European Journal of Pain xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

Review

Use of oral ketamine in chronic pain management: A review

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ARTICLE INFO

Article history:
Received 29 June 2009
Received in revised form 31 August 2009
Accepted 20 September 2009
Available online xxxx

Keywords:
Chronic pain
Ketamine
Oral administration
Neuropathic pain
Review

ABSTRACT

The analgesic effect of ketamine is primarily based on the antagonism of the *N*-methyl-D-aspartate (NMDA) receptor. Activation of NMDA receptors may play a crucial role in the pathogenesis of chronic pain. Little formal research has been performed on the efficacy and safety of ketamine in chronic pain, especially concerning long-term oral administration. This review provides an overview of the available clinical data on the use of oral ketamine in chronic pain management. A literature search was performed in MEDLINE, EMBASE and the Cochrane Library, resulting in 22 relevant articles. Because most retrieved articles were of a descriptive nature (e.g. case reports and case series) a quantitative analysis was not possible. There was no consistent dose–response relation. A recommended starting dosage in ketamine-naive patients is 0.5 mg/kg racemic ketamine or 0.25 mg/kg S-ketamine as a single oral dose. The dosage is increased by the same amount if required. For a continuous analgesic effect it is usually given 3–4 times daily. The injection fluid can be taken orally. When parenteral ketamine is switched to oral administration the daily dosage can be kept equal and, depending on clinical effect and/or adverse effects, is slowly increased. The pharmacologically active metabolite norketamine is believed to contribute to the analgesic effect of oral ketamine. Lack of evidence regarding efficacy, and the poor safety profile, do not support routine use of oral ketamine in chronic pain management. Oral ketamine may have a limited place as add-on therapy in complex chronic pain patients if other therapeutic options have failed.

1. Introduction

Ketamine is a phencyclidine anaesthetic, increasingly used in subanaesthetic doses as an analgesic in a wide range of pain settings (Visser and Schug, 2006). The analgesic effect of ketamine is primarily based on the antagonism of the *N*-methyl-D-aspartate (NMDA) receptor (Fisher et al., 2000). Activation of NMDA receptors results in central sensitization, which may play a crucial role in the pathogenesis of chronic pain (Bennett, 2000; Eide, 2000). Besides acting on the NMDA receptor, ketamine also acts on nicotinic, muscarinic and opioid receptors (Jensen et al., 2008). Ketamine both has an anti-nociceptive and anti-hyperalgesic effect, the latter especially occurring in the lower dosage ranges (Persson 2008).

Administration of ketamine is reported to reduce pain in patients with neuropathic pain of various origins, including postherpetic neuralgia (Eide et al., 1995), complex regional pain syndrome (CRPS) (Kiefer et al., 2008), cancer pain (Mercadante et al., 2000; Okon, 2007), orofacial pain (Mathisen et al., 1995) and phantom limb pain (Eichenberger et al., 2008). It is commercially available as injection solution containing a 1:1 racemic mixture of ketamine or the S-ketamine isomer. S-ketamine is approximately twice as potent in analgesia as the racemic mixture of ketamine (Arendt-Nielsen et al., 1996). Literature is not conclusive about the differences in safety profiles of ketamine as racemic mixture and S-ketamine (Kohrs and Durieux, 1998). When used in chronic pain management routes of administration include parenteral (intravenous, subcutaneous, intramuscular, epidural, intra-articular), oral, topical, intranasal and sublingual (Kronenberg, 2002; Hocking and Cousins, 2003; Visser and Schug, 2006; Ben-Ari et al., 2007). In long-term use oral administration is preferred. Orally administered ketamine undergoes extensive first-pass metabolism in the liver, resulting in a bioavailability of approximately 16% (Grant et al., 1981; Clements et al., 1982). The primary metabolic pathway involves hepatic *N*-demethylation via the cytochrome P450 system to form norketamine, a pharmacologically active metabolite (White et al., 1982). Oral administration of ketamine is associated with higher serum levels of norketamine compared to other routes of administration (Grant et al., 1981; Clements et al., 1982). The elimination half-life is 2–3 h for ketamine (Grant et al., 1981) and approximately 4 h for norketamine (Product information leaflet, 1999). Norketamine is thought to contribute to the analgesic effect and the duration of effect after oral administration of ketamine

