Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes

Roger L. Schmid[a,1], Alan N. Sandler[a, b], Joel Katz[a, b, c,*]

[a]Acute Pain Research Unit, Department of Anaesthesia, The Toronto Hospital and Mount Sinai Hospital, Toronto, Ontario, Canada
[b]Department of Anaesthesia, University of Toronto, Toronto, Ontario, Canada
[c]Department of Public Health Sciences, University of Toronto, Toronto, Ontario, Canada

Abstract

Ketamine hydrochloride is a well known general anesthetic and short acting analgesic in use for almost 3 decades. The role of the NMDA receptor in the processing of nociceptive input has led naturally to renewed clinical interest in N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine. This paper reviews the use and efficacy of low-dose ketamine in the management of acute postoperative pain. The literature was obtained from a computer search of the MEDLINE® database from 1966 through December 1998. Studies were included for review if they were randomized, prospective, controlled, double-blind and reported pain scores. We evaluate the clinical literature and discuss the efficacy of low-dose ketamine in the management of acute postoperative pain when administered alone or in conjunction with other agents via the oral, intramuscular, subcutaneous, intravenous and intraspinal routes. Low-dose ketamine is defined as a bolus dose of less than 2 mg/g when given intramuscularly or less than 1 mg/kg when administered via the intravenous or epidural route. For continuous i.v. administration low-dose ketamine is defined as a rate of ≤ 20 μg/kg per min. We conclude that ketamine may provide clinicians with a tool to improve postoperative pain management and to reduce opioid related adverse effects. The evidence suggests that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to local anesthetics, opioids, or other analgesic agents. Further research is required in the following areas: (a) dose-finding studies for ketamine as an adjunct to opioids and local anesthetics (b) efficacy and optimal route of administration (c) the role of S(+)-ketamine; (d) the influence of ketamine on long-term outcome such as chronic pain (e) long-term physical and chemical stability of mixtures containing ketamine (f) spinal toxicity of ketamine and (g) effects of low-dose ketamine on cognitive and memory functioning after surgery. © 1999 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Ketamine; Postoperative Pain; Pharmacodynamics

1. Introduction

A variety of substances and modalities are currently in use for the management of postoperative pain. To optimize pain management and outcome there is a continuous search for new analgesics and alternative routes of delivery. Ketamine is a well known general anesthetic and short acting analgesic in use for almost 3 decades. The recent discovery of the N-methyl-D-aspartate (NMDA) receptor (Foster and Fagg, 1987) and its links to pain processing and spinal neural plasticity triggered renewed interest in ketamine as a potential anti-hyperalgesic agent (Wilcox, 1991) given its actions as a non-competitive NMDA-receptor antagonist.

Ketamine has found a niche as a general anesthetic agent for various procedures in anesthesia and emergency medicine. Its usefulness, however, has been limited by its undesirable psychic emergence effects and cardiovascular stimulating properties. It therefore, remains a controversial drug to many anesthetists who remain wary of its adverse effects. However, it is becoming increasingly clear that a distinction must be made between the use of high-dose ketamine as an anesthetic agent and the use of low-dose ketamine for analgesic or anti-hyperalgesic effects. There may even be a third dose range in which ketamine has no analgesic potency on its own but when used in combination with an opioid, yields an opioid sparing effect and superior pain relief than either drug alone (Chapman and Dickenson, 1992; Dickenson, 1993).

In this review we briefly summarize the pharmacology of ketamine. We then evaluate and discuss the effectiveness and usefulness of low-dose ketamine in its different modes of application in the management of postoperative pain. Finally, we offer clinical recommendations and suggestions for future research.

For the purpose of the present review, low-dose ketamine is defined as a bolus dose of less than 2 mg/kg when given intramuscularly or less than 1 mg/kg when administered via the intravenous or epidural route. For continuous i.v. administration low-dose ketamine is defined as a rate of ≤ 20 $\mu g/$ kg per min.

2. Pharmacology

Ketamine (CI-581, Ketalar®) was developed in a search for an 'ideal' anesthetic. Ketamine was first synthesized by Stevens (1963) as a further development of phencyclidine and its congener cyclohexamine and was approved for clinical use in 1970. The ketamine molecule 2-(o-chlorophenyl)-2-(methylamino) cyclohexanone has a molecular weight of 238 (Silvay, 1983), is soluble in water to 20% (Corssen and Domino, 1966), and has a pK_a of 7.5 (Cohen and Trevor, 1974). The aqueous solutions of ketamine hydrochloride in clinical use have a pH range from 3.5 to 5.5. Under physiologic conditions the uncharged form of ketamine is highly lipid soluble (10 times that of thiopentone (Reich and Silvay, 1989)). It is available as a racemic mixture that contains equal amounts of the two isomers S(+)-ketamine and R(−)-ketamine. In both animals and humans S(+)-ketamine is 3–4 times more potent than R(−)-ketamine for pain relief (Marietta et al., 1977; Ryder et al., 1978; White et al., 1985; Oye et al., 1992; Mathisen et al., 1995;) and in equianalgesic doses, produces fewer psychic disturbances and less agitation than R(−)-ketamine or the racemate (Marietta et al., 1977; Ryder et al., 1978; White et al., 1980; Calvey, 1995) but see (Schuttler, 1992; Mathisen et al., 1995).

2.1. Pharmacodynamics

Ketamine acts on a variety of receptors, including nicotinic (Scheller et al., 1996) and muscarinic (Hustveit et al., 1995) receptors. Ketamine blocks peripheral and human central nervous system sodium channels (Scheller et al., 1996), it interacts with mu (μ), delta (δ), and kappa (κ) opioid receptors (Smith et al., 1980; Finck and Ngai, 1982; Hustveit et al., 1995) and interacts with monoaminergic and voltage sensitive Ca^{++} channels (Hirota and Lambert, 1996). Ketamine also acts as a non-competitive antagonist (see below) at the phencyclidine receptor site in the NMDA receptor complex channel (Willetts et al., 1990; Yamamura et al., 1990).

The role of the NMDA receptor in the processing of nociceptive input led naturally to renewed clinical interest in NMDA receptor antagonists such as ketamine (Ilkjaer et

al., 1996). Low-dose ketamine induces a use-dependent, non-competitive blockade (Dickenson, 1995), also referred to as an 'uncompetitive blockade' (Rogawski, 1993; Orser et al., 1997), meaning that the rate of onset and recovery of the block depends on agonist binding at a different receptor site. This implies that the receptor channel has to be in the open state before ketamine can bind to or dissociate from the blocking site presumed to be situated within the channel pore (Orser et al., 1997). This raises the possibility that ketamine can become 'trapped' in the receptor channel until the channel reopens after agonist activation (Foster and Fagg, 1987). A second NMDA receptor binding site for ketamine has been reported that is associated with the hydrophobic domain of the protein (Orser et al., 1997). Binding at the former receptor site (in the channel) decreases channel open time, whereas binding at the latter site decreases the frequency of channel opening.

