

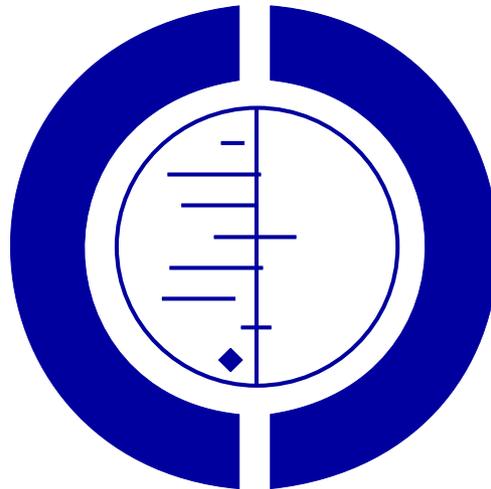
Paper III

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Bell RF, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. A qualitative systematic review. J Pain Symptom Manage 2003;26;3:867-875

Ketamine as an adjuvant to opioids for cancer pain (Review)

Bell R, Eccleston C, Kalso E



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ABSTRACT

Background

Ketamine is a commonly used anaesthetic agent, and in subanaesthetic doses is also given as an adjuvant to opioids for the treatment of cancer pain, particularly when opioids alone prove to be ineffective. Ketamine is known to have hallucinogenic side effects. To date no systematic review of the benefits and harms of adjuvant ketamine for cancer pain has been undertaken.

Objectives

To determine the effectiveness and adverse effects of ketamine as an adjuvant to opioids in the treatment of cancer pain.

Search strategy

Studies were identified from MEDLINE (1966-2001), EMBASE (1980-2001), CancerLit (1966-2001), the Cochrane Library (Issue 1, 2001); by handsearching reference lists from review articles, trials, and chapters from standard textbooks on pain and palliative care. The manufacturer of ketamine (Pfizer Parke-Davis) provided search results from their in-house database, PARDLARS.

Selection criteria

RCTs of adult patients with cancer and pain being treated with an opioid, and receiving either ketamine (any dose and any route of administration) or placebo or an active control.

Data collection and analysis

Two independent reviewers identified four RCTs for possible inclusion in the review, and 32 case studies/case series reports. Quality and validity assessment was performed by three independent reviewers, and two RCTs were excluded because of inappropriate study design. Patient reported pain intensity and pain relief was assessed using visual analog scales, verbal rating scales or other validated scales, and adverse effects data were collated.

Main results

Two trials were eligible for inclusion in the review and both concluded that ketamine improves the effectiveness of morphine in the treatment of cancer pain. However, pooling of the data was not appropriate because of the small total number of patients (30), and the presence of clinical heterogeneity. Some patients experienced hallucinations on both ketamine plus morphine and morphine alone and were treated successfully with diazepam. No other serious adverse effects were reported.

Authors' conclusions

Current evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of cancer pain. More randomized controlled trials are needed.

PLAIN LANGUAGE SUMMARY

The benefits and harms of adding ketamine to strong pain-killers such as morphine for the relief of cancer pain are not yet established.

Morphine-like drugs (opioids) are frequently prescribed for moderate and severe cancer pain, but in some cases these drugs are not effective. Ketamine, an anaesthetic agent, is used to improve analgesia when opioids alone are ineffective. However, evidence for the

effectiveness of this practice is limited. Two small trials suggest that when ketamine is given with morphine it may help to control cancer pain. However, these data are insufficient to assess the effectiveness of ketamine in this setting.

BACKGROUND

Opioids (for example, morphine, fentanyl, hydromorphone, oxycodone, codeine) are frequently prescribed for the relief of moderate and severe cancer pain. However, not all cancer pain is sufficiently relieved by opioids alone. Clinical reports indicate that, when added to opioids, low subanaesthetic doses of ketamine may give improved analgesia (Sosnowski 1993; Fine 1999; Bell 1999). The practice of using ketamine as an adjuvant to opioids in the treatment of cancer pain that does not respond to opioids alone, or to opioids in combination with adjuvant analgesic drugs, is discussed in several pain and palliative care textbooks (Cherny 1999; Twycross 1997; Portenoy 1998; Stannard 1998). Ketamine is not licensed for this purpose and, to date, no systematic review of the literature to establish the evidence base for this practice has been undertaken.

Ketamine hydrochloride has been used as a general anaesthetic agent for over 30 years, and is commonly given intravenously or intramuscularly for surgical anaesthesia (Fisher 2000). Ketamine causes dissociative anaesthesia and also has analgesic effects (Grahame-Smith 2002); because it increases sympathetic nervous system activity, it is a useful anaesthetic for poor-risk patients who require a high degree of sympathetic activity to maintain cardiovascular function. However, the benefits are tempered by the high incidence of hallucinations and other transient psychotic sequelae when ketamine is used for anaesthesia in adults (BNF 2002).

In the 1980s ketamine was discovered to have N-methyl-D-aspartate (NMDA) receptor antagonist properties and acts by blocking excitatory glutamate receptors in the central nervous system. There is an association between nociceptive activity involving the NMDA receptor and hyperalgesia/allodynia, and reduced opioid sensitivity (Dickenson 1994). The NMDA receptor plays a role in the development of opioid tolerance (Mao 1995; Mayer 1995).

Evidence from experimental animal models, human volunteer studies and small clinical trials indicates that subanaesthetic doses of ketamine alleviate various chronic and neuropathic pain syndromes (Fisher 2000). However, the use of ketamine at subanaesthetic dose levels has also been restricted by unpleasant adverse effects, typically sedation, nausea, disagreeable psychological disturbances or hallucinations (Willets 1990).

Racemic ketamine is a mixture of two stereoisomers: R(-) and S(+). Recently S-ketamine has been introduced. S(+) ketamine produces longer hypnosis than the (-) isomer, and causes a greater rise in blood pressure and heart rate, less locomotor activity, and a shorter recovery time, but equipotent analgesia. S(+) ketamine is thought to have a safer adverse effect profile (Grahame-Smith 2002).