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1090-3801/$36.00
doi:10.1016/j.ejpain.2009.09.005

Please cite this article in press as: Blonk MI et al. Use of oral ketamine in chronic pain management: A review. Eur J Pain (2009), doi:10.1016/j.ejpain.2009.09.005

(White et al., 1982; Ebert et al., 1997; Holtman et al., 2008). Although the use of ketamine as an analgesic is now generally accepted, the evidence base remains poor. Little formal research has been performed on the efficacy and safety of ketamine in chronic pain management, especially concerning long-term oral administration. Oral formulations of ketamine are not commercially available. The parenteral formulation is given as an oral solution or an extemporaneous preparation is made. In general, off-label use of medication has to be based on evidence about efficacy and safety.

The aim of this review is to provide an overview of the available evidence regarding the efficacy and safety of oral ketamine in chronic pain management.

2. Methods

A literature search for this review was performed in the MEDLINE database from 1966 to March 2009, the EMBASE database from 1950 to March 2009 and the Cochrane Library in February 2009. Keywords or MeSH terms used in the search strategy were: 'ketamine', 'administration, oral', 'chronic pain', 'pain', 'neuropathic pain', 'cancer pain'. The keywords with 'pain' were separated using the word 'OR'. Articles describing a study based on animal research and research about acute postoperative pain were excluded by entering the term 'NOT' in the search strategy. Furthermore, the search option 'related articles' in MEDLINE was used. The titles and abstracts obtained from the search were assessed for relevance.

To be included the article had to meet the following criteria: (1) the study is performed in adults, (2) ketamine or S-ketamine is administered orally as an analgesic, (3) the indication of ketamine is chronic pain, (4) ketamine treatment is evaluated, (5) the article is written in English, and (6) it is an original article (duplicates and reviews are excluded). There was no restriction on the type of report or the design of the study. Case reports and short communications were also included. In addition, a secondary search was performed by handsearching the reference lists from the collected reviews and relevant articles.

The articles were analysed by two reviewers. They collected information about the number of included patients receiving oral ketamine, study design, pain type, dosage regimen, efficacy and adverse effects. The methodological quality of the individual studies was rated according to the classification levels presented in Table 1 (Hocking and Cousins, 2003).

3. Results

3.1. Literature search

With the literature search we identified 88 articles. Seven duplicates could be removed. Based on the inclusion and exclusion criteria another 57 articles were withdrawn. Additional searching in the reference lists of the related articles and reviews resulted in the identification of two extra articles. After reviewing the full text of the remaining 26 articles, 22 articles could be included in our review. The literature selection procedure and reasons for exclusion are shown in Fig. 1. Table 2 lists the 22 included studies and provides information about each study in order of methodological quality, followed by publication date. Due to the small number of trials and patients, and the heterogeneity of data, it was not possible to perform a quantitative analysis. Most retrieved articles were of a descriptive nature, such as case reports and case series. The comparative trials that were relevant in this review included small numbers of patients with a variety of study objectives, designs and outcome measurements. None of the included studies had a high-quality methodological design. Of the 22 included studies, 16 were non-comparative observational studies or anecdotal reports about oral ketamine. Four of those were case series and 12 were case reports. The remaining six published reports describe comparative studies in which oral ketamine is studied as add-on therapy with morphine (Lauretti et al., 1999) or compared to placebo (Eide and Stubhaug, 1997; Nikolajsen et al., 1997; Haines and Gaines, 1999; Rabben et al., 1999; Furuhashi-Yonaha et al., 2002). Two of the comparative studies are *N* of 1 trials in which one patient re-

Table 1
Classification of the methodological quality of the included publications.