3. Use of ketamine for postoperative pain management

3.1. Data identification

The literature referenced in this review was obtained from a computer search of the MEDLINE® database from 1966 through December 1998.

Of the 50 studies identified, those publications which fulfilled the following criteria were chosen for in depth analysis and discussion: randomized, prospective, controlled, double-blind and reporting pain scores. A total of 28 publications (56%) met the above criteria. The 22 (44%) remaining studies which did not fulfill these criteria are identified in Table 1 without additional comment. Due to the different study objectives and study designs, a meta-analysis of the published data was not deemed appropriate.

4. Routes of administration

In this section, we describe the different routes of ketamine administration in the treatment of postoperative pain. This is followed by a brief summary of outcomes based on the studies that fulfill the above stated criteria.

4.1. Oral, rectal and intranasal ketamine

The oral, rectal, and intranasal routes of administration of ketamine have been evaluated extensively to provide premedication for general anesthesia (Weksler et al., 1993; Alderson and Lerman, 1994; Warner et al., 1995; Cioaca and Canavea, 1996) or sedation for a variety of surgical procedures (Abrams et al., 1993; Alfonzo-Echeverri et al., 1993; Louon and Reddy, 1994). The analgesic efficacy of oral ketamine has only been examined in children requiring laceration repair (Hollman and Perloff, 1995). The analgesic effects of oral, rectal and intranasal ketamine in the postoperative setting either as an adjunct

Table 1
Studies not fulfilling inclusion criteria[a]

Author and year	Route	Criteria not fulfilled
Mathisen et al., (1995)	i.m.	R, C, DB
Bristow and Orlikowski (1989)	s.c.	DB, P
Ito and Ichiyanagi (1974)	i.v.	R, C, DB,P
Austin (1981)	i.v.	R, C, DB
Dick et al., (1983)	i.v.	C, DB
Knoche et al. (1983)	i.v.	C, DB
Forestner (1988)	i.v.	R, C, DB, P
Hartvig et al. (1993)	i.v.	R, C, DB, P
Islas et al. (1985)	Epidural	R, C, DB
Chung et al. (1986)	Epidural	R, C, DB
Naguib et al. (1986)	Epidural	C, DB
Ravat et al. (1987)	Epidural	C, DB
Kawana et al. (1987)	Epidural	P
Jiang et al. (1988)	Epidural	DB
Naguib et al. (1991)	Epidural	C, DB
Cook et al. (1995)	Epidural	DB, P
Semple et al. (1996)	Epidural	DB, P
Yanli and Eren (1996)	Epidural	P
Kucuk et al. (1998)	Epidural	DB
Weir and Fee (1998)	Epidural	P
Findlow et al. (1997)	Epidural	C, DB, P

[a] R, randomized; C, controlled; DB, double-blind; P, patient-rated pain.

to opioid analgesia or as the sole agent have not been determined.

4.2. Intramuscular ketamine

Ketamine is rapidly absorbed after intramuscular injection with an absorption half life of 2–17 min. After injection it appears in the plasma in less than 4 min (= lag time) and has a bioavailability of 93%. The mean ± SE terminal plasma half life is 155 ± 12 min (Clements and Nimmo, 1981).

A variety of doses have been administered ranging from 0.44 mg/kg (Sadove et al., 1971; Parkhouse and Marriott, 1977) to 1.0 mg/kg (Dich-Nielsen et al., 1992) (Table 2). Ketamine has been given as a single bolus injection (Sadove et al., 1971; Parkhouse and Marriott, 1977; Hagelin and Lundberg, 1981; Mathisen et al., 1995) or on demand (Dich-Nielsen et al., 1992) to patients undergoing a variety of surgical procedures (e.g. abdominal surgery, orthopedic surgery, thoracic surgery and orofacial surgery). Intramuscular ketamine has been administered as a sole analgesic agent (Sadove et al., 1971; Mathisen et al., 1995) or in combination with meperidine (Parkhouse and Marriott, 1977; Hagelin and Lundberg, 1981; Dich-Nielsen et al., 1992).

The results of these studies indicate that an intramuscular bolus of ketamine alone (0.5–1.0 mg/kg) is effective with a 1–2 fold analgesic potency (mg/mg) of that of i.m. pethidine. Most studies involved only single injections. Pain relief was rapid in onset (within 5 min) and lasted from 0.5 h (Sadove et al., 1971) to 2 h (Hagelin and Lundberg, 1981). Combining ketamine with an opioid may prolong analgesia compared with opioids or ketamine alone (Parkhouse and Marriott, 1977). Low-dose intramuscular ketamine (0.5–1 mg/kg) does not appear to have hemodynamic or respiratory depressant effects (Hagelin and Lundberg, 1981; Dich-Nielsen et al., 1992). Sedation, psychotomimetic effects and other adverse reactions associated with low-dose i.m. ketamine are infrequent and dose-related (see Table 2).

4.3. Subcutaneous ketamine

Subcutaneous (s.c.) administration of drugs has the potential advantage of relatively even and slow absorption into the bloodstream (Schwinn et al., 1994). This prevents high peak blood levels that occur after intravenous bolus administration. Low-dose (1.7 μg/kg per min) s.c. ketamine administered after major abdominal surgery did not produce adverse effects and provided postoperative analgesia equivalent to a s.c. morphine infusion of 2 mg/h (Bhattacharya et al., 1994).

4.4. Intravenous ketamine

Ketamine is distributed rapidly after intravenous administration with a bioavailability of 93% (Grant et al., 1981). Thereafter, plasma levels fall rapidly; however, the mean terminal half life is 186 ± 10 min fitting a two compartment open model (Clements and Nimmo, 1981). The studies using i.v. ketamine have heterogeneous designs (Table 3). Ketamine has been administered as either a single bolus injection (Maurset et al., 1989; Ngan Kee et al., 1997), bolus injection followed by a continuous infusion (Joachimsson et al., 1986; Owen et al., 1987; Jahangir et al., 1993), continuous infusion (Clausen et al., 1975), continuous infusion combined with either an opioid or a benzodiazepine (Edwards et al., 1993; Jahangir et al., 1993; Stubhaug et al., 1997; Wilder-Smith et al., 1998), or via a patient-controlled device (PCA) (Javery et al., 1996). In some studies opioid rescue medication was made available to patients. Studies in Table 3 can be categorized as follows: bolus injection, bolus injection plus continuous infusion, continuous infusion, or patient-controlled.