OBJECTIVES

To determine the effectiveness and adverse effects of ketamine as an adjuvant to opioids in relieving cancer pain.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized, placebo- or active-controlled trials, with or without crossover, in in-patient and out-patient settings were included. There was no language restriction and all identified trials, published and unpublished, were considered eligible. Studies were classified as double-blind if they were described as such in the text.

Types of participants

The population addressed by the review included adult patients (over 18 years) with cancer and pain currently treated by an opioid agonist, (eg, morphine, fentanyl, oxycodone), in any dose and by any route. Patients who were on an established NMDA-receptor antagonist treatment before the study began were excluded. Volunteer studies were not considered.

Types of intervention

The intervention considered by this review was the addition of ketamine, given by any route of administration, in any dose, to pre-existing opioid treatment given by any route and in any dose.

Types of outcome measures

The primary outcome measure was patient-reported pain intensity and pain relief, assessed using validated measures on movement and at rest (eg, visual analogue scales (VAS)) and verbal rating scales).

Secondary outcome measures were:

- total opioid consumption over the study period
- rescue medication
- adverse events
- study withdrawals and dropouts

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Pain, Palliative and Supportive Care Group methods used in reviews.

The following electronic data bases were searched:

- MEDLINE on Silver Platter 1966 -2002
- EMBASE on Silver Platter 1980 -2002
- CancerLit 1966-2002
- Cochrane Controlled trials Register and Database of Systematic Reviews (Cochrane Library, Issue 1 2001)
- Specialized Register of the Cochrane Pain, Palliative and Supportive Care group (2001)
- PARDLARS, the in-house database of Pfizer UK

Date of the most recent search: February 2002

A sensitive search strategy was applied to all databases. Where appropriate, MeSH and free text search terms were used:

- ketamine
- ketalar
- dextromethorphan
- amantadine
- memantine
- NMDA receptor antagonist

AND

- cancer
- malignant disease
- neoplasm
- palliative

This search yielded a large number of irrelevant trials so the search was re-run using the terms “ketamine” OR “ketalar” AND “cancer”.

Several clinical studies undertaken in Japan were retrieved, and an attempt was made to access appropriate Japanese journals not indexed in either MEDLINE or EMBASE. The UK Cochrane Centre and Australasian Cochrane Centre (the reference Cochrane Centre for Japan) were contacted to see if any relevant hand searching activities were taking place. In addition, an enquiry was made to the curator of the Japanese literature at the Bodleian Library, Oxford. Despite exhaustive searching, these sources did not yield any relevant trial reports.

REFERENCE LISTS

Reference lists from review articles and chapters from standard textbooks on pain and palliative care were hand searched, as were reference lists from papers retrieved through electronic searching.

PERSONAL COMMUNICATION

A letter was sent to the manufacturers of ketamine (“Ketalar”), Pfizer, requesting access to relevant research material and

unpublished data. Napp Pharmaceuticals in the UK were also contacted regarding an unpublished study.

METHODS OF THE REVIEW

TRIAL SELECTION

The titles and abstracts from each of the electronic databases searched were assessed independently by two reviewers (RB and EK) for relevance. Potentially relevant trial reports were retrieved in full and assessed for inclusion in the review by three reviewers (RB, CE, EK). Case studies and review articles were also retrieved for information purposes.

The broad search in EMBASE identified 531,163 items, 294 of which were considered possible reports for inclusion. Further assessment of abstracts led to the retrieval of three RCTs. The MEDLINE search identified 223,723 items, 120 of which were considered possible reports for inclusion. These yielded four RCTs (one new). A refined search on CancerLit gave 50 possible items, including two previously found RCTs. Pfizer’s PARDLARS database gave 90 references, including the four RCTs already retrieved. The search of the Cochrane Controlled Trials Register yielded 176 references: one new review article and the same four RCTs; and the Specialised Register of the Cochrane Pain, Palliative and Supportive Care Register yielded 8 references and the same four RCTs. A final search on MEDLINE in February 2002 gave three additional reports, but no new RCTs. Details of the Napp study were not available in July 2002.

Handsearching of reference lists in review articles and textbooks did not yield any additional trial reports. Enquiries regarding the Japanese literature did not result in the identification of additional trials.

DATA EXTRACTION

A data extraction form was designed, and the following data items were collected independently by all three reviewers:

1. Publication details
2. Patient population, number of patients, age, condition
3. Description of the intervention(s) and control
4. Outcomes: pain relief, pain intensity, total analgesic consumption, rescue medication
5. Adverse effects (major and minor)
6. Quality (evaluated using the Oxford scale (Jadad 1996))
7. Validity (evaluated using the Oxford Pain Validity Scale (OPVS) (Smith 2000))

This information is recorded in the ‘Characteristics of Included Studies’ table.

STUDY QUALITY AND VALIDITY

The four RCTs retrieved were assessed for both quality and validity. Quality assessment included a consideration of the methods of randomization/allocation concealment; details of blinding

measures (Colditz 1989; Schulz 1995); withdrawals and dropouts. Each trial was evaluated against the Oxford scale (Jadad 1996), and the result reported in the 'Characteristics of Included Studies' table. Validity was evaluated using the Oxford Pain Validity Scale (OPVS) (Smith 2000) and the results for each included study are reported in the 'Characteristics of Included Studies' table.

ANALYSIS

It was hoped that there would be sufficient data and homogeneity between studies to undertake pooling. However, the small number of trials, small number of patients recruited to the studies, and heterogeneity of data meant that quantitative analysis was not possible. Information regarding the studies that met the inclusion criteria is given in the 'Results' section below.

Because of the paucity of data available from RCTs the authors considered information presented in case studies and case series reports of ketamine for chronic cancer pain, and this is presented in the 'Discussion' section below.

DESCRIPTION OF STUDIES

Four randomized, controlled studies appeared to meet the inclusion criteria (Yang 1996; Lauretti (a) 1999; Lauretti (b) 1999; Mercadante 2000). Two studies were carried out in an outpatient setting (Lauretti (a) 1999; Lauretti (b) 1999). One trial (Lauretti (a) 1999) was not blinded and considered to be methodologically flawed (using morphine as control and morphine consumption as outcome measure). This trial scored 1 on the OPVS scale and was excluded from the review. The second Lauretti study (Lauretti (b) 1999), which scored 7 of 16 possible points on the OPVS, used the same kind of control, a fixed baseline dose of morphine and a fixed maximum daily dose of rescue medication. This study was also considered to be methodologically flawed and was excluded from the review.