I	Systematic review (meta-analysis)
II	Randomized double-blind controlled trials of sufficient size and consistency
III	Randomized clinical trial of moderate quality or insufficient size or other comparative trials (non-randomized, cohort studies, crossover studies)
IV	Non-comparative trial, observational study, case series, comparative trial with one patient (*N* of 1 trial)
V	Case report

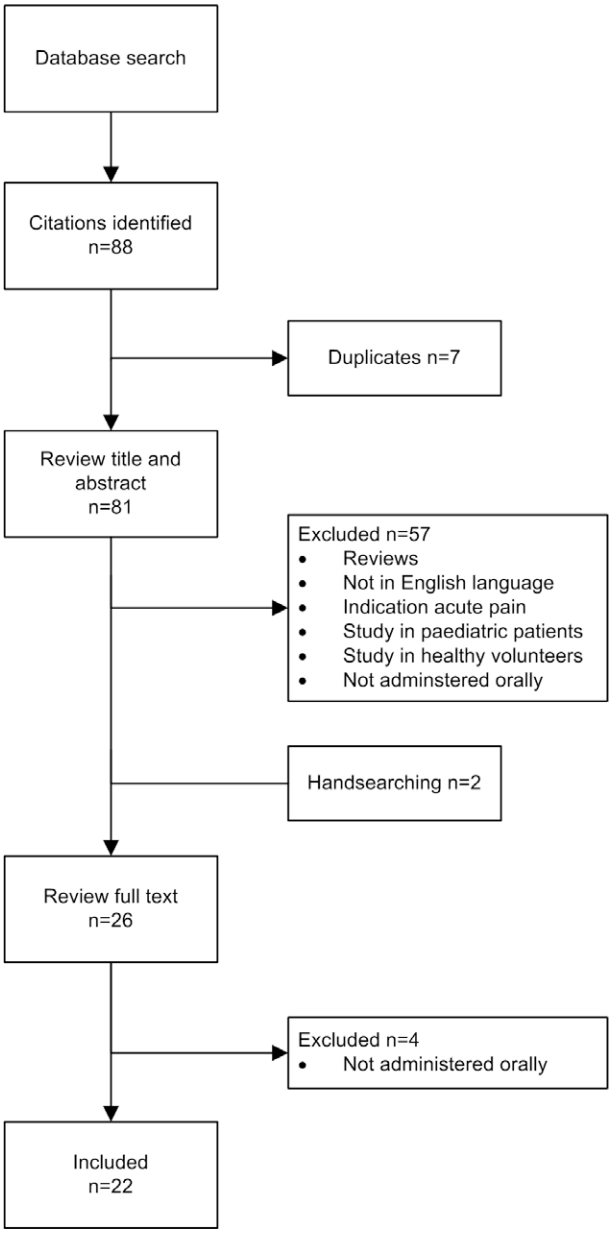

Fig. 1. Overview of the literature search and selection procedure.

Table 2
Published reports concerning oral administration of ketamine in chronic pain.

