Morphine sparing effect of low dose ketamine during patient controlled analgesia

FJ Smith[a], **CGJ Briel**[a], **PJ Becker**[b]
[a] *Department of Anaesthesiology, School of Medicine, Faculty of Health Sciences, University of Pretoria and Pretoria Academic Hospital,*
[b] *Unit for Biostatistics, Medical Research Council, Pretoria, South Africa.*

KEY WORDS: *Ketamine, morphine sparing effect, patient controlled intravenous analgesia.*

Abstract

Objective: *To compare the quality of intravenous patient controlled analgesia (PCIA) of low dose morphine plus ketamine with morphine.* ***Design:*** *Double blind case control study.* ***Setting:*** *Academic hospital.* ***Patients:*** *Thirty-six patients scheduled for elective abdominal hysterectomy were randomly divided into two groups to receive patient controlled intravenous analgesia (PCIA).* ***Interventions:*** *Group M received morphine 21 μg/kg as a bolus, Group MK received morphine 7 μg/kg plus ketamine14 μg/kg as a bolus. The lockout period in both groups was 7 minutes.* ***Measurements:*** *Morphine consumption, visual analogue pain score (VAPS), pulse oximetry oxygen saturation (SpO_2), respiratory rate (RR), verbal descriptive sedation score (VDSS), nausea, pruritis, dreaming, and hallucinations were recorded at 1, 4, 24 and 48 hours. Equivalence of the two groups was assessed by comparing the 95% confidence interval (CI) for the effect with the equivalence delta (10%).* ***Results:*** *Morphine consumption was significantly lower in Group MK after 24 and after 48 hours ($p < 0,05$). VAPS was significantly higher in Group MK at 4 hours ($p < 0,05$), but VAPS was always clinically lower than in Group MK at all times (Equivalence delta > 10%). SpO_2 at 4 hours was marginally higher in Group MK ($p = 0,0809$).* ***Conclusion:*** *Morphine-ketamine PCIA, in doses used in this study, provided analgesia inferior to that of morphine PCIA, but may improve the respiratory side effect profile of morphine. The analgesia of morphine and ketamine are additive rather than synergistic.*

Morphine remains the gold standard for analgesia against which the effectiveness of newer drugs and combinations are measured. It has been the standard analgesic for many years, and the effects of newer analgesics are often expressed in terms of the effect of morphine. The search for good analgesics should not only focus on analgesia. As far as analgesia is concerned, morphine is an excellent drug, but morphine lacks quality of analgesia due to its side effects. These side effects include sedation, respiratory suppression, nausea and vomiting, and pruritis. These side effects may be avoided or reduced by the co-administration of other analgesics, e.g. ketamine.

Apart from postoperative analgesia, ketamine has found application in other fields of analgesia. An oral ketamine suspension has been found superior to a paracetamol-codeine-diphenhydramine suspension as analgesic and sedative for wound care procedures in children.[1] Oral ketamine may also have potential in the treatment of neuropathic pain, including stump pain.[2] The effect of co-administered drugs depends on pharmacodynamic (agonism or antagonism) and pharmacokinetic interactions. When drugs with the same end point (analgesia) affect different receptors, they may be synergistic. C and Aδ fibres conduct nociceptive stimuli to the cell bodies in dorsal ganglia. Axons from these cells release glutamate, aspartate, and substance P. These neurotransmitters stimulate N-methyl-D-aspartate (NMDA) receptors on the cell bodies in the dorsal horn this and gives rises to delayed, prolonged and increased pain (spinal wind up).[4,5,6] Opioids stimulate presynaptic m and k receptors on these axons which inhibit the release of the stimulatory neurotransmitters.[7,8,9] Ketamine is a non-competitive antagonist at NMDA-receptors[10] and is analgesic in subanaesthetic doses.[11] Small doses of co-administered morphine and ketamine may be required to produce the endpoint i.e. analgesia, but with a better side effect profile.

The aim of this study was to compare the quality of analgesia provided by morphine and low dose morphine plus ketamine during patient controlled intravenous analgesia (PCIA).