Two RCTs met the inclusion criteria: Mercadante 2000 and Yang 1996.

STUDY DESIGN

The two included studies (Yang 1996; Mercadante 2000) had a crossover design. The trial conducted in Italy by Mercadante 2000 was a placebo-controlled trial and was conducted over a three-hour period. The trial conducted in Taiwan by Yang 1996 used morphine as the active control. The time period over which the intervention was assessed in Yang 1996 was not stated in the trial report, but there is an implication that the study was conducted over a period of days. (Attempts to contact the author to confirm the trial duration have not been successful.)

STUDY POPULATION

The trial participants were:

Yang 1996: 20 hospitalised patients (10 men and 10 women) aged 22-69 years with cancer pain that was being treated effectively

with opioids. The primary cancer sites were stomach, cervix, liver, lung, colon, pancreas.

Mercadante 2000: 10 patients (seven men and three woman) aged 21-69 years who had pain unrelieved by their dose of morphine, and a Karnofsky status of 50 or more. The primary cancer sites were: bladder, rectum, lung, histiocytoma and uterus. In this study the pain was classified as being "neuropathic" or having a "neuropathic component".

INTERVENTION

Mercadante 2000 assessed two doses of ketamine (0.25 mg/kg and 0.5 mg/kg) administered intravenously as a bolus as adjuvant to morphine, compared with saline. Patients were randomly assigned to receive in turn either 0.25 mg/kg or 0.5 mg/kg ketamine or saline, with a two-day washout period between each intervention/control.

Yang 1996 assessed intrathecal 1.0 mg/kg ketamine as adjuvant to morphine, compared with morphine alone. Morphine dose was titrated until patients' pain relief had been stable for 48 hours, then patients randomly crossed over (no washout period) to morphine plus ketamine (1.0 mg/kg dose) or continued on morphine (control), administered intrathecally twice a day.

Morphine was the only opioid patients received in the included studies. It is assumed that racemic ketamine was used in both studies.

RESCUE MEDICATION

Yang 1996: In this trial a rescue dose of 5 mg morphine was administered intramuscularly as needed. Mercadante 2000 does not report the use of rescue medication.

OUTCOMES

Mercadante 2000 measured patient-reported pain intensity (0-10 numerical scale) at 30, 60, 90, 120, and 180 minute intervals; and adverse effects. Yang 1996 measured patient reported pain (0-10 numerical, 10 worst pain imaginable); pain frequency (4 point verbal ordinal scale), group morphine dose, total titrated intrathecal morphine, total rescue medication, frequency of intrathecal titration.

METHODOLOGICAL QUALITY

The included studies were assessed by three independent reviewers using two quality measures: the Oxford scale (Jadad 1996) and the Oxford Pain Validity Scale (Smith 2000).

The trial reports of the two included studies stated that patients were randomized to treatment and control groups, but in neither trial was the process of randomization described. Patients, investigator and nurses were blinded in Yang 1996; and the drugs were prepared in identical syringes by a person not involved in the study in Mercadante 2000. Neither study reports withdrawals and dropouts.

QUALITY ASSESSMENT

Quality scores derived using the Oxford quality scale were 3 for both Mercadante 2000 and Yang 1996.

Using the method derived by Smith 2000, the two included trials (Yang 1996, Mercadante 2000) scored 13 and 12 respectively on the Oxford Pain Validity Scale.

RESULTS

It was not possible to perform a quantitative meta-analysis because of the small number of patients and heterogeneity of the data. A description of the results from the two included trials is given below.

EFFECTIVENESS

- KETAMINE 0.25 mg/kg

One trial (Mercadante 2000) assessed pain intensity over three hours. Mean pain intensity scores showed a reduction in pain intensity after 30 minutes compared with saline solution; after 60 minutes the analgesic effect of ketamine began to diminish but continued to have an effect for a period of three hours.

- KETAMINE 0.5 mg/kg

One trial (Mercadante 2000) assessed pain intensity over three hours. Mean pain intensity scores showed a significant reduction in pain intensity after 30 minutes compared with saline solution and the analgesic effect of ketamine continued throughout the three-hour period.

- KETAMINE 1.0 mg/kg

One trial (Yang 1996) assessed adjuvant ketamine 1.0 mg/kg, but the time scale of the trial was not specified. This trial concludes co-administration of 1.0 mg/kg ketamine intrathecally reduced the intrathecal dose of morphine required for the control of cancer pain, and was as effective as intrathecal morphine alone.

ADVERSE EFFECTS

- Hallucinations

Three patients experienced hallucinations whilst receiving 0.25 mg/kg and 0.5 mg/kg ketamine, and one further patient suffered hallucinations when taking the 0.5 mg/kg. All were treated with diazepam 1 mg (Mercadante 2000). Two of these four patients also experienced light flashes, a 'buzzing' feeling in the head, and sensation of insobriety. Diazepam resolved these symptoms.

- Other adverse effects

Information on the following adverse effects were sought in the trial conducted by Mercadante 2000:

- drowsiness
- nausea and vomiting

- dry mouth
- confusion

These effects were assessed on a scale from 0 to 3, where 0 was 'not at all', and 3 was 'awful'. Patients treated with 0.25 and 0.5 mg/kg ketamine reported increased drowsiness.

On direct questioning, patients reported a number of adverse effects during the trial conducted by Yang 1996:

- pruritis
- constipation
- urinary retention
- difficulty in urinating
- nausea and vomiting
- hallucinations
- respiratory depression

However, these adverse effects could not be attributed specifically to the study treatments as some were present prior to the commencement of the study. One patient in the morphine only arm of the Yang 1996 study reported hallucinations.

No study withdrawals or dropouts were reported in either trial, and both trials reported that the adverse effects of ketamine were not serious.