Study	Number of patients	Design (quality)[a]	Pain type	Oral ketamine		Outcomes	
				Daily dosage/ number of divided doses	Duration of treatment	Efficacy	Adverse effects
Rabben et al. (1999)	26	CO, PC, SB (III)	Secondary trigeminal neuralgia	4 mg/kg/1 (at night) after KET IM 0.4 mg/kg vs. pethidine 1.0 mg/kg single dose	3 days	Five patients significant but variable pain relief. Non-responders to KET IM no response to KET PO.	Dizziness, sedation, dry mouth, blurred vision, altered hearing, sensory illusions
Haines and Gaines (1999)	21	CO, PC (III)	Neuropathic pain	20 up to 100 mg/1 (dose escalation), average 45 mg/1 (PC)	1 week (run-in) + 3 × 1 week KET vs. 1 week PL	10/21 withdrew after run-in open-dose escalation period due to SE. 9/21 entered PC study. 3/9 patients reported to have benefit from KET	Light headedness, dizziness, tiredness, headache, nervous floating feeling, bad dreams
Lauretti et al. (1999)	15	RCT (III)	Chronic cancer pain	1 mg/kg/2 (patients randomized to one of 4 groups ($N = 15$): morphine (control), morphine + KET PO, + nitroglycerin or + dipyrone)	1 month	After day 15 daily morphine consumption was statistically significant reduced in KET-group due to analgesic and/or opioid-sparing effect	Hallucinations; less somnolence compared to control group
Furuhashi-Yonaha et al. (2002)	8	CO, PC (III)	Neuropathic pain (CRPS, phantom pain, PHN, visceral pain)	2 mg/kg/4, in long-term treatment 25–136 mg per day (positive response to KET IV test-dose)	1 week, in long-term treatment 9–54 months	Statistically significant reduction of VAS score (average 30%) after 1 week of. 4/8 patients received long-term treatment. No tolerance	Nightmares and dizziness, headache
Nikolajsen et al. (1997)	1	N1, PC (IV)	Post-amputation stump pain	200 mg/4 (also KET IV 0.42 mg/kg single dose (vs. PL DB))	3 months	KET PO 50 mg (vs. PL SB) gave complete pain relief in 10 min and lasted up to 6 h. Ongoing pain relief when four times daily. No tolerance	No AE
Eide and Stubhaug (1997)	1	N1, PC, DB (IV)	Glossopharyngeal neuralgia	360 mg/6 (KET IV 0.065 mg/kg; optimal PO dose was found in open-dose escalation trial)	10 × 2 days	Statistically significant pain relief in VAS scores by KET PO in 8/10 treatment periods	Fatigue, dizziness
Enarson et al. (1999)	21	CS, R (IV)	Central and peripheral neuropathic pain	100 mg, adjusted to 40–500 mg (average 220 mg)/number of divided doses not mentioned	<10 days up to > 1 year	7/21 ↓ pain. 3/7 responders continued in long-term treatment	Dissociative feeling, somnolence, insomnia, sensory changes
Rabben and Oye (2001)	13	CS (IV)	Neuropathic orofacial pain	4 mg/kg/1 (at night) (after KET IM 0.4 mg/kg test-dose)	3 days	8/13 patients reduced pain intensity or complete analgesia	Anxiety and hallucinations, 'near death' experience, dizziness
Kannan et al.(2002)	9	CS (IV)	Neuropathic cancer pain	1.5 mg/kg (adjusted 70 mg average)/3	2 months	Mean NRS ↓ of 3.6 (±1.5) points after 24 h. In 7/9 patients continuous ↓ by ⩾3 points. No tolerance was observed	Anorexia, nausea, vomiting, sedation. 3/9 stopped due to AE
Cvrcek (2008)	32	CS (IV)	PHN and diabetic polyneuropathy	150 mg/5 (initial KET IV single dose)	3 months	Statistically significant ↓ of VAS score	Dizziness, dry mouth, sedation, nausea, euphoria, memory deterioration
Hoffmann et al. (1994)	1	CR (V)	Ophthalmic PHN	3 mg/kg (240 mg)/6, up to 12.5 mg/kg (1000 mg)/5 (KET IM bolus 0.2 mg/kg and SC 0.06 mg/kg/h followed by PO)	5 weeks	Pain relief. Other analgesics were decreased. KET was stopped with no recurrence of pain after 5 weeks	Local inflammation SC infusion site. No AE PO treatment

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Table 2 (*continued*)