Taken together these studies suggest that analgesic efficacy of i.v. ketamine depends on infusion rate, initial loading dose and whether concomitant opioids are administered (Table 4). Ketamine produces effective but short acting pain relief when administered as a single bolus of > 300 μg/kg (Maurset et al., 1989). Ketamine does not have any effect on postoperative pain or morphine consumption when administered (without a loading dose) as a continuous infusion of less than 4 μg/kg per min (Edwards et al., 1993). In combination with a loading dose however, ketamine infusion rates of 1–6 μg/kg per min provide evidence of anti-hyperalgesic, analgesic and opioid sparing effects (Owen et al., 1987; Jahangir et al., 1993; Stubhaug et al., 1997). At higher doses, ketamine appears to provide an equivalent degree of postoperative pain relief as do opioids, but onset can be

Table 2
Studies of intramuscular ketamine fulfilling inclusion criteria[a]

Author	Groups (timing)	Population	Design	Obs. time (h)	Bolus (μg/kg)	Blood conc.	Pain	Bad dreams (n)	Hallucinations (n)	Cv (n)	Resp. (n)	Other adverse effects (n)
Sadove et al. (1971)	(1) i.m. K (AS); (2) i.m. placebo (AS)	25 patients, general surg., orthopedic surg.	R, PC, DB	1	440	Ø	Four point rating scale. Observer rated pain (1) < (2)	No data	No data	BP ⇔ HR ⇔	RR ⇔ RMV ⇔	Dizziness, (8/25); euphoria, (2/25); blurred vision, (2/25); incoordination, (1/25); agitation, (1/25); difficulty in communicating, (4/25); sedation, (25/25)
Parkhouse and Marriott (1977)	(1) i.m. K + Mp 50 mg (AS); (2) i.m. Mp 50 mg (AS); (3) i.m. Mp 100 mg (AS); (4) i.m. placebo + conventional analgesics	65 patients, general orthopedic + genito-urinary surg.	R, PC, DB	6	430	Ø	Pain relief score. Patient + observer rated pain ⇓ . Pain relief: (1) = (2) = (3) > (4); duration of pain relief: (1) > (2) = (3) > (4)	No data	No data	No data	No data	Not specific to K
Hagelin and Lunderberg (1981)	(1) i.m. Mp 70 mg (AS); (2) i.m. K 35 mg (3) (AS) i.m. K 70 mg (AS)	42 patients, abdominal surg.	R, C, DB	5	500* 1000*	Ø	Four point rating scale. Patient rated pain ⇓ from 2/4 to 1/4. Pain relief: (1) = (2) = (3); duration of pain relief: (1) = (3) > (2).	No data	No data	BP ⇔ HR ⇔ RPP ⇔	RD ⇓ PCO_2 ⇓	Dizziness Group 2:3, (8/13):(6/16); diplopia, (1/13):(4/16); flushing, (1/13):(2/16); nausea, (1/13):(3/16)
Dich-Nielsen et al. (1992)	(1) i.m. K 1 mg/kg (AS); (2) i.m. Mp 1 mg/kg (AS) + injections repeated when in pain	30 patients, thoracotomy	R, DB	3	1000 q0.5h, prn	Ø	VAS patient rated pain ⇓ 7/10 to 3/10 (1) = (2) but P > K first 2 h, K > P after 2 h	1/30	0/30	BP ⇔ HR ⇔	RR ⇔ PCO_2 ⇓	Dizziness, (1/30); anxiety, (1/30); illusion, (1/30)

[a] Obs., observation; Cv, cardiovascular effects; Resp, respiratory effects; K, ketamine; F, fentanyl; Mp, meperidine; Me, methadone; P, placebo; i.m., intramuscular; Surg., surgery; AS, after surgery; PCL, peritoneal closure; VAS, visual analogue scale; R, randomized; DB, double blind; C, controlled; PC, placebo controlled; BP, blood pressure; HR, heart rate; RPP, rate pressure product; RR, respiratory rate; RD, respiratory depression; RMV, respiratory minute volume; ⇓, decrease; ⇑, increase; ⇔, no change; =, equal to; <, less than; >, greater than; *rate calculated on the basis of the mean weight of study group or if not available on a weight of 70 kg.

Table 3
Studies of intravenous ketamine fulfilling inclusion criteria[a]