DISCUSSION

The objective of this systematic review was to assess the effectiveness and adverse effects of ketamine as an adjuvant to opioids in the treatment of cancer pain. Electronic searching and hand searching retrieved only four RCTs and, of these, the poor methodological quality of two meant that they had to be excluded from the review. The two small studies (30 patients) that met the inclusion criteria provided insufficient data to enable any evidence-based conclusions about the benefits and harms of adjuvant ketamine to be drawn.

OTHER REPORTS

In addition to the four RCTs retrieved, searching identified 32 case reports or open label uncontrolled trials studies describing improvement of opioid analgesia with ketamine.

Whilst the design of these studies and the issue of publication of positive outcomes preclude the inclusion of any data from these reports in this systematic review, the studies are discussed here in order to provide a full review of the literature on this topic.

The 32 reports retrieved describe the use of ketamine to treat refractory cancer pain, frequently described as neuropathic pain. The total number of patients treated with ketamine in these reports

was 246. The route of ketamine administration included oral, intramuscular bolus, subcutaneous bolus and infusion, intravenous bolus and infusion, epidural bolus, and intrathecal infusion. Ketamine doses ranged from 1 mg/kg/day subcutaneous infusion to 600 mg/day iv and 67.2 mg/day intrathecally. Treatment duration ranged from four hours to one year. Treatment was in most cases adjuvant to opioid and other drugs. Twenty-eight reports described improved analgesia with ketamine. Where ketamine was administered as an adjuvant to opioids, the most commonly used opioid was morphine, but in some cases ketamine was given as an adjuvant to fentanyl (Bell 1999; Ventura 1993), hydromorphone (Fine 1999) or diamorphine (Garry 1996), or combinations of these. Ketamine was also used as sole analgesic in three reports (Oshima 1990; Parada 1971; Whizar-Lugo 1987).

Sixteen reports described dramatic relief of refractory cancer pain with ketamine:

- “complete cessation of pain” (Ventura 1993)
- “complete relief of pain” (Tarumi 2000)
- “disappearance of pain” (Parada 1971; Garry 1996)
- “no pain” (Fine 1999)
- “pain free” (Mitchell 1999)
- “mostly pain free” (Lloyd-Williams 2000)
- dramatic reduction in VAS scores including VAS 100 reduced to 0 (Bell 1999)
- average VAS score 8.3 reduced to 1 (Kanamaru 1990)
- average VAS score reduced from 5.9 +/- 2.0 to 0.3+/- 0.8 (Ogawa 1994)
- VAS 7/10 reduced to 1/10 (Wood 1997)
- reduction of VAS 7/10 to below 2/10 (Lossignol 1999)
- “dramatic drop in VAS” (Lossignol 1992)
- “remarkable analgesia” (Fukuida 1981)
- “excellent analgesia” (Sosnowski 1993; Mercadante 1995).

The most commonly reported adverse effects in this literature were sedation and hallucination. In general, adverse effects were not reported as severe and only two studies reported patient withdrawal from treatment because of unacceptable “adverse cognitive effects” (Garry 1996), and pronounced sedation (Klahr 1997). One report described sedation which improved on tapering the opioid dose (Bell 1999). Other side effects described included evoked nystagmus (jerky eye movements) during treatment with iv ketamine (Lossignol 1999), and inflammation of syringe driver sites during subcutaneous treatment (Mitchell 1999; Oshima 1990). One report described generalized hyperalgesia and allodynia after abrupt termination of subcutaneous ketamine infusion (Mitchell 1999).

One postmortem report described subpial vacuolar myelopathy in a patient who had received continuous intrathecal ketamine infusion (Karpinski 1997) while another described focal lymphocytic vasculitis close to the intrathecal catheter site (Stotz 1999). One report described maintenance of syringe driver sites with topical 0.1% hydrocortisone cream (Lloyd-Williams 2000).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence base for ketamine as an adjuvant to opioids for the treatment of cancer pain is insufficient to allow for any recommendations for practice.

Implications for research

TRIAL DESIGN

Conducting scientifically sound trials in a population of terminally ill cancer patients is a considerable challenge, and this is perhaps reflected in the small number of published trials available for this review. It is difficult to recruit large numbers of patients from this population. Crossover designs, as used in the two included studies, may be more appropriate than placebo-controlled studies.

PATIENT GROUPS

Larger studies are needed in order to assess whether adjuvant ketamine provides effective analgesia for all types of cancer pain. There is also an issue in relation to opioid tolerance. Ketamine is a NMDA receptor antagonist. The NMDA receptor is believed to play a role in the development of opioid tolerance and ketamine has recently been shown in a rat model to prevent fentanyl-induced hyperalgesia and subsequent acute morphine tolerance (Larcher 1998). Whether reduction of opioid tolerance is an important factor in this effect remains to be studied. It has been suggested that pharmacological tolerance to opioid may develop early (Laulin 2002) but it is not clear how often it is a clinical problem in cancer patients. It may be difficult in this patient population to distinguish between tolerance and disease progression, both of which require an increase in opioid dose. In patients who appear to have a problem tolerating opioids ketamine may be a treatment option.

INTERVENTIONS

In the trial by Mercadante 2000 the type of pain was defined and the patients were on moderate doses of morphine. In the second included study Yang 1996, the type of pain was not described and the patients were on low doses of morphine. Insufficient information is given to judge the appropriateness of the intervention to these patients.

Trials with S-ketamine as an adjuvant to opioids might be appropriate, and also trials with other commonly prescribed opioids for cancer pain eg, fentanyl, hydromorphone and oxycodone.

ROUTE OF ADMINISTRATION

More information is needed on whether the route of administration of ketamine has an impact on its effectiveness as an analgesic. If ketamine is used spinally, issues of neurotoxicity should be considered (Karpinski 1997).

OUTCOMES

Outcomes should be clearly defined, and triallists should also restrict study outcomes to those that are the most clinically useful, such as which route of administration, which dose is effective, and the cost to the patient in terms of adverse events. For example, for the purposes of this systematic review should the standard outcome be relief of neuropathic pain, reduction of tolerance or reduction of morphine consumption?