Patients and methods

The study was approved by the Ethics Committee of the University of Pretoria. Thirty-six ASA I and II patients aged 18 to 60 years scheduled for elective abdominal hysterectomy were included. The study was double blind. Patients were randomised into Group M or Group MK. Group M received PCIA consisting of morphine 21 μg/kg with a lockout period of 7 minutes. Group MK received PCIA consisting of morphine 7 μg/kg plus ketamine 14 μg/kg with a lockout period of 7 minutes. Both groups received a standardised anaesthetic consisting of propofol 1 to 2 mg/kg, vecuronium, sufentanil, and isoflurane. Sufentanil 0,2 μg/kg was administered at induction and 0,1 μg/kg when more than 1,5 MAC isoflurane (end tidal concentration) was needed to keep the mean arterial blood pressure lower than 115% of the preoperative mean arterial pressure. Patients with allergy, asthma, nausea, vomiting, dreaming, hallucinations, pruritis, a history of drug abuse, psychosis or participation in any clinical trial during the previous three months were excluded.

Correspondence:
Prof FJ Smith
fjsmith@medic.up.ac.za

Postoperatively patients received morphine 30 μg/kg (Group M) or morphine 10 μg/kg plus ketamine 20 μg/kg (Group MK) every 10 minutes until they were pain free. PCA consisted of a bolus of morphine 21 μg/kg (Group M) or morphine 7 μg/kg plus ketamine 14 μg/kg (Group MK); the lock out time was 7 minutes in both groups. No other analgesics were allowed.

The following measurements were made: Sufentanil dose, morphine consumption during the first and second 24 hours, number of PCA requests, pain score (Visual Analogue Pain Score, VAPS), verbal descriptive sedation score (VDSS), haemoglobin saturation on the pulse oximeter at room air (SpO_2), respiratory rate (RR). These were done preoperatively and 1, 4, 24 and 48 hours postoperatively.

Statistics

Null hypothesis: The quality of analgesia provided by morphine or low dose morphine plus ketamine do not differ. The response variable was the VAPS. Calculation of the sample size made use of the expected variation (standard deviation = total variation/6), i.e. the range of pain associated with the different treatments. For a standard deviation of 10 mm, resulting from a expected pain range of 60 mm, and an equivalence delta of 10 mm, a sample size of 36 subjects has a power of 80% at the significance level of 0,05.

All continuous variables were analysed using the Student t test for unequal variance (Welch). Discrete variables were analysed using Fischers exact test. Testing was done at the 0,05 level of significance. At each point in time (1, 4, 24 and 48 hours) Groups M and MK were compared with respect to the continuous variables VAPS, SpO_2, and RR, using analysis of covariance (ANCOVA) with morphine consumption in the appropriate 24 hour period and VAPS as covariates. SpO_2 and RR were analysed with VAPS as the covariate. Equivalence of the two groups was assessed by comparing the 95% confidence interval (CI) for the effect with the equivalence delta (10%).

Results

There was no significant difference between Group M and MK in age (39,33 years vs. 39,39 years; p = 0,9781), body mass (72.06 kg vs. 73,39; p = 0,7786), duration of surgery (102,50 min vs. 100,56 min; p = 0,8476) and sufentanil dose (0,189 μg/kg vs. 0,205 μg/kg; p = 0,5269).

Group MK used significantly less morphine than Group M during the first 24 hours (623,83 μg/kg vs. 885 μg/kg; p = 0,0316), as well as during the second 24 hours (264,89; 413,44; p = 0,0373). The morphine dose in both groups was significantly higher during the first than during the second 24 hour period (p < 0,001). The total number of boluses was significantly higher in Group MK than in Group M (394,5 vs. 156,5; p = 0,0057). Within the groups, there were significant differences in the number of boluses between the first and second 24 hours (p < 0,001) (Table 1, Figure 1).

