed neither short term nor long term changes in somatosensory mechanical or thermal pain and detection thresholds.

4.1. Plasma concentrations after intranasal (S)-ketamine

Average doses of (S)-ketamine were comparable to the ketamine doses administered in the study by Carr and colleagues, when adjusting for the higher analgesic potency of (S)-ketamine (Carr et al., 2004). Intranasal drug administration induced a rapid (S)-ketamine plasma-peak within 15 min, followed by a fast decline below a level of 10 ng/ml within 60 min in both groups. The resulting plasma concentrations of (S)-norketamine, which is the major metabolite of (S)-ketamine synthesized in the liver, exceeded a level of 10 ng/ml between 30 and 180 min after drug administration in both groups. As the intranasal route of administration bypasses the first pass metabolism by the liver, resulting (S)-norketamine concentrations are lower when compared to similar oral or rectal

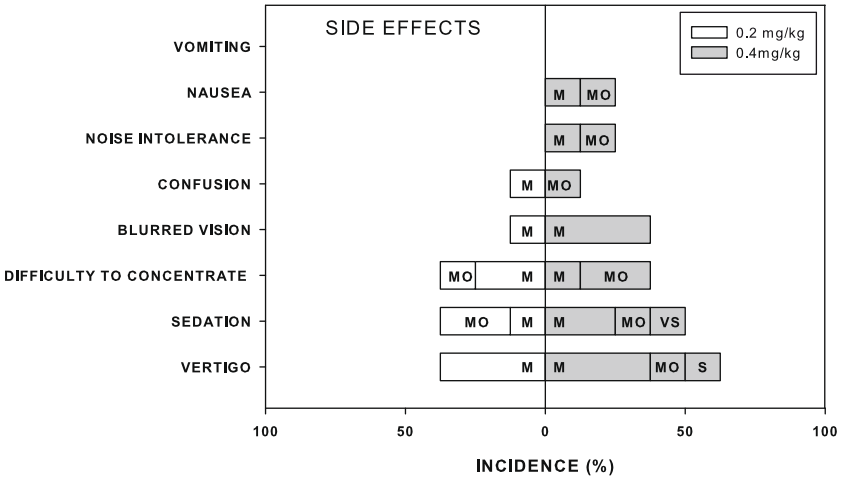

Fig. 5. Side effects after intranasal (S)-ketamine application. Side effects were approximately doubled in the higher dose group (weighted scores: 14 vs. 32; $p < 0.05$). Vertigo, sedation and subjective difficulties to concentrate represented the most frequently reported side effects. M: mild; MO: moderate; S: severe; VS: very severe.

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dosing (Yanagihara et al., 2003). While oral (S)-ketamine administration may result in higher concentrations of (S)-norketamine, intranasal administration possesses the advantage of a rapid increase in (S)-ketamine concentration, and may therefore be more suitable for the treatment of breakthrough pain (Fitzgibbon et al., 2003; Carr et al., 2004). Furthermore, given its primarily use in palliative cancer care, an intranasal spray can be more easily manufactured than a drug containing tablet (Bell et al., 2003). However, we observed a high inter-individual variability in peak plasma concentrations of (S)-ketamine and, owing to the parallel group design, we thus were not able to show significant differences in (S)-ketamine concentrations between both study groups. This variability may be explained by the obvious problem for some patients to sniff the complete study dose (3 ml). They swallowed a substantial portion of (S)-ketamine. The swallowed proportion of the medication subsequently underwent excessive first pass metabolisms in the liver, thereby causing increased (S)-norketamine concentrations. Consequently, (S)-norketamine concentrations displayed significant differences between both groups. However, since we were not able to quantify this specific portion, the precise amount of intranasally applied (S)-ketamine finally remains unclear and therefore no further pharmacokinetic conclusions were drawn. The use of preparations with a higher concentration of (S)-ketamine (and thus a lesser volume of fluid) might help to solve this problem.

4.2. Side effects

The incidence of psychotropic side effects was significantly higher in the 0.4 mg/kg dose group, which is in line with studies demonstrating a linear dose response relationship for the psychedelic effects of ketamine (Bowdle et al., 1998). However, (S)-ketamine appears to have a more favourable side effect profile than racemic ketamine (Pfenninger et al., 2002). Interestingly, antinociceptive doses of (S)-norketamine in animal studies were, just as in this study, not accompanied by significant side effects (Holtman et al., 2008). Therefore, a dosing as low as 0.2 mg/kg of intranasal (S)-ketamine might be suitable for achieving an adequate therapeutic action (analgesia) combined with minor side effects. Finally, the possibility of substance abuse must be taken into account, and therefore treatment of breakthrough cancer pain in a palliative care setting seems to be the most prudent indication for this rapid-acting drug administration (Bell and Kalso, 2004).