Study	Number of patients	Design (quality)[a]	Pain type	Oral ketamine		Outcomes	
				Daily dosage/ number of divided doses	Duration of treatment	Efficacy	Adverse effects
Broadley et al. (1996)	2	CR (V)	Axonal sensorimotor neuropathy	2.4 mg/kg (150 mg)/ 3, up to 13 mg/kg (800 mg)/4	2 weeks + 1 month	Pain free at KET SC 4.8 mg/kg/day followed by PO. Worsening of pain after withdrawal of KET	Vivid dreams. Inflammation at needle side with KET SC
			Central neuropathic pain with sympathetic dependent pain	0.9 mg/kg (75 mg)/ 3, up to 5.7 mg/kg (400 mg)/4	3 + 4 months	Daily dose increased until pain free for 3 months when symptoms returned. After switching to other analgesic back on KET PO and remained pain free for >4 months	No AE
Klepstad and Borchgrevink (1997)	1	CR (V)	PHN	300 mg/6 (after using KET IV, SC (100 mg/24 h) and IM 10 mg/day switch to KET PO)	2 months	Good pain relief. After recurrence of gastric ulcer switched back to KET IM with adequate pain relief	Headache, nausea, abdominal pain, recurrence of gastric ulcer (relation to KET unclear)
Fisher and Hagen (1999)	1	CR (V)	Neuropathic pain of spinal origin	30 mg/3, up to 75 mg/3 (after 120 mg/24 h SC)	5 months	Continuous pain relief after switching to PO	No AE with PO treatment
Friedman et al. (2000)	1	CR (V)	Cancer pain	Single dose of 75 mg		Patient was temporarily pain free	Visual hallucinations and paranoid ideation
Vick and Lamer (2001)	1	CR (V)	Central post-stroke pain	0.7 mg/kg (50 mg)/ 1, up to 2.1 mg/kg (150 mg)/3 (KET IV (total 0.3 mg/kg) followed by KET PO)	9 months	Pain relief, reduced allodynia and hyperalgesia Opioid-sparing effect. Worsening of pain after withdrawal of KET. No evidence of tolerance	No AE (with prophylactic use of diazepam). Dysphoria, confusion, depression at high dose
Fitzgibbon et al. (2002)	3	CR (V)	Neuropathic, ischemic and mixed pain (predominantly neuropathic)	30–225 mg/3 (KET SC/IV followed by PO adjusted to an effective dose)	3 weeks–6 months	Pain relief (↓ VAS score). In 2/3 patients opioid reduction possible	No AE with prophylactic use of hypnotic drugs, inflammation at SC site
Kapur and Friedman (2002)	2	CR (V)	RLS and neurogenic claudication	60–80 mg/2	6 months and > 1 month	Pain relief (↓ VAS score with 4–5 points), improvement of RLS symptoms	No AE
Benitez-Rosario et al. (2003)	4	CR (V)	Neuropathic pain	150–375 mg/3 (KET SC, followed by KET PO titrated up to effective dose)	3–5 weeks	Marked pain relief (assessed by VAS)	Minor and transitory mental AE in one patient
Sakai et al. (2004)	1	CR (V)	Pain and allodynia associated MS	20 mg/1 up to 40 mg/2 (after KET IV 15 mg test-dose)	>1 year	KET PO was more effective than dextromethophan (average ↓ VAS score by >5 points). Positive effect on quality of life	Some dizziness
Villanueva-Perez et al. (2007)	1	CR (V)	CRPS I	90 mg/3, up to 240 mg/4	>5 months	Reduction of pain (↓ VAS score by 4–5 points) with concurrent use of other analgesics. Slight progression of pain after 4–5 months	Nausea and vomiting (controlled with haloperidol)
Okon (2007)	1	CR (V)	Complex nociceptive-neuropathic pain	60 mg/3, down to 30 mg/2	>4 months	Pain relief and decrease in opioid consumption. Worsening of pain after stop of KET PO	Somnolence, no AE after dose reduction

Abbreviations: AE = adverse effects, CO = crossover, CR = case report, CRPS = complex regional pain syndrome, CS = case series, DB = double-blind, IM = intramuscular, IV = intravenous, KET = ketamine (racemic mixture), MPQ = McGill pain questionnaire, MS = multiple sclerosis, N1 = *N* of 1 trial, NRS = numeric rating score, PC = placebo-controlled, PHN = postherpetic neuralgia, PL = placebo, PO = per os, PPT = pressure-pain threshold, R = retrospective, RCT = randomized controlled trial, RLS = restless legs syndrome, SB = single-blind, SC = subcutaneous, VAS = visual analogue scale.

[a] Classification of methodological quality (Table 1).

ceives both the study drug and a placebo (Eide and Stubhaug, 1997; Nikolajsen et al., 1997). Three of the four remaining comparative studies have a crossover placebo-controlled design in which all participants receive all the interventions. The 22 studies

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describe a total of 166 patients receiving oral ketamine in the period 1994 up to 2008. The chronic pain patients had a broad range of pain types. In most cases the pain was diagnosed as neuropathic pain or as having a neuropathic component (for pain types: see Table 2).