SEARCHING

With regard to search strategy, the PARDLARS search gave an excellent gain, compared to the other searches. Of the 90 retrieved titles, 41 were relevant for the review. This would suggest that collaboration with the pharmaceutical companies may be important to enable maximum retrieval of information when preparing systematic reviews involving drug treatments.

POTENTIAL CONFLICT OF INTEREST

None known.

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T A B L E S**Characteristics of included studies**

Study	Mercadante 2000
Methods	Randomized but procedure not described. Blinded study: Drugs prepared in identical syringes by a person not involved in the test sessions Placebo control Crossover Study duration: 30-180 minutes
Participants	Cancer patients with neuropathic pain unrelieved by morphine N= 10 per group (crossover) Mean age of patients: 57 years
Interventions	Treatment 1: saline (IV) Treatment 2: KET bolus 0.25 mg/kg (IV) Treatment 3: KET bolus 0.5 mg/kg (IV)

Characteristics of included studies (Continued)

Outcomes	Pain intensity Adverse effects
	Results: Low dose KET IV + Mo (PO, SC, IV) significantly reduced pain intensity
Notes	Acute treatment. Washout period ("at least 2 days") Rescue medication: none Withdrawals: not described Adverse effects: ketamine gave central adverse effects (hallucinations, drowsiness, confusion) in 4 of 10 subjects. Quality/ validity OPVS score: 12 Oxford score: 3
Allocation concealment	B
Study	Yang 1996
Methods	Randomized but procedure not described Blinded study: double dummy Crossover, no washout Active control (morphine) Study duration: not defined
Participants	Hospitalized patients with terminal cancer pain N = 20 per group (crossover)
Interventions	Treatment 1: Mo (IT) Treatment 2: KET 1.0 mg (IT) b.i.d. + Mo (IT)
Outcomes	Pain intensity Pain frequency Total titrated Mo dose (IT). Total rescue medication. Frequency of IT titration. Results: Co-administration of low-dose KET reduces the amount of IT Mo required to control cancer pain.
Notes	Chronic treatment. Rescue medication: "Mo 5 mg IM as needed" Withdrawals/ dropouts: not described Adverse effects: Side effects including pruritus, constipation, urinary retention, nausea, vomiting and hallucination were not serious. The frequency of side effects did not show a significant statistical difference between phase M and phase M+ K. Quality/ validity: OPVS score: 13 Oxford score: 3

Characteristics of included studies (Continued)

Allocation concealment B

OPVS: Oxford Pain Validity Scale

KET: Ketamine

Mo: morphine

IV: intravenous

IM: intramuscular

IT: intrathecal

Characteristics of excluded studies

Lauretti (a) 1999 Open label study ("pilot work"). Described as placebo-controlled, but in fact used active control (morphine). Design flaw with fixed maximum baseline morphine dose PO and primary outcome measure: daily consumption of morphine. OPVS score:1 Oxford Quality Scale score:2

Lauretti (b) 1999 Described as placebo-controlled, but in fact used active control (morphine). Design flaw with fixed baseline dose of morphine ED, fixed maximum daily dose of morphine ED and primary outcome measure: daily consumption of morphine ED. OPVS score:7 Oxford Quality Scale score: 3

PO: oral

ED: epidural

OPVS: Oxford Pain Validity Scale

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [adverse effects; *therapeutic use]; Chemotherapy, Adjuvant; Hallucinations [chemically induced]; Ketamine [adverse effects; *therapeutic use]; Morphine [adverse effects; *therapeutic use]; Neoplasms [*complications]; Pain [*drug therapy; etiology]; Palliative Care; Randomized Controlled Trials

MeSH check words

Adult; Humans

COVER SHEET

Title	Ketamine as an adjuvant to opioids for cancer pain
Authors	Bell R, Eccleston C, Kalso E
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Review Article

Ketamine as Adjuvant to Opioids for Cancer Pain. A Qualitative Systematic Review

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Abstract

Ketamine is increasingly being used as an adjuvant to opioids in the treatment of refractory cancer pain. This systematic review examines the available evidence. Randomized, controlled trials, with or without crossover, were included. Studies were identified from MEDLINE, EMBASE, CANCELIT, the Cochrane Library, handsearched reference lists from review articles and chapters from standard textbooks on pain and palliative care and reference lists from papers retrieved. Four randomized, controlled studies were identified. Two were excluded due to poor quality. Both included studies concluded that ketamine improves morphine treatment in cancer pain. Quantitative meta-analysis was not possible. The available evidence is not sufficient to conclude that ketamine improves the effectiveness of opioid treatment in cancer pain. High quality, randomized, controlled trials with larger numbers of patients and standardized, clinically relevant routes of administration of ketamine are needed. J Pain Symptom Manage 2003;26:867–875. © 2003 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Ketamine, opioids, cancer pain, systematic review, Cochrane

Introduction

Ketamine hydrochloride is commonly given intravenously or intramuscularly for surgical anesthesia. During the last decade, it has become apparent that low, subanesthetic doses of ketamine may improve opioid analgesia.

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist. There is good evidence from experimental animal models, human

volunteer studies and small clinical trials that NMDA receptor antagonists relieve some types of neuropathic pain.¹ However, their use is restricted by unpleasant adverse effects, such as hallucinations. The NMDA receptor also seems to play a role in the development of opioid tolerance.^{2,3} Ketamine in low doses (for example, 1 mg/kg/24 hrs as a subcutaneous infusion) has been suggested to reverse or partially reverse opioid tolerance.⁴ Clinical reports^{4–6} indicate that ketamine in low doses as an adjuvant to opioid treatment may improve analgesia with tolerable adverse effects.

Ketamine is now increasingly being used as an adjuvant to opioids in the treatment of refractory cancer pain, that is, cancer pain which

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does not respond to opioids alone or opioids in combination with adjuvant analgesic drugs. Such use of ketamine is advocated in several pain/palliative care textbooks.⁷⁻¹⁰ So far, there is little clinical evidence to support this practice.