In both groups, the mean pain scores (mean of VAPS at rest and during movement) were the highest at 1 hour. The mean VAPS did not differ significantly between groups at 1, 24 and 48 hours, but was significantly lower in Group M than in Group MK at 4 hours (22,36 mm vs. 38,33 mm; p = 0,0113). Although VAPS was not statistically significantly different between groups at 1, 24, and 48 hours, the criterion for equivalence (10%) was not reached. If the equivalence delta is set at 15%, pain scores were nearly equivalent at 24 hours and at 48 hours (Table 1, Figure 1). In Group M the pain score was significantly lower at 4 hours than 1 hour (p = 0,0128), but in Group MK the pain scores did not differ between 1 hour and 4 hours (p = 0,7035). In both groups, pain scores decreased after 1 hour with scores signifi-

Figure 1: Mean VAPS at different times. At 4 hours (*) VAPS was significantly higher in Group MK than in Group M (p = 0113). Time = 0 = preoperative.

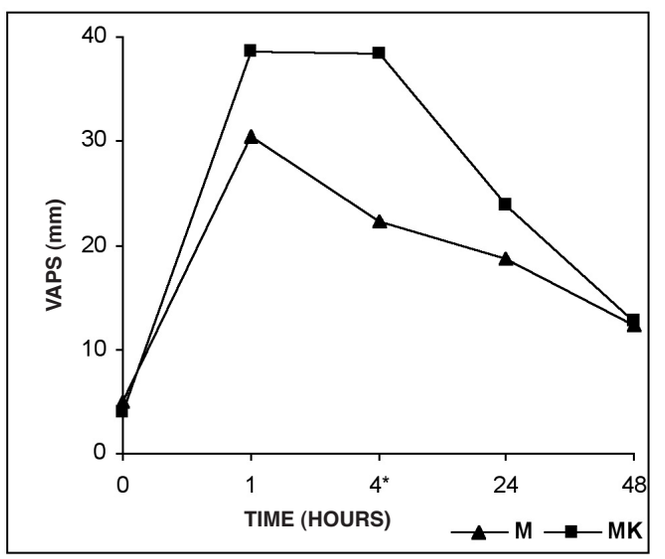

Table 1: Summary statistics for drug consumption (μg/kg) and number of PCIA boluses requested, VAPS, SpO_2 (%) and respiratory rate (min-1) (SD)

Variable	*M (n = 18)*	*MK (n = 18)*	*p*	*CI for difference -10% ≤ CI ≤ 10%)*	*Equal (for difference*
Morphine 1st 24 h	885,74 (417,66)	623,83 (259,36)	0,0316	24,84; 499,27	No
Morphine 2nd 24 h	413,44 (244,61)	267,89 (140,07)	0,0373	9,25; 281,86	No
Boluses 1st 24 h	118,67 (127,39)	292,83 (228,38)	0,0088	-300,72; -47,61	No
Boluses 2nd 24 h	37,83 (42,64)	101,67 (103,86)	0,0214	-118,63; -9,04	No
Mean VAPS 1 h	30,42 (14,76)	36,23 (20,30)	0,3313	-6,19; 17,85	No
Mean VAPS 4 h	22,36 (14,36)	38,33 (20,72)	0,0113	3,86; 28,08	No
Mean VAPS 24 h	18,75 (9,21)	23,89 (14,20)	0,2073	-3,00; 13,28	No
Mean VAPS 48 h	12,36 (10,94)	12,64 (11,20)	0,9405	-7,21; 7,77	No
SpO2 1 h	93,61 (6,82)	95,94 (3,13)	0,1996	-5,98; 1,32	Yes
SpO2 4 h	90,78 (6,44)	94,17 (4,69)	0,0809	-7,11; 0,44	Yes
SpO2 24 h	91,00 (5,66)	93,22 (5,52)	0,2304	-5,92; 1,48	Yes
SpO2 48 h	93,11 (4,47)	94,94 (2,80)	0,1512	-4,38; 0,71	Yes
RR 1 h	15,16 (2,87)	16,50 (3,03)	0,3445	-2,95; 1,06	Yes
RR 4 h	15,00 (3,53)	16,44 (2,77)	0,1816	-3,60; 0,71	Yes
RR 24 h	15,61 (3,09)	16,39 (3,26)	0,5406	-2,86; 1,53	Yes
RR 48 h	16,11 (3,03)	17,11 (3,51)	0,3668	-3,22; 1,22	Yes

cantly lower at 24 hours than at 4 hours and at 48 hours significantly lower than at 24 hours. In both groups pain scores were still significantly higher at 48 hours than preoperatively ($p < 0,05$). In neither Group M nor Group MK was any significant correlation (Spearman) found between VAPS at 1, 4 and 24 hours, and the number of boluses during the first 24 hours, or between VAPS at 48 hours and the number of boluses during the second 24 hours.