3.2. Dosage, dosage form and efficacy of oral ketamine

In the non-comparative studies or anecdotal reports (classes IV and V) two approaches to pain treatment with oral ketamine were described. Either the patient started directly with oral ketamine with a low daily dose which, based on clinical effect and/or adverse effects, is increased. Or, the patient started with parenteral ketamine, either a single test dose or continuous treatment with usually intravenous or subcutaneous ketamine, after which the patient is switched to an equipotent oral dose of ketamine. The effective daily dosages ranged from (approximately) 45 mg to 1000 mg. There was no consistent dose–response relation. In the case reports the ratio between equianalgesic potency of ketamine subcutaneous/ketamine per os in daily dose ranged from 1:0.3 to 1:8.5, with a median of 1:1 (Hoffmann et al., 1994; Broadley et al., 1996; Klepstad and Borchgrevink, 1997; Fisher and Hagen, 1999; Fitzgibbon et al., 2002; Benitez-Rosario et al., 2003). The number of divided doses necessary for continuous analgesic effect also ranged from once daily up to a frequency of 6 times daily (on average 3–4 times daily). The duration of effect after a single dose (if there was any effect) ranged from a few hours to 24 h or more. In all the included studies, only the racemic mixture of ketamine was administered. Ketamine was primarily ingested as an oral liquid. Usually the injection fluid was used, in some cases mixed with fruit juice or syrup to mask the bitter taste. Two of the studies used extemporaneously prepared ketamine capsules (Rabben et al., 1999; Vick and Lamer, 2001). In most of the evaluated studies pain assessment was performed with a visual analogue scale (VAS) or numeric rating scale (NRS). Measurement outcomes were expressed as a reduction of the VAS score in points or in percentages. However, especially in the case reports, pain relief was not always objectified by VAS or NRS. In the randomized controlled trial where a combination of oral ketamine and morphine is compared to morphine alone, both the VAS scores and the daily morphine dose were evaluated (Lauretti et al., 1999). VAS scores were similar between the two groups, but the daily morphine consumption was significantly reduced in the ketamine group. Opioid reduction is also observed in other studies (Vick and Lamer, 2001; Fitzgibbon et al., 2002; Furuhashi-Yonaha et al., 2002; Okon, 2007). There is an inverse relation between the number of included patients in a study and the claimed efficacy of ketamine. About 90% of the case reports present positive results about the efficacy of ketamine, while the larger comparative controlled trials show an efficacy of approximately 25%.

3.3. Adverse effects

A high number of withdrawals due to adverse effects were seen. In a study with 21 patients with neuropathic pain, 10 patients withdrew after a run-in open-dose escalation period (Haines and Gaines, 1999). A similar drop-out rate was seen in a non-comparative trial, despite good pain relief in half of the patients who withdrew (Enarson et al., 1999).

The most frequently observed adverse effects were effects on the central nervous system, such as sedation, somnolence, dizziness, sensory illusions, hallucinations, nightmares, dissociative feeling and blurred vision. The psychotomimetic adverse effects, such as hallucinations, were considered the most disturbing. One case report describes a patient with hepatocellular carcinoma and severe hepatic disease. The patient developed serious adverse effects (e.g. hallucinations and paranoid ideation) starting after a single oral dose of 75 mg ketamine, which resolved quickly (Friedman et al., 2000). The authors suggest that the cause could be high peak plasma levels of ketamine due to an impaired first-pass metabolism. Patients also mentioned gastrointestinal adverse effects, such as nausea, vomiting, anorexia and abdominal pain. One patient developed a gastric ulcer, although the association with ketamine use remained unclear (Klepstad and Borchgrevink, 1997). Rabben et al. (1999) described qualitatively similar adverse effects in patients treated with intramuscularly (0.4 mg/kg) compared to orally (4 mg/kg) administered ketamine, but there were fewer side-effects in the latter group. Disturbing adverse effects disappeared in some patients when the dosage was reduced (Lauretti et al., 1999; Vick and Lamer, 2001; Okon, 2007). Kannan et al. (2002) observed an improvement of the drowsiness in some patients after 2 weeks of treatment. Also, hypnotics and haloperidol were used to prevent or to treat adverse effects of ketamine with variable success (Fisher and Hagen, 1999; Rabben and Oye, 2001; Vick and Lamer, 2001; Fitzgibbon et al., 2002; Furuhashi-Yonaha et al., 2002; Villanueva-Perez et al., 2007).