From published literature, it would appear that ketamine prescribed with opioids for the treatment of cancer pain is used in several countries including the UK, Scandinavia, Italy, Belgium, Japan and Australia. Treatment with low dose ketamine is relatively inexpensive and would be suitable for use in developing countries. This systematic review was performed to determine the effectiveness of ketamine as an adjuvant to opioids in relieving cancer pain.

A more detailed review will be published and updated in the *Cochrane Database of Systematic Reviews*.

Methods

Criteria for Considering Studies for This Review

Studies. Randomized, controlled trials (RCTs), with or without crossover were included. Trials using placebos or active controls, or both, were included. There was no language restriction. All identified trials, published and unpublished, were considered eligible.

Participants. The population addressed by the review included adult patients (over 18 years) with cancer and pain currently treated by an opioid agonist, in any dose and by any route. Patients who were on an established NMDA-receptor antagonist treatment before the study began were excluded. Healthy volunteer studies were not considered.

Interventions. The intervention considered by this review was the addition of ketamine, given by any route, in any dose, to pre-existing opioid treatment given by any route and in any dose.

Search Strategy

The following electronic data bases were searched:

- MEDLINE on Silver Platter from 1966 onwards
- EMBASE on Silver Platter from 1980 onwards
- CANCERLIT from 1966 onwards

- Cochrane Library Controlled Trials Register and Database of Systematic Reviews (Cochrane Library, Issue 1, 2001)
- Specialized Register of the Cochrane Pain, Palliative and Supportive Care Group

A broad search was performed, combining MeSH terms and a free text search. The following terms were used: "ketamine," "ketalar," "dextromethorphan," "amantadine," "memantine," "NMDA receptor antagonist," "cancer," "malignant disease," "neoplasm," and "palliative" using the Boolean operators "OR" and "AND."

As this search resulted in a large number of irrelevant trials a more refined search was performed using the terms "ketamine," "ketalar," and "cancer" using the Boolean operators "OR," and "AND."

Reference lists from review articles and chapters from standard textbooks on pain and palliative care, and reference lists from papers retrieved through electronic searching were handsearched.

A letter was sent to the manufacturers of ketamine (Ketalar®), Pfizer, requesting access to relevant research material and unpublished studies. Because these searches revealed several clinical studies from Japan, an attempt was made to access appropriate Japanese journals not indexed in Medline and Embase. An enquiry was made to the Australasian Cochrane Centre and to the Bodleian Library. Napp Pharmaceuticals in the UK were also contacted regarding an unpublished study.

The last electronic search was performed in February 2002.

Data Collection

All identified records from each of the databases were examined. The titles and abstracts of studies were assessed independently by two reviewers (RFB, EK) and potentially relevant studies, including review articles, were selected for assessment for inclusion in the review. Each trial report that appeared to meet the criteria was independently assessed for inclusion by three reviewers (RFB, CE, EK).

A data extraction form was designed, and the following data were collected independently by the three reviewers:

1. Publication details.
2. Patient population, number of patients, age, condition.

3. Description of intervention.
4. Quality (randomization/allocation concealment, details of blinding measures,^{11,12} withdrawals and dropouts, overall quality score). Studies to be included in the review were evaluated using the Oxford Quality Scale.¹³
5. Validity was assessed using the Oxford Pain Validity Scale (OPVS).¹⁴

Studies were classified as double-blind if they were described as such in the text.

Results

The broad search in EMBASE gave 531,163 items identified, 294 possible items and then, with abstracts read, 3 randomized controlled trials. The Medline search gave 223,723 items identified, 120 possible items after the refined search, 4 randomized controlled trials after reading the abstracts. A refined search on Cancerlit gave 50 possible items, including 2 randomized, controlled trials, while the PARDLARS (Pfizer) search gave 90, including 4 randomized, controlled trials. A final search on Medline in February 2002 gave 3 additional reports, but no new RCT's. Details of the Napp study were, in July 2002, not yet available.

A total of 4 randomized, controlled trials with a total of 57 patients were identified. Hand-searching of reference lists in review articles and textbooks gave no added trials. A search of the Cochrane Library gave one review article, but no new trials. Enquiries regarding the Japanese literature did not result in the identification of additional trials.

Three independent reviewers assessed the quality of the four identified trials using a standard data extraction sheet and Oxford scales for quality and validity. Two trials^{15,16} were included in the review (Table 1) and two were excluded due to poor methodological quality.

The total number of patients in the included trials was 30. Both studies were positive with regard to the effect of ketamine. Ketamine was found to reduce morphine requirements in cancer patients and to significantly reduce pain intensity in cancer pain with a neuropathic component. Ketamine did not cause serious adverse effects. Adverse effects in the chronic setting were generally milder than in the control group; this was considered to be due to ketamine's morphine-sparing effect and subsequent

reduction of opioid-related adverse effects. Ketamine caused hallucinations in 4 patients in the acute study,¹⁶ whereas morphine caused hallucinations in one patient in the chronic study.¹⁵ In the acute study, ketamine added to morphine gave significant increases in drowsiness; this effect was dose-related with the higher dose (0.5 mg/kg) causing more drowsiness.

It was not possible to perform a quantitative meta-analysis due to the small number of trials, small number of patients and the heterogeneity of the data. Only two studies could be included, but all four studies will be discussed for the methodological implications. Conclusions regarding effectiveness are based on the two included studies.

Description of Studies

Four randomized, controlled studies were identified.¹⁵⁻¹⁸ The studies were published between 1996 and 2000. All were published in English. Two studies were undertaken in Brazil, one in Taiwan and one in Italy.

Populations. All studies were conducted with adults aged from 21 to 74 years. The populations were defined as patients with "cancer pain unrelieved by systemic opioid or NSAID therapy;" "terminal cancer pain" and "cancer pain unrelieved by morphine, Karnofsky 50 or more." Two studies were carried out in an outpatient setting^{17,18} and one study¹⁵ was with hospitalized patients. The fourth study¹⁶ did not describe whether the patients were hospitalized or ambulant.

Pain. The primary site of the lesion that lead to pain was described in all studies and included: oropharynx, stomach, liver, colon, pancreas, kidney, lung, cervix, uterus and prostate. Only one study¹⁶ described the possible mechanisms of pain. In this study the pain was classified as being "neuropathic" or having a "neuropathic component."