The number of boluses was significantly higher in Group MK during both the first and second 24 hours(Table 1). As the number of boluses determine the morphine consumption, the contribution of ketamine to analgesia must be determined, i.e. would the number of boluses differ had the bolus in both groups contained the same morphine dose? In order to investigate the influence of ketamine on pain scores at each of the postoperative times, ANCOVA was used with morphine consumption, adjusted for the first (754,86 μg/kg) and second 24 hours (340,67 μg/kg) as covariates. With ANCOVA, the mean VAPS at 4 hours was still significantly higher in Group MK than in Group (36,94 mm vs. 23,23,75; $p = 0,0450$). Apart from VAPS at 4 hours, the therapies may be regarded as equi-analgesic (Table 2).

The SpO_2 and respiratory rate was higher in Group MK throughout the postoperative period. The only difference that was marginally statistically significant, was SpO_2 at 4 hours postoperatively (90,78% vs. 94,17%; $p = 0,0809$). The SpO_2 readings fell within the equivalence delta of 10%. The lowest SpO_2 occurred at 4 hours and 24 hours (Table 1, Figure 2). In order to investigate the influence of ketamine on SpO_2 and respiratory rate at each of the postoperative times, ANCOVA was used with the morphine consumption adjusted for the first (754,86 μg/kg) and second 24 hours (340,67 μg/kg), as well as for the VAPS at 1 hour (33,33 mm), 4 hours (30,34 mm), 24 hours (21,32 mm) and 48 hours (12,50 mm) as covariates. With morphine as covariate, the marginal significant difference in SpO_2 4 hours disappeared ($p = 0,2660$). With the relevant morphine dose as covariate, the RR at 4 hours was now marginally significantly higher in Group MK ($p = 0,0860$) but can still be regarded as equal to the RR in Group M (Table 2). With VAPS as covariate, SpO_2 was always higher in Group MK, but the difference was never statistically significant. Ketamine therefore seems to have had a positive, however no statistically significant effect on SpO_2. If the patients in the different groups had the same VAPS at the different times, the respiratory rate would also not have differed at any stage. Therefore, with the morphine dose as covariate, the marginally significant difference in SpO_2 between Groups MK and M disappeared but a significant difference in respiratory rate at 4 hours appeared, and with the VAPS as covariate, no significant difference in respiratory rate or SpO_2 between groups was found; the lower dose of morphine and not the amount of pain was therefore probably responsible for the higher respiratory rate and SpO_2 in Group MK. There was no significant difference in sedation scores (VDSS) between groups at any stage. No sedation of VDSS > 2 was observed. No statistical significant difference was detected between groups in the incidence of nausea and vomiting, pruritis or dreaming and hallucinations at any of the times.

Discussion

The choice of doses of combinations of analgesics is hampered by a lack of information regarding interactions (pharmacodynamic and pharmacokinetic) between analgesics. In this study we investigated the analgesic interaction of morphine and ketamine. The VAPS did

Figure 2: SpO_2 at different times. The saturation was marginally significantly higher in Group MK at 4 hours (p = 0,0809*). Time 0 = preoperative