Author	Groups (timing)	Population	Obs.time (h)	Design	Bolus (μg/kg)	Inf. rate (μg/kg/min)	Blood conc. ng/ml (mean)	Pain	Bad dreams	Hallucinations	Cv	Resp.	Other adverse effects
Clausen et al. (1975)	(1) Cont. i.v. M (AS); (2) cont. i.v. K (AS); (3) i.v. Placebo (AS)	36 Patients, major surg.	6	R, PC, DB	Ø	14*	Ø	Five point rating scale. Observer rated pain ⇩ 50%: (1) = (2) at 6 h, K = P h 0–3, K = M h 3–6	No data	No data	No data	PF ⇑	No data
Joachimsson et al. (1986)	(1) i.v. cont. K (AS); (2) Placebo (AS) + Kb prn for all groups	40 Patients, abdominal surg., ventilated	8	R, PC, DB	400	14	Ø	Four point rating scale. Observer rated pain ⇩ (1) = (2), total rescue (1) < (2) 80% Kb sparing effect	2/20	4/20	BP ⇩, HR ⇩, RPP ⇩	Ventilated	Floating in space
Owen et al. (1987)	(1) cont. i.v. K (BI); (2) cont. i.v. M + PCA-M for abdominal surg. all groups	60 Patients,	25	R, C, DB	1000	4	126–256 (179)	Four point rating scale. Observer rated pain scores (1) = (2); total M consumption, (1) < (2), 50% M sparing effect in group (1)	0/30	0/30	BP ⇔, HR ⇔	RR ⇔	No data
Maurset et al. (1989)	(1) i.v. K 0.3 mg/kg (AS); (2) i.v. Mp 0.7 mg/kg	Six women, oral surg.	1	R, C, X, DB	300	Ø	Ø	VAS patient rated pain ⇩ 80%. Pain relief: K = Mp, duration: K < Mp	0/6	0/6	No data	No data	Dizziness, floating sensation
Edwards et al. (1993)	(1) cont. i.v. M 1 mg/h (BI); (2) cont. i.v. M + K 5 mg/h (BI); (3) cont. i.v. M + K 10 mg/h (BI); (4) cont. i.v. M + K 20 mg/h (BI); + PCA-M for all groups	40 Patients, >60 years, Abdominal surg.	24	R, C, DB	Ø	(2) 1.4*, (3) 2.5*, (4) 4.7*	Ø	Five point rating scale. Patient rated pain ⇩. Pain relief: (1) = (2) = (3) = (4); PCA-M consumption: (1) = (2) = (3) = (4)	(2) 0/10, (3) 0/10, (4) 0/10	No data	HR ⇔, BP ⇔	RR ⇔, PF ⇔, FEV1 ⇔, FVC ⇔, RD	Seven withdrawals: 4 RDs (1,2,3); 1 drowsiness (2); 1 bad dream (4); 1 confusion (4)
Jahangir et al. (1993)	(1) cont. i.v. K-Mz (AS); (2) i.m. Mp q4h (AS)	60 Women with asthma TAH	25	R, C, DB	500	5.88–6.42	Ø	VAS patient rated pain ⇩ 5/10 to 1/10. Pain relief: K-Mz > Mp	2/31	0/31	BP ⇔, HR ⇔	RR ⇔, TV ⇔, FEV ⇔	Nausea 1/31
Javery et al. (1996)	(1) PCA-M + K (AS); (2) PCA-M (AS)	42 Patients, microdisectomy	Data at 24 h	R, C, DB	PCA: 1 mg/bolus 6 min lockout	Ø	Ø	VAS patient rated pain ⇩. Pain relief: M + K > M; Total M consumption (1) < (2) ⇒ K has 50% M sparing effect	0/21	0/21	No data	No RD	Nausea ⇩, pruritus ⇩, sedation ⇒, dysphoria 1/22
Stubhaug et al. (1997)	(1) cont. i.v. K (BI); (2) placebo (BI); + PCA-M + intercostal nerve block for all patients (AS)	20 Patients, living kidney donors	7 Days	R, PC, DB	500	2 (24 h) + 1 (48 h)	± 50	VAS patient rated. Hyperalgesia:(1) < (2); PCA-M consumption:(1) < (2) first 6 h, TFR (1) ≫ (2)	No data	No data	No data	No data	No psychotomimetic effects; nausea (1) < (2); vomiting (1) < (2); dizziness (1) = (2)
Ngan Kee et al. (1997)	(1) Thiopentone (BI); (2) K (BI); + PCA-M for all patients	40 Women, Cesarean section	24	R,C DB	1000	Ø	Ø	VAS patient rated. TFR (1) < (2). Pain relief: (1) = (2), PCA-M consumption:(1) > (2)	0/40	No data	No data	No data	No data
Wilder-Smith et al. (1998)	(1) fentanyl (BI); (2) ketamine (BI); (3) Mg^{2+}(BI) + PCA-M + backround inf.	45 Women, TAH	5 Days	R, C, DB	500 + 250/30 min until end of surgery	Ø	Ø	VRS patient rated. Pain relief: (1) = (2) = (3); PCA-M consumption: (1) = (2) = (3); spinal hypersensitivity ⇩ in all groups	No data	No data	No data	No data	Sedation: (1) = (2) = (3)

[a] Inf., infusion; Obs., observation; Cv, cardiovascular effects; Resp, respiratory effects; K, ketamine; Kb, ketobemidone; M, morphine; Mp, meperidine; Mz, midazolam; B, bupivacaine; P, placebo; cont., continuous; i.v., intravenous; im, intramuscular; AI, after incision; BI, before incision; AS, after surgery; PCA, patient-controlled analgesia; Surg., surgery; TAH, total abdominal hysterectomy; VAS, visual analogue scale; VRS, verbal rating scale; OP, day of operation; D, postoperative day; R, randomized; DB, double blind; C, controlled; PC, placebo controlled; X, crossover; BP, blood pressure; HR, heart rate; RPP = rate pressure product; RR, respiratory rate; RD, respiratory depression; PF, peak flow; TV, tidal volume; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; N&V, nausea and vomiting; ⇩, decrease; ⇑, increase; ⇔, equal to; gr., group; yr., years; < , less than; > , greater than; = , equal to; * rate calculated on the basis of the mean weight of study group or if not available on a weight of 70 kg.

Table 4
Analgesic efficacy of intravenous ketamine with or without bolus administration or concomitant opioids

Reference	Ketamine regime			Outcome	
	Infusion (μg/kg per min)	Bolus (μg/kg)	Concomitant opioid	Analgesic effect	Opioid sparing effect
Maurset et al. (1989)	No	300	No	Yes	–
Javery et al. (1996)	No	14	Yes	?	Yes
Wilder-Smith et al. (1998)	No	500/250	Yes	Yes[a]	No
Edwards et al. (1993)	<4	No	Yes	No	No
Stubhaug et al. (1997)	1–2	500	Yes	Yes[b]	Yes
Owen et al. (1987)	4	1000	Yes	Yes	Yes
Jahangir et al. (1993)	6	500	No	Yes	–
Clausen et al. (1975)	14	No	No	Yes	–
Joachimsson et al. (1986)	14	500	Yes	Yes	Yes

[a] Anti-hyperalgesic.
[b] Anti-hyperalgesic and analgesic (6 h).

delayed by several hours if a loading dose is not also administered. A value for the analgesic potency of ketamine alone cannot be calculated from the available studies.

Low-dose i.v. ketamine is a potent and safe adjunct to systemic opioid analgesia. When ketamine (1.0–14.0 μg/kg per·min following a loading dose) is combined with opioid administration, the combination is associated with better pain relief and an opioid-sparing effect as large as 50%. When compared with opioids alone, the PCA opioid-sparing effect of ketamine is evident even at minimal bolus doses (e.g. 14.0 μg/kg i.v. ketamine) (Javery et al., 1996). At the doses reported above, ketamine has not been found to cause any significant cardiovascular or respiratory effects. Sedation, dreams, hallucinations and other psychotomimetic adverse reactions are infrequent and the incidence increases with dose.

4.5. Intraspinal ketamine

Intraspinal techniques include caudal ketamine or caudal ketamine with local anesthetics, lumbar epidural ketamine, lumbar epidural ketamine with local anesthetics and/or opioids and thoracic epidural ketamine with opioids. Ketamine is rapidly absorbed from the epidural space into the systemic circulation with a mean bioavailability (± SD) of 77 ± 22%. However, slow release from the CSF results in decreased levels of metabolites (Pedraz et al., 1987).

Animal studies have demonstrated the safety of intrathecal 1% ketamine with preservative after a single dose (Brock-Utne et al., 1982) and for ketamine without preservative after multiple doses (Borgbjerg et al., 1994). However, both the preservative itself (Malinovsky et al., 1993) and preservative-free (Yaksh, 1996) ketamine may induce spinal toxicity and therefore, should not be injected intraspinally in humans. It should be noted that ketamine has not been licensed for epidural administration anywhere in the world.