4.3. Analgesic action of intranasal (S)-ketamine

Overall, the pharmacokinetic data derived in this study were comparable to those encountered in three healthy volunteers after intranasal administration of 25 mg racemic ketamine (Yanagihara et al., 2003). As our study was not intended as a proof-of-concept study, no placebo control was included. Nevertheless, the analgesic effect of (S)-ketamine in neuropathic pain conditions was confirmed in our study, and the causative relation to drug administration was signalled by the close correlation between (S)-ketamine plasma concentrations and concomitant pain score reduction. Interestingly, the plasma concentrations of (S)-norketamine were even closer correlated to pain scores, therefore accounting for a substantial fraction of the pain reduction observed. However, as maximum pain reduction in group 2 preceded the maximum concentrations of (S)-norketamine, a delayed (S)-ketamine effect, and an actually anti-analgesic effect of (S)-norketamine must likewise be taken into account. On the other hand, recent findings from animal studies, emphasized the antinociceptive properties of norketamine and especially (S)-norketamine (Holtman et al., 2008; Ebert et al., 1997).

Remarkably, multiple regression analyses enabled precise prediction of pain reduction, assigning roughly similar regression weights to (S)-ketamine and (S)-norketamine concentrations which however covered different times ranges. Therefore we conclude that rapid onset, as well as prolonged pain reduction observed after low-dose intranasal (S)-ketamine, depends on the achieved plasma concentrations of both (S)-ketamine (covering the first 30 min), and (S)-norketamine (covering any time frame >30 min). All effects were achieved by a dose as low as 0.2 mg/kg body weight.

4.4. Effects of (S)-ketamine and (S)-norketamine on somatosensory function

QST is a fundamental clinical tool in order to characterize sensory changes in neuropathic pain disorders, and therefore to reveal underlying pathomechanisms of neuropathic pain syndromes. Furthermore, it may help to draw conclusions regarding the mechanisms of action of analgesic drugs, thereby potentially contributing to mechanism-based diagnosis and mechanisms-based pharmacological treatment (Huge et al., 2008; Woolf and Max, 2001; Woolf, 2004; Geber et al., 2008; Klein et al., 2008). The neuropathic pain patients in the study at issue displayed two major pathological findings in their QST profiles: first, a tendency towards higher detection thresholds for thermal and mechanical stimuli on the affected side (i.e. sensory loss), and secondly, a significant hyperalgesia for blunt pressure in the painful area (i.e. nociceptive gain). Low-dose intravenous (S)-ketamine has been shown to reduce secondary hyperalgesia in human surrogate pain models (Klein et al., 2007; Koppert et al., 2001). However, the absence of pin prick hyperalgesia, the hallmark sign of central sensitization, in our patient group suggests no decisive role for central sensitization in the investigated cohort (Klein et al., 2005).

If any, effects of ketamine on normal pain perception occur only at much higher doses in human and animal experiments (Arendt-Nielsen et al., 1995; Petrenko et al., 2006; Kern et al., 2008). These results are in line with recent findings, demonstrating that inhibition of the protein tyrosine kinase Src, a key enhancer of NMDAR function, blocks neuropathic and inflammatory pain responses, but does not affect basal sensory thresholds or acute nociceptive responses in mice (Liu et al., 2008).

Taken together, the results of this study indicate that low-dose intranasal administration of (S)-ketamine is a feasible method to produce a rapid onset of intravenous (S)-ketamine concentrations followed by sustained (S)-norketamine concentrations. This treatment displays significant analgesic properties on pathological neuropathic pain, but no effects on normal somatosensory function. We conclude that low-dose intranasal (S)-ketamine administration offers a beneficial tool for the ad hoc treatment of breakthrough pain, additionally containing a longer acting analgesic component through (S)-norketamine.

Conflict of interest

This work was supported by Pfizer, Germany. The authors had full, unrestricted access to the data. The funding source had no role in analysis or interpretation of the data.

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