Regional Anesthesia and Pain

Loss of intrathecal morphine analgesia in terminal cancer patients is associated with high levels of excitatory amino acids in the CSF

[La perte d'analgésie morphinique intrathécale chez les patients atteints de cancer terminal est associée à des niveaux élevés d'acides aminés excitateurs dans le LCR]

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Purpose: To examine excitatory amino acid (EAA) levels in the cerebrospinal fluid (CSF) of patients on long-term morphine treatment for terminal cancer pain relief and to correlate these with morphine's analgesic effect.

Methods: Fourteen terminal cancer patients suffering severe pain and requiring long-term opioid treatment for pain relief were included. An intrathecal (IT) catheter was implanted at the L_{3-4}/L_{4-5} level and advanced 10 cm in a cephalad direction. IT morphine injection was started at 100 μg q 12 hr with a daily incremental dose of 50 μg until the effective dose was reached. The CSF was sampled (2 mL) as follows: 1) before the first IT morphine injection, 2) when the effective dose of morphine was reached, 3) when loss of morphine's analgesic effect at the effective dose (pain visual analogue scale > 5), and 4) after consecutive increases of the morphine dose (50 μg, IT, daily) for satisfactory pain relief and up to double the effective dose. The concentrations of glutamate and aspartate in the CSF were determined.

Results: CSF levels of glutamate and aspartate at the effective dose of morphine were lower than the baseline levels and increased when pain intensity increased and when morphine's analgesic effect was lost.

Conclusion: Long-term IT morphine administration was accompanied by an increase of EAA level in the CSF that was associated with a loss of morphine's analgesic effect.

Objectif : *Vérifier les niveaux d'acides aminés excitateurs (AAE) dans le liquide céphalo-rachidien (LCR) de patients en traitement prolongé avec de la morphine pour soulager la douleur d'un cancer terminal et établir une correspondance avec l'effet analgésique de la morphine.*

Méthode : *Quatorze patients atteints de cancer terminal ressentant de vives douleurs et nécessitant un traitement prolongé avec opioïdes ont été recrutés pour l'étude. Un cathéter intrathécal (IT) a été implanté au niveau de L_{3-4}/L_{4-5} et poussé de 10 cm en direction céphalique. L'injection de morphine IT a été amorcée avec 100 μg q 12 h et augmentée chaque jour d'une dose progressive de 50 μg jusqu'a l'obtention d'une dose efficace. Le LCR a été échantillonné (2 mL) comme suit : 1) avant la première injection IT de morphine, 2) quand la dose efficace de morphine a été atteinte, 3) au moment de la perte d'effet analgésique de la morphine administrée selon la dose efficace (score > 5 à l'échelle visuelle analogique) et 4) après les augmentations consécutives des doses de morphine (50 μg, IT, quotidiennes) nécessaires au soulagement de la douleur et jusqu'au double de la dose efficace. Les concentrations de glutamate et d'aspartate dans le LCR ont été déterminées.*

Résultats : *Les niveaux de glutamate et d'aspartate dans le LCR pour une dose efficace de morphine ont été plus bas que les niveaux de départ et ont augmenté avec l'intensité de la douleur et avec la perte de l'effet analgésique de la morphine.*

Conclusion : *L'administration prolongée de morphine IT s'accompagne d'une hausse du niveau d'AAE dans le LCR, laquelle est associée à une perte de l'effet analgésique de la morphine.*

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OPIOIDS have been used for analgesia for decades. However, long-term opioid administration may induce tolerance. In clinical pain management, loss of opioid's analgesic effect is one of the most frequently encountered problems when long-term administration is required, in particular via systemic administration in terminal cancer patients. In addition to receptor uncoupling from G-protein and receptor down-regulation,[1,2] the excitatory amino acid (EAA) receptors, especially the N-methyl-D-aspartate (NMDA) receptor, have been suggested to be involved in opioid tolerance. Evidence is accumulating that opioid tolerance is inhibited by NMDA receptor antagonists.[3–5] Trujillo and Akil first demonstrated that the non-competitive NMDA receptor antagonist MK-801 attenuated opioid tolerance and dependence without affecting the antinociceptive effect of morphine.[3] Recently, we also demonstrated that both competitive and non-competitive NMDA receptor antagonists inhibit the development of morphine tolerance in a rat spinal model.[5] Moreover, we also found an increase of EAA in the nucleus accumbens, locus coeruleus neurons, and the striatal system in morphine-tolerant and naloxone-precipitated rats.[6] In the spinal cord, EAA are found in opioid-sensitive primary afferent neurons.[7] In rats, intrathecal (IT) administration of NMDA produces a hyperalgesic state,[8] whereas IT administration of D-(-)-2-amino-5- phosphonovaleric (D-AP5) depresses the nociceptive responses.[9] All these reports suggest that activation of EAA receptors, particularly the NMDA receptor, may contribute to the attenuation of opioid antinociceptive effect, and that blockade of the NMDA receptor may preserve or enhance opioid's analgesic effect. Furthermore, we demonstrated an increased [^{3}H]MK-801 binding affinity in the morphine-tolerant rat spinal cord, and this increase was prevented by IT co-infusion of MK-801 and morphine.[10] On the basis of these findings, we proposed that activation of EAA receptors might be responsible for loss of the analgesic effect of morphine during treatment of terminal cancer pain. In the present study, we examined EAA levels in the cerebrospinal fluid (CSF) of patients on long-term IT morphine administration for terminal cancer pain relief and attempted to correlate these with morphine's analgesic effect.