Case reports, comments and studies of epidural ketamine are numerous (Mankowitz et al., 1982; Amiot et al., 1985; Islas et al., 1985; Ivankovich and McCarthy, 1986; Naguib et al., 1986; Kawana et al., 1987; Ravat et al., 1987; Van der Auwera et al., 1987; Naguib and Adu-Gyamfi, 1988). However, excluding studies in which ketamine is administered pre-emptively (described below), there are only three controlled clinical studies (Table 5) in which the efficacy of epidural ketamine has been assessed. These studies indicate that epidural ketamine as the sole agent does not provide effective postoperative analgesia (Peat et al., 1989; Wong et al., 1997). In combination with epidural morphine, low-dose ketamine exerts an opioid-sparing effect and provides improved pain relief compared with epidural morphine alone (Wong et al., 1997; Chia et al., 1998).

5. Preemptive ketamine

The rationale for preemptive analgesia in the management of postoperative pain has been reviewed in detail (Katz et al., 1992; Coderre et al., 1993; Dahl and Kehlet, 1993; Woolf and Chong, 1993; Katz, 1995). Since ketamine is an NMDA-receptor antagonist, it is hypothesized to prevent or reverse (already established) central sensitization and thus to reduce postoperative pain. Initial results using ketamine preemptively are encouraging. Studies investigating preemptive analgesic effects of ketamine fall into two groups depending on the route of administration; either i.v. or epidural (Table 6).

Low-dose ketamine administered i.v. (Murray et al., 1987; Roytblat et al., 1993; Tverskoy et al., 1994; Fu et al., 1997) or via the epidural route (Choe et al., 1997; Wong et al., 1997; Abdel-Ghaffar et al., 1998) resulted in reduced postoperative pain intensity and/or analgesic consumption. This appears to be the case whether ketamine is given in conjunction with an opioid or a local anesthetic or as the sole agent.

Table 5
Studies of epidural ketamine fulfilling inclusion criteria[a]

Author	Groups (timing)	Population	Obs. time (h)	Design	Epidural bolus (mg)	Inf. (μg/kg per min)	Level	Pain	Bad dreams	Hallucinations	Cv	Resp.	Other adverse effects
Peat et al. (1989)	(1) K (PCL); (2) DM (PCL)	20 Women, TAH	24	R, C, DB	30	Ø	L1–3	VAS K > DM. All patients were switched to DM	0/10	1/10	No data	RR ⇑	Nausea 50%, vomiting 10%, NS between groups
Wong et al. (1996) Part I	(1) M 0.5 mg (AS); (2) M 1.0 mg (AS); EA: L + (3) M 2.0 mg (AS); TKR, THR (4) K 10 mg (AS); (5) K 20 mg (AS); (6) K 30 mg (AS); (7) N/S (AS)	36 Patients, TKR, THR	12	R, PC, DB	(4) 10, (5) 30, (6) 20	Ø	L1–3	VAS patient rated pain ⇔, No difference from group (7)	No	No data	No data	No RD	No data
Wong et al. (1996) Part II	(1) N/S (AS); EA: (2) K (AS); (L + (3) M 2 mg (AS); (4) K + M 0.5 mg (AS); top up q12h + i.m. Mp prn, q4h (AS)	L + 40 patients, TKR, THR	12	R, PC, DB	(2) 10, (4) 10, EA: 30 mg top up	Ø	L1–3	VAS patient rated. Pain relief at rest (4) > (3) > (2); motion (4) = (3) > (2) = (1); rescue analgesia (4) = (3) < (2) = (1)	No data	No data	No data	No RD	Psychotomimetic effects 3/40: n = 2 (3) n = 1 (4) drowsiness, N&V, pruritus, n = 1 all ⇓ compared with control and M-groups
Chia et al. (1998)	EA: (1) M + B (AS); (2) M + B + K (AS) + PCEA same solutions	91 Patients, major surg.	72	R, C, DB	PCEA 1 mg/ bolus	1 mg/h	T9–L1, T5–9	VAS patient rated: at rest (1) > (2); motion (1) > (2); M total mg (1) > (2)	0/91	0/91	No data	No data	Pruritus, N&V: (1) = (2)

[a] Inf, infusion; Obs., observation; Cv, cardiovascular effects; Resp, respiratory effects; A, adrenaline; B, bupivacaine; C, clonidine; DM, diamorphine; K, ketamine; L, lidocaine; M, morphine; Mp, meperidine; Glc, glucose; N/S, normal saline; GA, general anesthesia; EA, epidural anesthesia; AS, after surgery; BI, before incision; PCL, peritoneal closure; VAS, visual analogue scale; OPS, objective pain scale; TFR, time to first analgesic request; gyn., gynecological; TAH, total abdominal hysterectomy; TKR, total knee replacement; THR, total hip replacement; i.v., intravenous; im., intramuscular; cd, caudal; R, randomized; DB, double blind; C, controlled; PC, placebo controlled; BP, blood pressure; HR, heart rate; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; RR, respiratory rate; RD, respiratory depression; N&V, nausea and vomiting; ⇓, decrease; ⇔, no change; ⇑, increase; <, less than; =, equal to; >, greater than; gr., group; NS, not significant; yr., years; Ø, not performed.

Table 6
Studies of preemptive ketamine fulfilling inclusion criteria[a]