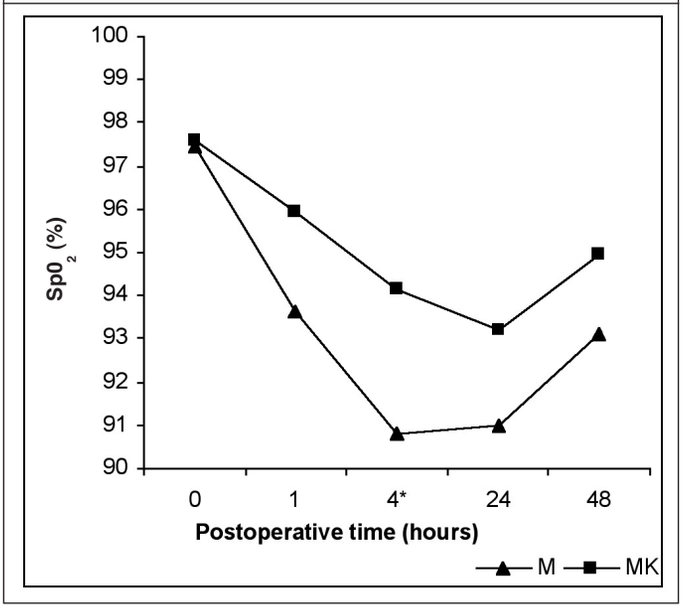

Table 2: Influence of ketamine on VAPS, SpO_2 and RR with morphine dose and VAPS as covariates.

Variable	*Covariate*	*Group*	*1 hour*	*4 hours*	*24 hours*	*48 hours*
VAPS	Morphine dose	M MK p	30,34 36,33 0,3580	23,75 36,94 0,0450	18,99 23,64 0,2910	10,41 14,59 0,243
SpO_2	Morphine dose	M MK p	94,27 95,29 0,5800	91,36 93,59 0,2660	91,39 92,83 0,4630	93,03 95,02 0,1480
RR	Morphine dose	M MK p	15,42 16,64 0,2600	14,73 16,71 0,0860	15,53 16,35 0,4890	16,34 16,88 0,644
SpO_2	VAPS	M MK p	93,61 95,94 0,2100	90,96 93,98 0,1590	91,15 93,07 0,3120	93,11 94,95 0,1500
RR	VAPS	M MK p	15,63 16,43 0,4290	15,16 16,28 0,3480	15,51 16,38 0,4380	

not reach equivalence (within 10%) at any stage of the study, with Group MK experiencing more pain. The morphine consumption was significantly lower in Group MK: 29% lower in the first 24 hours and 35% lower in the second 24 hours, taking into account that Group MK requested many more boluses during both the first and the second 24 hours. Apart from the significantly higher VAPS in Group MK at 4 hours, the VAPS did not differ significantly (Table 1). ANCOVA showed that Group MK would experience significantly more pain than Group M at 4 hours, even if they had received the same dose of morphine during the first 24 hours. It thus appears as though ketamine had some anti-analgesic effect at 4 hours (Table 2). Using the significance level for statistical significant difference, outcome parameters VAPS, VDSS, SpO_2, and respiratory rate did not differ between groups (apart from lower VAPS and SpO_2 in Group M at 4 hours), the study partly confirms the null hypothesis, namely that the two PCA techniques are equivalent in the doses used. However, when equivalence of the two groups was assessed using an equivalence delta of 10%, Group M experienced less pain, used more morphine, and less boluses than Group MK, while the side effects did not differ significantly. The two analgesic regimens can therefore, in the doses used, not be regarded equivalent (Table 1).

The number of boluses demanded by patients in Group MK was significantly higher than those in Group M during both the first and the second 24 hours. It may be that the analgesia produced by the lower dose of morphine in Group MK was shorter lived than was the higher dose in Group M. In spite of the significantly higher number of boluses in Group MK, the total dose of morphine was both clinically and statistically lower in Group MK than in Group M. The higher number of boluses in Group MK may be ascribed to amnesia. This might have caused the patient to forget that she had already pushed the button and then would push it again. On the other hand, tolerance to ketamine, or even in these early stages, drug seeking behaviour might have emerged. If the latter had been the case, one would expect the number of demands to increase with time. As this was not the case, the higher number of boluses in Group MK was unlikely to have resulted from the development of tolerance, or drug seeking behaviour.

The total lack of correlation between the VAPS at 1, 4 and 24 hours and the number of boluses during the first 24 hours or the VAPS at 48 and the number of boluses during the second 24 hours casts doubt on the applicability of PCA in the population used (often an inability to communicate due to language barriers). It has been noted that some patients push the button when they think of it, demonstrate it to visitors, etc.