The duration of treatment was often limited due to adverse effects. Some patients who experienced good pain relief continued to take oral ketamine for several months up to a maximum of more than one year for a few patients (Enarson et al., 1999; Furuhashi-Yonaha et al., 2002; Sakai et al., 2004). No adverse effects caused by long-term treatment were described. A slight progression of pain was seen in one patient after a treatment of 4–5 months, but it is unclear if progression of disease or tolerance to ketamine played a role (Villanueva-Perez et al., 2007). Cognitive impairment and psychological wellbeing were not studied. One case series ($N = 32$) is included which specifically studied the side-effects of ketamine in the long-term treatment (3 months) of neuropathic pain (Cvrcek, 2008). During the entire study period blood pressure values and heart rate remained normal. Clinical chemical parameters measured before and at the end of the study did not show any differences in liver enzymes and other parameters. The electroencephalograph performed at 3 months did not show epileptogenic activity. Differences in adverse effects over time were not specifically mentioned.

4. Discussion and conclusions

Evidence on the effect of oral ketamine in chronic pain is limited and the quality of the studies is not very high. The majority of the included studies were non-comparative trials or case reports. The evidence that is available shows that chronic pain patients can have limited benefit from the use of oral ketamine. The dosages that are recommended and the adverse effects that can be expected are discussed below in more detail, resulting in some advice for clinical practice.

4.1. Optimal dosage of oral ketamine

The range in effective dosages of orally administered ketamine varies extensively between patients. There seems to be no clear dose–response relation when clinical data are observed. Variability in hepatic metabolism resulting in an increased or reduced bioavailability and variance in plasma levels of norketamine can lead to intra-individual variability. The pharmacokinetic studies performed in healthy volunteers did not show large differences, although only a small number of participants were included (Grant et al., 1981; Clements et al., 1982). It is likely that the variation in dose response and efficacy can be explained by the anti-hyperalgesic effect in low dosages and the anti-nociceptive effect in higher

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dosages (Persson, 2008) and perhaps other, yet unknown, mechanisms.

Several case reports describe patients switching from a subcutaneous continuous infusion to an effective oral dosage of ketamine. Considering the substantial differences seen in practice, it is difficult to give a standard conversion factor to calculate an equipotent oral dose. Oral administration of ketamine is associated with higher serum levels of norketamine compared to other routes of administration. The oral bioavailability of ketamine, defined as area under plasma concentration time curve (AUC), after a single oral dose of 0.5 mg/kg is about one fifth of the availability after an intravenous injection. On the other hand, the oral bioavailability of norketamine is similar between the two types of administrations, with much higher peak plasma concentrations (200 ng/ml) reached after oral administration (Grant et al., 1981; Clements et al., 1982). When ketamine is administered as a racemic mixture, both S-norketamine and R-norketamine is formed. S-norketamine is approximately five times weaker than S-ketamine in both binding assay and functional experiments (White et al., 1982; Holtman et al., 2008). Analgesic effects of ketamine were observed with plasma levels of 100–200 ng/ml (sum of S- and R-isomer) following intramuscular and intravenous administration. Effective analgesia following oral dose occurs at much lower concentrations of ketamine (40 ng/ml) (Grant et al., 1981). Considering this and the relatively high plasma concentrations of norketamine reached, norketamine is believed to contribute to the analgesic effects of orally administered ketamine (Bushnell and Craig, 1995; Fisher et al., 2000). Therefore, conversion from parenteral to oral administration in an equipotent dose is complex and is not solely based on a reduced bioavailability. The median conversion rate from subcutaneous to oral ketamine used in the case reports was 1:1. In all the described studies, only the racemic mixture of ketamine was administered. S-ketamine has an analgesic potency which is approximately twice as potent as the racemic mixture (Arendt-Nielsen et al., 1996). In a ketamine-naive patient, oral administration of ketamine can start with a single dose of 0.5 mg/kg ketamine racemic mixture or 0.25 mg/kg S-ketamine to evaluate the effect on pain relief and the duration of effect. Doses can be increased in steps of 0.5 or 0.25 mg/kg according to the efficacy and adverse effects, respectively. The average dosing frequency of 3–4 times daily found in the clinical studies corresponds well with the elimination half-lives of ketamine (2–3 h) (Grant et al., 1981) and norketamine (4 h) (Product information leaflet, 1999).