Methods

Patients and protocol

Fourteen hospitalized patients, six men and eight women aged 25–72 yr, were included in this study approved by the Protection of Human Subjects Institutional Review Board of our institute. Written informed consent was obtained from each patient prior to entry into the study. All patients were receiving long-term opioid treatment for pain relief before inclusion in the study (Table I). All patients were referred to us by the attending physicians because of unsatisfactory pain relief, the intensity of pain being variable and relatively high during the pre-study period (Table II). All patients agreed to undergo IT prot-A-cath (HDC, San Jose, CA, USA) implantation for morphine administration for pain relief. Other concomitant medications, such as tranquillizers, sedatives, bronchodilators, or laxatives, were continued as previously. To avoid infection of the incision site, IT morphine administration (100 μg) was started three days after catheter implantation. Before starting the IT morphine injection, *iv* morphine 5 mg (q 2 hr, *prn*) injection was prescribed for pain relief on request. The dose of IT morphine was increased daily by 50 μg until acceptable analgesia was reached (effective dose; ED). A rescue dose of morphine (5 mg, *iv*) was given as required for further pain relief. All other previous analgesic treatments were discontinued. The effective dose of IT morphine was defined as the dose at which the patient asked for no more than two rescue doses of morphine (5 mg, *iv*) per 24 hr and had a pain visual analogue score (VAS) lower than 3 in the resting state, and at which IT morphine could provide satisfactory pain relief for 48 hr. When the effective dose was no longer able to provide satisfactory pain relief in the resting state (VAS > 5), an incremental dose of morphine (50 μg, IT, daily) was given for further pain relief on the following morning until twice the ED was reached. The IT morphine was given every 12 hr. The self-assessment scoring systems used for pain intensity, effects on daily life activities, and sleep deprivation were on a 0–10 numeric rating scale (0 = no pain or no effect, 10 = worst imaginable pain or greatest possible effect on daily life activities and sleep during the night). Pain frequency was evaluated on a four-point verbal ordinal scale (0 = none to rare, 1 = occasional, 2 = frequent; 3 = constant). Opioid-related side effects (nausea, vomiting, pruritus, constipation, urinary retention, drowsiness, and respiratory depression) were also recorded. Respiratory depression was defined by a respiratory rate < 10 breaths·min^{-1}. All evaluations were performed daily by our pain management team.

CSF sampling

The CSF was sampled as follows: 1) before the first IT morphine injection (baseline), 2) at the ED of IT morphine (ED), 3) at the time of loss of analgesic (LOA) effect (VAS > 5) at the effective dose (LOA),

TABLE I Profile of patients before inclusion in the study

Sex	*Age (yr)*	*Primary cancer site*	*Location of pain (days)*	*Duration*	*VAS pain score (least/worst)*	*Opioid usage and dose*
F	52	lung	lower back	21	4.5/8	meperidine (1 mg·kg^{-1}, q 4 hr, *prn*, *im*) + tramadol (50 mg, q 4 hr, *po*)
M	72	rectum	lower back, lower abdomen	26	4/7	MST (60 mg, q 8 hr, *po*) + fentanyl patch (50 µg·hr^{-1})
F	51	bile duct	upper abdomen	32	6/7	morphine (80 mg·day^{-1}, *iv* infusion)
F	44	breast	upper back, shoulder	37	4/8	meperidine (1 mg·kg^{-1}, q 4 hr, *prn*, *im*) + tramadol (50 mg, q 6 hr, *iv*)
F	72	lung	upper back, right chest	28	3.5/7	tramadol (50 mg, q 6 hr, *im*)
F	65	pancreas	upper abdomen, lower back	24	3/6	MST (90 mg, q 12 hr, *po*)
F	49	lung	upper back, right chest	28	4/6	MST (60 mg, q 8 hr, *po*)
M	65	pancreas	upper abdomen	25	4/8	meperidine (1 mg·kg^{-1}, q 3 hr, *prn*, *im*)
M	48	lung	right, shoulder	23	5/6	morphine infusion (75 mg·day^{-1}, *iv*)
M	57	liver	upper abdomen	25	4.5/8	meperidine (1 mg·kg^{-1}, q 4 hr, *prn*, *im*)
M	25	lung	lower back	26	5/6	MST (60 mg, q 8 hr, *po*)
F	57	cervix	lower abdomen	37	5/7	MST (60 mg, q 8 hr, *po*) + fentanyl patch (50 µg·hr^{-1})
M	65	colon	back, abdomen	41	6/8	morphine infusion (120 mg·day^{-1}, *iv*)
F	67	stomach	upper abdomen	31	4/6	MST (90 mg, q 12 hr, *po*)