Author	Groups (Timing)	Population	Obs. time (h)	Design	Bolus (μg/ kg)	Inf. rate (μg/kg per min)	Route/level	Pain	Bad dreams	Hallucina- tions	Cv	Resp.	Other adverse effects
Murray et al. (1987)	(1) K (BI); (2) N/S (BI) + tilidine drops for all patients	40 Children, > 4 years, Tonsillectomy	1.5	R, C, DB	500	∅	i.v.	Five point rating scale, patient rated. Preemptive effect: yes. Pain relief: (1) > (2) after 30 min (1) = (2), rescue analgesia: (1) < (2)	No data	0/40	No data	No data	No complications
Roytblat et al. (1993)	(1) GA; (2) GA + K (BI) + PCA-M for all patients (AS)	22 Patients, Cholecystectomy	24	R, C, DB	150	∅	i.v.	VAS patient rated. Preemptive effect: yes. Total M: (1) > (2). Pain relief: (1) < (2) first 5 h then (1) = (2)	0/22	0/22	BP ⇓, HR ⇓	No data	N&V 3/11
Tverskoy et al. (1994)	(1) GA; (2) GA + F bolus + F Inf. (BI); (3) GA + K bolus + K Inf. (BI) + i.v. Mp all patients (AS)	27 Women, TAH	48	R, C, DB	2000 at induction of anesthesia	20	i.v.	VAS patient rated. Preemptive effect: yes. Pain relief: (1) = (2) = (3), TFR: (3) = (2) > (1), wound hyperalgesia: (1) > (2) = (3)	No data	No data	No data	No data	No data
Fu et al. (1997)	(1) K bolus + K infusion (BI); (2) K bolus (AS); + PCA-M for all patients (AS)	40 Patients, abdominal surg.	48	R, C, DB	500	10	i.v.	VAS patient rated. Preemptive effect: yes. TFR: (1) = (2). Pain relief:(1) = (2). Total M: (1) < (2)	No data	0/40	No data	No data	No data
Choe et al. (1997)	(1) K + M 2 mg (BI); (2) K + M 2 mg (AD); + top up M +B 0.25% for all patients (AS)	60 Patients, gastrectomy	48	R, C, DB	60 mg	∅	Epidural/ T7–8	Numeric rating scale + PHS. Preemptive effect: yes, duration of pain relief: (1) ≫ (2). Rescue top ups (1) < (2)	No data	0/60	No data	0/60	N&V 4/60, urinary retention 9/60, pruritus 3/60, somnolence 8/60
Wong et al. (1997)	(1) GA: + (N/S + M + K) (AD); (2) EA: L + (L + M + K) (BD); (3) EA: L + (L + M + K) (AD); + top up (L + M + K) q12h + PCA for all patients (AS)	45 Patients, TKR	72	R, C, DB	20 mg, top up10 mg	∅	Epidural/ L1–3	VAS patient rated. Preemptive effect: yes. Pain relief: (2) > (3) > (1). TFR (PCA): (2) > (3) > (1). Total PCA: (2) < (3) < (1)	No data	No data	No data	No RD	Psychotomimetic effects 2/45; nausea 19/45, vomiting 15/45, drowsiness 16/45, pruritus 6/45
Abdel-Ghaffar et al. (1998)	(1) K (BI); (2) K (AD); (3) N/S + PCEA B + F	60 Patients, TAH	24	R, C, DB	30 mg	∅	Epidural/ T12–L1	VAS patient rated. TFR (1) = (2) > (3). PCEA-consumption: (1) = (2) < (3)	Not clear	(1) 0/21, (2) 1/20, (3) 1/20	No data	No data	Pruritus, N&V, hypotension (1) = (2) = (3)

[a] Inf., infusion; Obs., observation; Cv, cardiovascular effects; Resp, respiratory effects; F, fentanyl; K, ketamine; L, lidocaine; M, morphine; Mp, meperidine; N/S, normal saline; GA, general anesthesia; EA, epidural anesthesia; BI, before incision; AI, after incision; i.v., intravenous; Inf., infusion; PCA, patient-controlled analgesia; TAH, total abdominal hysterectomy; TKR, total knee replacement; VAS, visual analogue scale; PHS, Prince Henry score; TFR, time to first analgesic request; R, randomized; DB, double blind; C, controlled; BP, blood pressure; HR, heart rate; RD, respiratory depression; N&V, nausea and vomiting; ⇓, decrease; ⇑, increase; ⇔, no change; >, greater than; <, less than; =, equal to; gr., group; NS, not significant; yr., years; ∅, not performed.

6. Miscellaneous

In this section we summarize the studies that could not be categorized under one of the above headings.

The postoperative analgesic effects of preoperatively administered i.v. ketamine (0.2 mg/kg) or i.v. fentanyl (1 μg/kg) were evaluated followed by administration of bupivacaine or i.t. neostigmine and bupivacaine (Lauretti and Azevedo, 1996) (Table 7). Co-administration of ketamine with intrathecal neostigmine showed a clear and prolonged postoperative analgesic effect.

Tverskoy et al. (1996) compared the analgesic effects of wound infiltration after herniorrhaphy using a mixture of bupivacaine (0.5%) and ketamine (0.35%) or bupivacaine alone (0.5%). Addition of ketamine enhanced both the local anesthetic and analgesic effects of bupivacaine wound infiltration. Similar findings were also reported in which ketamine and bupivacaine or bupivacaine alone was infiltrated into the wound at the end of surgery. A peripheral mechanism of action of ketamine is suggested by these investigators.

7. Pharmacologic effects

Postoperative pain management is usually limited by adverse effects. In this section, we briefly summarize the pharmacological effects of low-dose ketamine on respiration, cardiovascular function, sedation, nausea and vomiting, urinary retention, constipation/prolonged adynamic postoperative ileus and psychological function. There is no evidence to indicate that low-dose ketamine (up to 1 mg/kg) causes or contributes to respiratory depression (Maduska and Hajghassemali, 1978; White et al., 1982; Bourke et al., 1987; Owen et al., 1987; Peat et al., 1989; Edwards et al., 1993; Jahangir et al., 1993; Bhattacharya et al., 1994).

Studies examining cardiovascular response to low-dose ketamine report minimal changes in heart rate and blood pressure (Sadove et al., 1971; Hagelin and Lundberg, 1981; Owen et al., 1987; Dich-Nielsen et al., 1992; Edwards et al., 1993; Jahangir et al., 1993; Bhattacharya et al., 1994). Two studies (Joachimsson et al., 1986; Roytblat et al., 1993) found a decrease in heart rate and blood pressure which was attributed to a decrease in pain.

Low-dose ketamine may cause mild sedation (Sadove et al., 1971) that is less than the sedation seen with opioids (Bristow and Orlikowski, 1989; Bhattacharya et al., 1994). In combination with opioids, low-dose ketamine does not appear to aggravate or contribute to opioid-induced sedation (Javery et al., 1996; Stubhaug et al., 1997).

Clinical studies have not investigated the emetic or antiemetic effects of low-dose ketamine. However, when low-dose ketamine was used alone or in conjunction with an opioid in the treatment of postoperative pain, the incidence of postoperative nausea and vomiting was significantly reduced compared with morphine alone (Bhattacharya et al., 1994; Gurnani et al., 1996; Javery et al., 1996; Stubhaug et al., 1997). This may be due to the opioid-sparing effect of ketamine. However, when low-dose ketamine is administered to healthy volunteers, incidence of nausea and vomiting appears to be greater than that reported in the clinical setting (Krystal et al., 1998; Sethna et al., 1998).

Urinary retention was found to be less common in patients using a PCA device administering a mixture of morphine and ketamine compared with PCA-morphine alone (Javery et al., 1996). Similar results were obtained when a continuous subcutaneous ketamine infusion was compared with a continuous subcutaneous morphine infusion (Bhattacharya et al., 1994).

There is no evidence that ketamine delays gastric emptying or gastro-coecal transit time (Grant et al., 1981; Freye and Knufermann, 1994).

8. Psychotomimetic effects and impairment in cognitive functioning

Disturbing emergence reactions (e.g. hallucinations, bad dreams) have limited the clinical usefulness of ketamine. The incidence varies from 5% to greater than 30% (White et al., 1982) after high dose ketamine anesthesia. Several factors associated with psychotomimetic effects include age, sex, subjects who normally dream or have a history of psychopathology, high doses of ketamine (> 2 mg/kg, i.v.) and rapid intravenous administration (> 40 mg/min) (White et al., 1982).