4.2. Adverse effects and long-term usage of ketamine

Oral ketamine has been suggested to produce fewer and less severe adverse effects than parenterally administered ketamine, for the following reasons. Smaller (peak) plasma levels of ketamine are reached after oral intake, resulting in fewer or less pronounced adverse effects. After oral intake, the main metabolite norketamine reaches much higher plasma levels due to extensive first-pass metabolism (Grant et al., 1981; Clements et al., 1982). Preclinical animal studies suggest that norketamine might have a more favourable safety profile than ketamine (Holtman et al., 2008). In a crossover placebo-controlled trial by Rabben and colleagues (1999), the adverse effects reported after oral ketamine 4 mg/kg were qualitatively similar but less pronounced compared to ketamine intramuscularly 0.4 mg/kg; it is unclear whether the doses used in this trial were equipotent. The information on adverse effects after long-term use, or development of tolerance to oral ketamine, in chronic pain patients is limited. Ketamine has been used in some patients for more than 1 year without observed tolerance or adverse effects associated with long-term use (Enarson et al., 1999; Furuhashi-Yonaha et al., 2002; Sakai et al., 2004).

After prolonged intrathecal administration of ketamine, neurotoxicity has been found to occur (Vranken et al., 2005). Both a local mechanism of toxicity (because of the intrathecal route) and a mechanism caused by excessive NMDA receptor antagonism may explain this neurotoxicity. The latter mechanism may play a role in prolonged oral administration as well and warrants continued prudence in using long-term oral ketamine.

Studies among recreational ketamine users suggest that frequent ketamine use is associated with impairments in working memory, episodic memory and aspects of executive function, as well as reduction in psychological wellbeing. No association was found with distinct cognitive impairments, although increased levels of delusional and dissociative symptoms were observed. Cognitive impairment may be reversible after stopping ketamine abuse. No impairment was observed in ex-ketamine users (Morgan et al., 2009). Prophylactic use of hypnotics or haloperidol, to prevent adverse effects such as hallucinations, is mentioned in several studies but is not common practice in oral ketamine treatment. Prophylactic medication should not be necessary if the patient starts with a low dose, which is increased slowly depending on clinical and/or adverse effects. If unacceptable adverse effects occur the dose should be reduced.

4.3. Advice for clinical practice

When prescribing oral ketamine for patients with chronic pain, one can encounter a number of practical problems. First of all, ketamine is not approved for this indication and is therefore used off-label (but so are many other medicines with good results). The evidence base for the use of oral ketamine in chronic pain management remains poor and information about long-term side-effects is lacking. Until more research is performed the physician has to weigh the possible risk/benefit ratio for every individual patient.

There is no commercially available oral formulation of ketamine. In the included trials and reports various oral formulations were used. The injection fluid can be taken as an oral solution, and mixed with fruit juice to mask the bitter taste. Some might prefer an extemporaneously prepared oral liquid out of the injection fluid, primarily to improve the taste. Another option is to have an extemporaneous preparation made of ketamine capsules containing ketamine as raw material. Ketamine is not widely available as raw material in pharmaceutical quality. It must be noted that the pharmacokinetic studies with oral ketamine were performed with oral liquid.

Irrespective of which oral formulation is used the question of potential abuse remains important, especially in patients with a history of drug abuse. Ketamine is increasingly being used as a street drug because of its psychotomimetic effects. Ketamine can be bought on the illegal market and is primarily administered through snorting or inhaling lines of the powder form. The powder form can also be obtained by heating the injection fluid. Ketamine abuse in the general population is usually part of a polysubstance disorder (Muetzelfeldt et al., 2008). It remains unclear whether long-term use in chronic pain patients produces dependence.

4.4. Conclusions

Efficacy and long-term adverse effects are insufficiently studied to promote the routine use of oral ketamine in chronic pain management. Some of the studies on oral ketamine show a disappointing success rate, either due to treatment failure or appearance of adverse effects. Wide clinical use of ketamine is limited due to psychotomimetic and other adverse effects. On the other hand, ketamine as an analgesic has proven to be of effect in patients with severe pain who have failed to respond to routine pharmacotherapy. In these patients with intractable pain the use of oral keta-

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mine can be beneficial. From that perspective, oral ketamine may have a limited place as add-on therapy in complex chronic pain patients when other therapeutic options have failed.

Conflicts of interests

The authors have no financial and material support to declare.

Acknowledgement

The authors like to thank Laraine Visser-Isles (The Language Bureau) for English-language editing.

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