The differences in VAPS and the number of boluses may have been caused by sedation caused by morphine. In this study no difference in sedation was found. The significantly higher number of boluses and VAPS in Group MK might have been caused by subjective side effects (strange feelings) of ketamine – even at analgesic levels.[13]

The changes in the morphine dose from the first 24 hours to the second 24 hours was -53,7% in Group M and -57,3% in Group MK ($p = 0,7804$). This difference was not significant. It is thus unlikely that the morphine sparing effect of ketamine involved the development of tolerance in the short term. The long-term effect of ketamine was not included into this study. It is therefore not possible to draw any conclusion about the possible effect of ketamine on tolerance to opioids. As neither pain scores nor the incidence of side effects differed significantly, it can be concluded that the quality of analgesia rendered by the two techniques was equivalent.

As sole analgesic ketamine is analgesic at about 360 μg/kg/hour and morphine at about 180 μg/kg/hour. If these drugs were synergistic, co-administration of about a third of these doses might have produced adequate analgesia, avoiding their dose dependent side effects. However, if drugs share the same side effect, these side effects may also be more pronounced in combination.

Several investigators have studied the co-administration of morphine and ketamine. Subcutaneous ketamine infusion (250 μg/kg followed by 100 μg/kg/hour) provided significantly better quality of analgesia than intravenous morphine (100 μg/kg followed by 100 mg/kg/hour) for the non-surgical care of musculoskeletal trauma. None of the ketamine patients requested additional morphine during treatment of fractures (splinting, manipulation, etc).[14]

The superior analgesia provided by the combination of morphine and ketamine reported by Javery *et al*[15] and Adriaensson *et al*[16] was achieved at larger doses of morphine and ketamine, namely 100 μg/kg/hour of each and morphine PCA in combination with a constant ketamine infusion 150 μg/kg/hour respectively. Javery *et al* used morphine and ketamine in equal doses (100 μg/kg/hour of each). Adriaenssen *et al* used morphine patient controlled analgesia (1 mg every 8 minutes; maximum of about 70 μg/kg/hour) in combination with a constant ketamine infusion (150 μg/kg/hour). At 1 hour postoperatively the morphine group experienced more pain than the ketamine plus morphine group (5,4 mm vs. 2,5 mm). Although the difference was statistically significant ($p < 0,01$), we do not regard the difference as clinically of note. The cumulative morphine consumption from 24 hours onward was significantly lower in the morphine-ketamine group. This finding is in accordance with our findings.

Edwards *et al* investigated the effect of ketamine on analgesia and lung function in elderly patients. They combined morphine PCA infusion of 1 mg/hour (14 μg/kg/hour) with ketamine 5 mg/hour, 10 mg/hour, or 20 mg/hour (54 μg/kg/hour to 468 μg/kg/hour adjusted for body mass). There was an increase in postoperative dreaming but without significant difference in morphine consumption or postoperative analgesia or lung function. No significant correlation was found between the ketamine dose and morphine consumption.[17] Inspection of their data suggests that a substantial number of patients experienced moderate to severe pain at 4 hours and 8 hours postoperatively. It therefore seems that the ketamine doses were too low to add to the analgesia provided by the low dose of morphine (14 μg/kg/hour). Owen et al found that analgesic levels of ketamine (100 μg/l to 150 μg/l[18]) could be achieved by an infusion of 240 μg/kg/hour.[19] A subcutaneous infusion of morphine 40 μg/kg/hour plus ketamine 600 μg/kg/hour has been found to provide reliable analgesia after abdominal hysterectomy.[20]

The question thus arises, whether the maximum doses of morphine and ketamine allowed in Group MK (60 μg/kg/hour and 120 μg/kg/hour respectively) were efficient to ensure adequate analgesia. Taking the findings of previous studies into account, it seems as though the doses of both morphine and ketamine were too low in Group MK. The significant difference in VAPS between MK and M might have been smaller had the morphine and ketamine doses been higher, say in the order of 90 μg/kg/hour and 180 μg/kg/hour respectively (about 11 μg/kg and 22 μg/kg with a lock out period of 7 minutes). These doses represent an additive rather than a synergistic interaction between morphine and ketamine.