Six studies have examined the effects of low-dose ketamine administered to healthy volunteers (Table 8). Only one study was specifically designed to assess the effects of low dose ketamine on cognitive functioning and experimentally induced pain (Sethna et al., 1998). In the remaining five studies ketamine was administered to evaluate the psychiatric effects of NMDA receptor antagonism. Taken together, the results of these studies suggest that i.v. low-dose ketamine given at an infusion rate < 2.5 μg/kg per min (estimated plasma levels: < 50 ng/ml) does not cause hallucinations (Krystal et al., 1994; 1998) or impairment of cognitive functioning (Krystal et al., 1994; Sethna et al., 1998). Other adverse effects such as a sense of intoxication, dizziness, blurred vision, itching or nausea and vomiting occur more commonly but the incidence of these adverse effects does not appear to differ from that of opioids (Sethna et al., 1998). At higher doses and plasma levels (200 ng/ml), incidence of cognitive and memory impairments, psychiatric symptoms, illusory experiences and other adverse effects increases (Krystal et al., 1994; 1998; Adler et al., 1998; Bowdle et al., 1998; Sethna et al., 1998).

In contrast to the research on healthy volunteers, studies of the effects of low-dose ketamine on perception, cognition and memory functioning in the acute postoperative setting have not been conducted. However, most trials do report the

Table 7
Miscellaneous studies fulfilling inclusion criteria[a]

Author	Groups (timing)	Population	Obs. time (h)	Design	Bolus dose	Pain	Bad dreams	Hallucinations	Cv	Resp.	Other adverse effects
Mathisen et al. (1995)	(1) i.m. K (R)-ketamine (AS); (2) i.m. K (S)-ketamine (AS)	Nine women, oral surg.	1.5	R, X, DB	(1) 1.8, mg/kg; (2) 0.45 mg/kg	VAS patient rated pain $\Downarrow$	No data	(1) 0/9, (2) 0/9	No data	No data	Blurred vision (S-9/9, R-7/9); altered hearing (S-7/9, R-6/9); dizziness (S-8/9, R-8/9); illusions (S-5/9, R-2/9); sedation (S-0/9, R-0/9); proprioceptive disturbance (S-9/9, R-5/9)
Tverskoy et al. (1996)	(1) w.i B + K (AS); (2) w.i. B (AS); + oral dipyrone or i.m. Mp for all patients (AS)	18 Patients, hemiorrhaphy	24	R, C, DB	30 mg	VAS + pressure algometry. Duration of pain relief: (1) > (2), pain threshold: $\Uparrow$ (1) > (2)	No data	No data	No data	No data	No data
Lauretti and Azevedo, 1996	(1) i.v. N/S + i.t. B + N/S (BI); (2) i.v. N/S + .t. B + Neost. (BI); (3) i.v. K + i.t. B + N/S (BI); (4) i.v. K + i.t. B + Neost. (BI); (5) i.v. F + i.t. B + N/S (BI); (6) i.v. F + i.t. B + Neost. (BI) + i.m. Diclofenac for all patients	60 Women, vaginoplasty	24	R, C, DB	0.2 mg /kg	VAS patient rated. Pain $\Downarrow$ at 24 h for (4), pain relief prolonged for (4), rescue analgesia $\Downarrow$ $\Downarrow$ for (4)	No data	No data	No data	No data	Postoperative nausea $\Downarrow$ for group (4)

[a] Obs., observation; Cv, cardiovascular effects; Resp, respiratory effects; B, bupivacaine; F, fentanyl; K, ketamine; Mp, meperidine; Neost., neostigmine; N/S, normal saline; i.v., intravenous; im, intramuscular; i.t, intrathecal; w.i, wound infiltration; BI, before incision; AS, after surgery; VAS, visual analogue scale; R, randomized; DB, double blind; C, controlled; X, crossover; N&V, nausea and vomiting; $\Downarrow$, decrease; $\Uparrow$, increase; >, greater than; <, less than.

Table 8
Studies involving low-dose ketamine administration to healthy volunteers[a]

Author/year	Design	Treatments	Ketamine i.v. bolus (μg/kg)[b]	Ketamine i.v. infusion (μg/kg per min)[b]	Ketamine i.v. infusion duration (min)	Ketamine total dose (mg)	Ketamine blood levels (ng/ml)	Acute pain paradigm	Impairment in cognitive functioning	Other adverse effects
Sethna et al. (1998)	R, DB, C, X	K1	10.0	1.9	35	5.0	∅	Yes	10% ⇓ in DSST&PST in K2, AK2 and A2	Intoxication, dizziness, blurred vision, itching, nausea reported in all groups
		K2	40.0	7.7	35	520	∅			
		AK2	5.0	0.9	35	2.5	∅			
		AK2	20.0	3.9	35	10.0	∅			
		A1	∅	∅	∅	0.0				
		A2	∅	∅	∅	0.0				
Adler et al. (1998)	R, DB, PC, X	K	120.0	10.8	60	54.0	∅	No	K > P at 45 min only	Not reported
		P	∅	∅	∅	0.0				
Krystal et al. (1998)	R, DB, PC, X	K	260.0	0.8	60	64.0	200	No	⇑ in WCST errors for K and KL	⇑ BPRS & CADSS for K and KL, nystagmus, emesis, anxiety, 'high' reported in K and KL
		L	∅	∅	∅	0.0	∅			
		KL	0.0	10.8	60	64.0				
		P	∅	∅	∅	0.0	∅			
Krystal et al. (1994)	R, DB, PC, X	K1	∅	2.5	40	7.0	25–50 estimated	No	K1 = K2 = P for MMSE K2 > K1 = P for errors on WCST, VF and 10 min delayed recall	↑ BPRS, CADSS, WPP-PAS, anxiety and 'high' for K2 only
		K2	∅	12.5	40	35.0	100–250 estimated			
		P	∅	∅	∅	0.0				
Bowdle et al. (1998)	R, SB, PC, X	K	not reported	not reported	30 min at each plasma level	not reported	0 → 50 → 100 → 150 → 200	No	∅	Plasma level related increases in psychedelic effects
		P								
Ghoneim et al. (1985)	R, DB, PC	K1	250.0 i.m.	∅	∅	17.5	∅	No	⇓ in immediate and delayed recall for K1 and K2	⇓ In mood for K1 and K2. High incidence of dreams, hallucinations, floating sensations dizziness, N&V, visual disturbance in K1 and K2
		K2	500.0 i.m.	∅	∅	35.0	∅			
		P	∅	∅	∅	0.0				