Interventions. The opioid in all studies was morphine. The morphine route differed between studies: oral, epidural, intrathecal, and in the most recent study,¹⁶ oral, subcutaneous and intravenous routes. Morphine doses varied

Table 1
Characteristics of Included Studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Mercadante 2000	Randomized but procedure not described.	Cancer patients with neuropathic pain unrelieved by morphine	Treatment 1: saline (IV)	Pain intensity Adverse effects	Acute treatment. Washout period ("at least 2 days") Rescue medication: none
	Blinded study: Drugs prepared in identical syringes by a person not involved in the test sessions	<i>n</i> = 10 per group (crossover)	Treatment 2: KET bolus 0.25 mg/kg (IV)	Results: Low dose KET IV + Mo (PO, SC, IV) significantly reduced pain intensity	Withdrawals: not described Adverse effects: ketamine gave central adverse effects (hallucinations, drowsiness, confusion) in 4 of 10 subjects
Yang 1996	Placebo control; Crossover; Study duration: 30–180 minutes		Treatment 3: KET bolus 0.5 mg/kg (IV)		Quality/validity OPVS score: 12 Jadad score: 3
	Randomized but procedure not described	Hospitalized patients with terminal cancer pain	Treatment 1: Mo (IT)	Pain intensity Pain frequency Total titrated Mo dose (IT)	Chronic treatment. Rescue medication: "Mo 5 mg IM as needed"
	Blinded study: double dummy Crossover, no washout	<i>n</i> = 20 per group (crossover)	Treatment 2: KET 1.0 mg (IT) bid + Mo (IT)	Total rescue medication Frequency of IT titration	Withdrawals/dropouts: not described Adverse effects:
	Active control (morphine)			Results: Co-administration of low-dose KET reduces the amount of IT Mo required to control cancer pain	Side effects including pruritus, constipation, urinary retention, nausea, vomiting and hallucination were not serious. The frequency of side effects did not show differences between phase M and phase M+K Quality/validity: OPVS score: 13 Jadad score: 3
	Study duration: not defined				

KET = ketamine; Mo = morphine; IT = intrathecal; IM = intramuscular; SC = subcutaneous; IV = intravenous.

between patients and between studies. The ketamine route differed between studies. Ketamine was administered by oral, epidural, intrathecal and intravenous routes. The ketamine doses also differed between studies and ranged from 0.5 mg/kg oral \times 2 to 0.5 mg/kg IV bolus. It is assumed that racemic ketamine was used in all reports. Rescue medication was morphine in three studies, and the fourth study¹⁶ did not involve rescue medication. The rescue medication route differed in the three studies and included oral and intramuscular routes. One study¹⁸ may have included epidural morphine as rescue medication; however, this was not clearly described.

Outcomes. A variety of outcomes were reported. All studies reported adverse effects. All studies registered pain intensity either using a Visual Analogue Scale (VAS) or a numerical rating scale (NRS). Other outcomes differed between studies and included daily morphine consumption,^{17,18} time to VAS 4 after study drug,¹⁸ pain frequency, group morphine dose, total titrated intrathecal morphine, total rescue medication, frequency of intrathecal titration, life interference and sleep deprivation.¹⁵

Study Duration. Duration differed between studies and ranged from 30 minutes to 30 days. In one study,¹⁵ it was not possible to elucidate study duration.

Methodological Quality of Studies

Two studies^{15,16} had a crossover design. Only one study used a placebo control,¹⁶ and one study¹⁵ used an active control (morphine). Two studies^{17,18} claimed to use a "placebo-controlled design" but in fact used an active control (morphine). The first of these studies¹⁷ was not blinded and was considered to be methodologically flawed (using morphine as control and morphine consumption as outcome measure). This trial scored 1 on the OPVS scale and was excluded from the review. The second study¹⁸ which scored 7 of 16 possible points on the OPVS, used the same kind of control, a fixed baseline dose of morphine and fixed daily dose of rescue medication. This study was also considered to be methodologically flawed and was excluded from the review.

The remaining trials^{15,16} scored 13 and 12 respectively on the OPVS scale and 3 on the

Oxford Quality Scale. Both were randomized, but the process of randomization was not described. Both studies were convincingly blinded. Neither study described withdrawals and dropouts. Both studies reported the statistical analysis used. In general, the most important methodological problems were: inadequate description of the pain to be treated and absent or inadequate description of rescue medication policy.¹⁵ One study¹⁵ examined the effect of chronic administration of ketamine while the other¹⁶ was an acute study examining the effect of bolus administration.

Thus, only two studies^{15,16} were included in the final analysis of efficacy. Both included studies were positive with regard to the effect of ketamine. Ketamine was found to reduce morphine requirements in cancer patients and to significantly reduce pain intensity in cancer pain with a neuropathic component. Ketamine gave no serious adverse effects. Adverse effects in the chronic setting were generally milder than in the control group; this was considered to be due to ketamine's morphine-sparing effect and subsequent reduction of opioid-related adverse effects. Ketamine presumably caused hallucinations in 4 out of 10 patients in the acute study,¹⁶ but was not associated with hallucinations in the chronic study. In the acute study, ketamine added to morphine gave significant increases in drowsiness; this effect was dose-related with the higher dose (0.5 mg/kg) causing more drowsiness.

Discussion

This systematic review examined the effect of ketamine as an adjuvant to opioids in cancer pain. With regard to search strategy, the PARDLARS search gave an excellent gain, compared to the other searches. Of the 90 possible titles, 41 were relevant for the review. This would suggest that collaboration with the pharmaceutical companies is important to enable maximum retrieval of information when preparing systematic reviews involving drug treatment.

In preparing this review, we addressed the difficulty of conducting scientific trials in a terminally ill, cancer patient population. The importance of study design needs to be emphasized. For example, the use of placebo control

may potentially expose the cancer patient to unnecessary pain and the study design must address this problem. Conducting scientifically sound trials in this patient population is a considerable challenge, reflected perhaps by the small number of published trials. It is difficult to recruit large numbers of patients from this population. A crossover design, as used by the two included studies may be a useful solution. It also may be difficult to resist the temptation to address several different outcomes in one study. Both excluded studies investigated several interventions at the same time, giving a complicated design and small numbers of patients in each group.