Theoretically, any drug with opioid sparing properties may attenuate the development of tolerance. Kissin has shown that ketamine in subanalgesic doses decreased alfentanil consumption in rats. He is of the opinion that ketamine attenuates the development of acute tolerance to alfentanil, as the ketamine dose was too small for any direct

antinociceptive action.[21]

The effect of ketamine on ventilation is uncertain. Both stimulation[22] as well as depression[23] of ventilation has been reported. In this study ANCOVA revealed that the reason for the difference in respiratory rate at 4 hours can be the presence of ketamine, and that the difference in SpO_2 disappeared if the two groups had received the same dose of morphine. As the morphine consumption was significantly lower in the morphine-ketamine group during the first 24 hours, as well as over 48 hours, while the VAPS did not differ significantly (apart from VAPS at 4 hour), the presence of ketamine in Group MK contributed significantly to analgesia, while attenuating the effect of morphine on SpO_2 and RR.

The effect of ketamine on respiratory rate is in accordance with the findings of Presson *et al*.[24] They found that analgesic concentrations of ketamine antagonized alfentanil-induced hypoventilation. Alfentanil induced a decrease in respiratory rate, without affecting tidal volume and respiratory drive. They ascribe the effect of ketamine on ventilation to two possible mechanisms. Firstly, ketamine caused subjective side effects in all subjects (e.g. strange feeling, body feels tight, arms and legs strange, body feels heavy, etc) that might have caused general arousal, thereby stimulating respiration indirectly. Secondly, being an NMDA receptor antagonist, ketamine may antagonize the effect of opioids on ventilation as the effect of opioids on the control of breathing may be through inhibition of glutaminergic transmission.[25,26]

No dreaming or hallucinations was reported. The ketamine dose was therefore high enough to have a morphine sparing effect, but lower than a dose that causes hallucinations. It is accepted that affective disturbances may affect pain experience. Subjective side effects of ketamine might have had an influence on the VAPS in this study. Apart from hallucinations, patients were however, not questioned about these side effects. This aspect should be taken into account in studies of this nature.

Conclusion

The low dose ketamine-morphine combination can, in the doses used, not be regarded as equal but rather inferior to morphine PCIA, but it may reduce the profile of respiratory side effects of morphine. The analgesic effects of morphine and ketamine are additive rather than synergistic. In appropriate doses morphine-ketamine combinations may find application in other fields of pain therapy, for example obstetrics and cancer, and deserve further investigation.

Acknowledgements

The authors wish to thank Prof Arthur Rantloane for his advice and proofreading of the text. We appreciate the nursing staff who were involved in the blinding of the study.