[a] A, alfentanil; K, ketamine; L, Lorazepam; im, intramuscular; i.v., intravenous; P, placebo; R, randomized; DB, double blind; SB, single blind; C, controlled; X, crossover; N&V, nausea and vomiting; ⇓, decrease; ↑, increase; >, greater than; <, less than; ∅, not performed; BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociative States Scale; DSST, Digit Symbol Substitution test: MMSE, Mini-Mental Status Exam; PST, Perception Speed Test; VF, Verbal fluency; WCST, Wisconsin Card Sorting Test; WPP-PAS, Wisconsin Psychosis Proneness-Perceptual Aberration Subscale Score.
[b] Rate calculated on the basis of the mean weight of study group or if not available on a weight of 70 kg.

presence or absence of adverse effects including alterations in perception. These are described as 'floating in space' (Joachimsson et al., 1986; Maurset et al., 1989) or as a 'feeling of unreality' (Ito and Ichiyanagi, 1974), are reported infrequently, and occur in the high end of the low-dose range. The incidence of bad dreams or hallucinations is low or equals that of opioids (Dich-Nielsen et al., 1992). However, in two studies by the same research group, a total of 5 of 85 patients had severe enough psychotomimetic effects to require benzodiazepines or to be withdrawn from the study (Wong et al., 1996; Wong et al., 1997).

Taken together, in the clinical postoperative setting, the pharmacologic profile of adverse effects of low-dose ketamine appears to be less worrisome than that of opioids or NSAIDs. The incidence of psychotomimetic effects and cognitive impairment is negligible at doses less than 2.5 μg/kg per·min i.v. and increases with higher doses. Within limits, and under appropriate monitoring, low-dose ketamine can be used safely either by itself or as an adjunct to traditional opioid analgesic therapy in the management of postoperative pain.

9. Conclusions and recommendations

Despite the many studies examining the use of ketamine in the treatment of acute postoperative pain, most are difficult to interpret due to fundamental problems with design, methods or statistical treatment of data. The following conclusions and recommendations are based only on studies that are randomized, prospective, double-blind, controlled and employ pain rating measures.

Low-dose ketamine as the sole analgesic agent reduces pain significantly using the following routes: i.m., s.c. and i.v. However a number of qualifications apply: i.m. ketamine may be suitable for short-term use only, and i.v. ketamine appears to provide satisfactory pain relief only at the upper end of the low-dose range (1 mg/kg) with an increased risk of psychotomimetic adverse effects. For certain clinical conditions (e.g. asthma, allergies) taking the risk–benefit relationship into consideration, ketamine (i.m., s.c., i.v.) might provide an alternative to conventional opioid analgesia (Jahangir et al., 1993).

There is little evidence that epidurally administered low-dose ketamine by itself provides effective postoperative analgesia, which is in line with recent findings in a rat model for postoperative pain (Zahn and Brennan, 1998). However, since both the preservative itself (Malinovsky et al., 1993) and preservative-free (Yaksh, 1996) ketamine may be associated with spinal toxicity it is recommended that ketamine not be injected intraspinally in humans.

There is a growing body of evidence that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to local anesthetics, opioids, or other analgesic agents. Duration of analgesia is increased when ketamine is added to a local anesthetic solution for wound infiltration (Tverskoy et al., 1996). Ketamine in combination with opioids, either i.v. (continuous infusion, PCA) or epidurally, not only reduces opioid consumption but also prolongs and improves analgesia (Joachimsson et al., 1986; Javery et al., 1996; Wong et al., 1996; Stubhaug et al., 1997). This has also been observed after addition of low-dose i.v. ketamine to i.t. bupivacaine and neostigmine (Joachimsson et al., 1986; Javery et al., 1996; Wong et al., 1996; Stubhaug et al., 1997). The concept of 'balanced analgesia' (Dahl et al., 1990) merits attention (Dickenson, 1993), given the limits of opioid analgesia (Kehlet et al., 1996).

Pharmacological studies suggest that synergistic analgesic effects can be achieved by adding low-dose ketamine to opioids with the consequence of low-adverse effect liability (Hance et al., 1989; Chapman and Dickenson, 1992; Honore et al., 1996). However, a recent study of healthy volunteers found an additive, but not a synergistic, effect of ketamine and alfentanil. (Sethna et al., 1998). An additive effect is most likely a result of the combination of presynaptic opioid inhibition reducing afferent transmission by diminished transmitter release, and postsynaptic NMDA blockade which reduces wind up and central sensitization (Dickenson, 1994). A second mechanism underlying reduced opioid consumption might be the role of the NMDA receptor in the development of morphine tolerance. Recent observations suggest that the development of hyperalgesia and morphine tolerance are closely related and based on common neural substrates and intracellular events (Trujillo and Akil, 1994; Mao et al., 1995). Thus, the effects of low-dose ketamine at the NMDA receptor should not be considered 'analgesic' in the traditional sense of the term, but rather 'anti-hyperalgesic', 'anti-allodynic' and possibly 'tolerance-protective'.

The potential of low-dose ketamine may lie in its complementary and synergistic effects when combined with other analgesic agents (Dickenson, 1993; Yaksh, 1996). In this context, the concerns about the use of ketamine in postoperative pain management (Hirota and Lambert, 1996) need reconsideration. As one of the two clinically available NMDA receptor antagonists, ketamine may provide clinicians with a tool to improve postoperative pain management and to reduce opioid related adverse effects.

Results of studies evaluating efficacy of preemptive ketamine are promising and consistent with the pharmacology and the physiological importance of NMDA receptors outlined earlier. However, further well designed studies are required before any final conclusion can be drawn. Taken together, the role of ketamine in the treatment of postoperative pain remains controversial. On its own, ketamine remains a rescue drug for situations in which other analgesics are contraindicated. However, as an adjunct in combination with opioids or local anesthetics, low-dose ketamine, especially in the 'sub-psychotomimetic' range (blood concentration < 50 ng/ml), may have an important role to play in the management of postoperative pain.

Further research is required in the following areas: (a)

dose-finding studies for ketamine as an adjunct to opioids and local anesthetics (b) efficacy and optimal route of administration (intravenous vs. epidural vs. spinal) (c) the role of S(+)-ketamine (d) the influence of ketamine on long-term outcome such as chronic pain (e) long-term physical and chemical stability of mixtures containing ketamine (f) spinal toxicity of ketamine and (g) effects of low-dose ketamine on cognitive and memory functioning after surgery.

Future studies should be carefully designed and whenever possible, conducted in a randomized, double-blind, controlled fashion. Pain should be rated by the patient using a reliable and valid pain scale (e.g. VAS). Rescue medication should be preferably administered using PCA. Outcomes other than pain and analgesic use (e.g., adverse effects, duration of hospital stay and cost -benefit analysis) should be included whenever possible.

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