It would seem wise to restrict the study outcome as much as possible. Outcomes should be clearly defined and the studies should provide clinically useful information, such as which route of administration/dose is effective and cost of treatment in terms of adverse events. There is a lack of consensus across the four identified trials as to the primary outcomes. Should the standard outcome be relief of neuropathic pain, reduction of tolerance or reduction of morphine consumption? In one study,¹⁶ the type of pain was defined and the patients were on moderate doses of morphine. In the three other studies, the type of pain was not described and the patients were on low doses of morphine. Insufficient information is given to judge the appropriateness of the intervention with these patients.

The main adverse effect of ketamine was hallucination and seemed to be dose-related. Recently S-ketamine has been introduced. Studies using S-ketamine would be of interest as it may have a safer adverse effect profile. If ketamine is used spinally, issues of neurotoxicity should be considered.¹⁹

In the two included studies, ketamine was found to improve morphine analgesia. Ketamine is an NMDA receptor antagonist. The NMDA receptor is believed to play a role in the development of opioid tolerance and ketamine has recently been shown in a rat model to prevent fentanyl-induced hyperalgesia and subsequent acute morphine tolerance.²⁰ Whether reduction of opioid tolerance is an important factor in the improvement of morphine analgesia remains to be studied. It has been suggested that pharmacological tolerance to opioid may develop early,²¹ but it is not

clear how often it is a clinical problem in cancer patients. It may be difficult in this patient population to distinguish between tolerance and disease progression, both of which require an increase in opioid dose. In those patients in whom opioid tolerance is suspected to be a problem, ketamine may be a treatment option. It should be noted that morphine was the opioid in both included studies, and that the results may not apply to all opioids.

The majority of titles identified by the electronic searches were case reports, open label audits or open label, uncontrolled trials. A total of 32 such reports was identified.^{4-6,19,22-38,40-50} Ketamine was used to treat refractory cancer pain, often described as neuropathic. Twenty-eight reports described improvement of analgesia with ketamine. In the majority of cases, ketamine improved opioid analgesia. The most common opioid was morphine, but in some cases ketamine was given as an adjuvant to fentanyl,^{4,22} hydromorphone⁶ or diamorphine,²³ or combinations of these opioids. Ketamine also was used as the sole analgesic.²⁴⁻²⁶ Sixteen publications report dramatic relief of refractory cancer pain with ketamine, including "complete cessation of pain,"²² "complete relief of pain"²⁷ "disappearance of pain,"^{23,25} "no pain,"⁶ "pain free,"²⁸ "mostly pain free,"²⁹ dramatic reduction in VAS scores including VAS 100 reduced to 0,⁴ average VAS score 8.3 reduced to 1,³⁰ average VAS score reduced from 5.9 ± 2.0 to 0.3 ± 0.8 ,³¹ VAS 7/10 to 1/10,³² reduction of VAS 7/10 to below 2/10,³³ "remarkable analgesia,"³⁴ and "excellent analgesia."^{5,35} Adverse effects were related to higher doses of ketamine. The most commonly reported adverse effects were sedation and hallucination. In general, adverse effects were not reported as severe or requiring cessation of treatment. Two reports describe pain relief with ketamine but discontinuance of treatment due to unacceptable adverse effects in the form of "adverse cognitive effects"²³ and pronounced sedation.³⁶ Other side effects described included evoked nystagmus under treatment with intravenous ketamine³³ and inflammation of syringe driver sites during subcutaneous treatment.^{24,28} One report described generalized hyperalgesia and allodynia after abrupt termination of subcutaneous ketamine infusion.²⁸ One postmortem report described subpial vacuolar myelopathy after continuous intrathecal

ketamine infusion,¹⁹ while another described focal lymphocytic vasculitis close to the intrathecal catheter site.³⁷ One report described sedation, which improved on tapering the opioid dose,⁴ while another report describes maintenance of syringe driver sites with topical 0.1% hydrocortisone cream.²⁹ The total number of patients treated with ketamine in these case reports was 246. The route of ketamine administration included oral, intramuscular bolus, subcutaneous bolus and infusion, intravenous bolus and infusion, epidural bolus, and intrathecal infusion. Ketamine doses ranged from 1 mg/kg/day subcutaneous infusion to 600 mg/day intravenously and 67.2 mg/day intrathecally. Treatment duration ranged from 4 hours to 1 year. Treatment was in most cases adjuvant to opioids and other drugs.

Despite the treatment being recommended in leading textbooks, there are at present only four randomized, controlled trials. Of these, two have poor methodological quality and could not be included in this review. Both included studies favor ketamine as an adjuvant to morphine in the treatment of cancer pain unrelieved by morphine. However, the total number of patients is small³⁰ and the two trials are difficult to compare since one is in a chronic setting, using intrathecal morphine and ketamine, while the other is in an acute setting, using ketamine as an intravenous bolus. The relevance of the acute study to chronic cancer pain may be questioned. However, an open label study describes long-term effects of a single ketamine infusion in cancer pain patients.³⁸ A recent randomized, controlled trial, although not in cancer pain, also reports lasting effect of a single ketamine infusion in patients with ischemic pain.³⁹

Conclusions

The evidence base for ketamine as an adjuvant to opioids for cancer pain is weak. The available literature allows for only a cautious conclusion that there is promise in the potential efficacy of ketamine as an adjuvant to opioids for cancer pain. The two RCT's of sufficient quality return broadly positive conclusions. In addition, there is a large number of case reports/open label studies describing improvement of opioid analgesia with ketamine.

Higher quality randomized controlled trials are needed with larger numbers of patients and standardized, clinically relevant routes of administration of ketamine. Studies using S-ketamine and other opioids would be of interest.

Acknowledgments

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The authors thank the Bodleian Library for their co-operation, and Pfizer Norway for access to the PARDLARS database.

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