References

1. *Humphries Y, Melson M, Gore D. Superiority of oral ketamine as analgesic and sedative for wound care procedures in the pediatric patient with burns. J Burn Care Rehabil, 1997; 18: 34-36.*
2. *Nicolajsen L, Hansen PO, Jensen TS. Oral ketamine theratpy in the treatment of postamputation pain. Acta Anasth Scand, 1997; 41: 427-429.*
3. *Dickenson, AH, Sullivan AF. Evidence of a role of the NMDA receptor in the frequency dependent potentiation of deep dorsal horn neurons following C-fibre stimulation. Neuropharmacology, 1987; 26: 1235-1238.*
4. *Dickenson AH, Sullivan AF. Differential effects of aminoacid antagonists on dorsal horn nociceptive neurons in the rat. Brain Research, 1990; 506: 31-39.*
5. *Dubner R, Ruda MA. Activity dependent neuronal plasticity following tissue injury and inflammation. Trends in Neurological Science, 1992; 15: 96-103.*
6. *Harley JA, Sullivan AF, Dickenson AH. Evidence for N-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. Brain Research, 1990; 518: 218-222.*
7. *Besson JM, Chaouch, A. Peripheral and spinal mechanisms of nociception. Physiol Rev, 1987; 67: 67-186.*
8. *Dickenson AH, Sullivan AF. Electrophysiological studies on the effects of intrathecal morphine on nociceptive neurones in the rat dorsal horn. Pain, 1986; 24: 211-222.*
9. *Kangra I, Randic M. Outflow of endogenous aspartate and glutamate from the rat spinal dorsal horn in vitro by activation of low- and high-threshold primary afferent fibres. Modulation by opioids. Brain Research, 1991; 553: 247-352.*
10. *Reader JC, Stenseth LB. Ketamine: a new look at an old drug. Current Opinion in Anesthesiology, 2000; 13: 463-468.*
11. *Rogawski MA. Therapeutic potential of excitatory amino-acid antagonists; channel blocks and 2,3-benzodiazepines. Trends in Pharmacological Sciences, 1993; 14: 325-331.*
12. *Pfenniger E, Baier C, Claus S, Hege G. Psychometric changes as well as analgesic action and cardiovascular adverse effects of ketamine racemate versus s-(+)-ketamine in subanesthetic doses. Der Anaesthetist, 1994; 43 (Supplement 2): S68-S75. [German]*
13. *Presson J, Scheinin H, Hellström G, Björkman S, Götharson E, Gustafsson LL. Ketamine antagonises alfentanil-induced hypoventilation in healthy male volunteers. Acta Anaesth Scand, 1999; 43: 744-752.*
14. *Gurnani A, Sharma PK, Rautela RS, Bhattacharya A. Analgesia for acute musculoskeletal trauma: Low-dose subcutaneous infusion of ketamine. Anaesth Intens Care, 1996; 24: 32-36.*
15. *Javery KB, Ussery TW, Steger HG, Coclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anesth, 1995; 43(3): 212-215.*
16. *Adriaenssens KM, et al. Postoperative analgesia with IV patient-controlled morphine: effect of adding ketamine. British Journal of Anaesthesia, 1999; 83 (3): 393-396.*
17. *Edwards ND, Flecher A, Cole R, Peacock JE. Combined infusions of morphine and ketamine for postoperative pain in elderly patients. Anaesthesia, 1993, 48 (2): 124-127.*
18. *Lements JA, Nimmo WS. Pharmacokinetics and analgesic effects of ketamine in man. Br J Aneasth, 1981; 53: 27-30.*
19. *Owen H, Reekie RM, Clements JA, Watson R, Nimmo WS. Analgesia from morphine and ketamine. A comparison of infusions of morphine and ketamine for postoperative analgesia. Anaesthesia, 1987; 42: 1051-1056.*
20. *Bristow A, Orlikowski C. Subcutaneous ketamine analgesia: postoperative analgesia using subcutaneous infusions of ketamine and morphine. Annals of the Royal College of Surgeons of England, 1989; 71: 64-66.*
21. *Kissin I, et al. The effect of ketamine on opioid-induced acute tolerance. Anesth Analg, 2000; 91: 1438-1488.*
22. *Soliman MG, Brindle GF, Kuster F. Response to hypercapnia under ketamine anaesthesia. Can J Anesth, 1975; 22: 486-494.*
23. *Freye E, Latasch L, Schmidhammer H. Pharmakodynamische Effekte von S-(+)-ketamin auf EEG, evoziertes Potential und Atmung. Anaesthetist, 1992; 41: 527-533.*
24. *Presson J, Scheinin H, Hellström G, Björkman S, Götharson E, Gustafsson LL. Ketamine antagonises alfentanil-induced hypoventilation in healthy male volunteers. Acta Anaesth Scand, 1999; 43: 744-752.*
25. *Pierrefiche O, Foutz AS, Denavit-Saubié M. Pneumotaxic mechanisms in the non-human primate: effect of the N-methyl-D-aspartate (NMDA) antagonist ketamine. Neurosci Lett, 1990; 119(1): 90-93.*
26. *Bianchi AL, Denavit-Saubié M, Champangnat J. Central control of breathing in mammals: Neuronal circuitry, membrane properties, and neurotransmitters. Physiol Rev, 1995; 75: 1-45.*