Duration represents the duration of pain management by the attending physician before consulting for further pain management. Opioid usage and dose = the analgesics and dose prescribed before consulting the pain clinic. MST = morphine sulfate continuous release; VAS = visual analogue pain scores (least/worst) refer to the least (resting state) and the worst pain scores (when moving) in 24 hr.

and 4) after consecutive increases in the IT morphine dose (50 µg daily) for further pain relief until double the effective dose (2 ED). The CSF sample (2 mL) was collected just before morphine (IT) injection at each specific time point described above, and was immediately frozen at -70°C and stored until analysis of glutamate and aspartate.

Measurement of EAA

The CSF samples were assayed by high performance liquid chromatography with fluorescence detector [Gilson model 121 (Middleton, WI, USA) set at 428 nm] as described previously,[7] with some modifications. In brief, glutamate was assayed by pre-column derivatization with an o-phthalaldehyde/t-butylthiol reagent (OPA reagent) and iodoacetamide/methanol scavenger. Derivatization was performed by adding 4 µL of OPA reagent to 40 µL of sample in a vial, which was then shaken for two minutes at room temperature. Four milimetres of reagent B (185 mg iodoacetamide/mL of methanol) was added and the reaction continued for another two minutes, then the derivatized sample was injected onto the C18 reversed phase column. A linear gradient of two eluents was used to separate the amino acids. Eluent A was 0.1 M sodium acetate buffer (pH = 6.8)/acetonitrile (80:20) and eluent B acetonitrile/double-distilled water (80:20) and the mobile phase flow rate was 0.4 mL·min^{-1}.

Data analysis

All data are presented as the mean ± SD. The statistical analysis methods used were the Kruskal-Wallis test with the Dunn procedure and ANOVA with the Student-Newmann-Keuls test, as appropriate. A P value of < 0.05 was considered statistically significant.

Results

The profile of each patient before inclusion is shown in Table I. Consistent with our previous report,[11] IT morphine provided superior pain relief. At the effective dose, the daily life activities, sleep deprivation, and pain frequency were much improved compared to systemic morphine treatment (Table II). The incidence of opioid-associated side effects were similar, however, less severe in post-IT morphine treatment (data not shown). As our previous report, the effective dose was reached around five to six days after the first IT morphine administration. The average baseline CSF levels of glutamate and aspartate are presented in Table III. At the effective dose (407 ± 69 µg), CSF glutamate and aspartate levels were lower than baseline levels. When IT morphine lost its analgesic effect at the ED, pain intensity increased to 7.5 ± 0.3 (Table II), and CSF glutamate and aspartate levels increased significantly, compared to ED levels. The interval from the effective dose reached to the loss of IT morphine's analgesic effect was variable (between two to four

TABLE II Pain intensity and frequency, effects on daily life activities, and sleep deprivation in patients before and after intrathecal morphine treatment, loss of the analgesic effect, and doubling of the effective dose

	Baseline	*ED*	*LOA*	*2 ED*
Pain intensity	7.1 ± 0.2	2.2 ± 0.1*	7.5 ± 0.3	7.1 ± 0.5
Pain frequency	2.3 ± 0.2	0.4 ± 0.1*	2.5 ± 0.4	2.9 ± 0.1
Daily life activities	7.8 ± 0.3	3.1 ± 0.5*	7.2 ± 0.2	8.2 ± 0.4
Sleep deprivation	6.7 ± 0.5	2.3 ± 0.3*	7.8 ± 0.4	7.1 ± 0.6

Baseline = before intrathecal (IT) morphine treatment; ED = observations performed on day three after the effective dose of IT morphine was reached; LOA = loss of the analgesic effect of morphine (IT) at the effective dose (visual analogue score > 5); 2 ED = double the effective dose of IT morphine. *$P < 0.01$ (when compared with all other columns).

TABLE III Levels of cerebrospinal fluid excitatory amino acids during intrathecal morphine treatment for pain relief at various time points in terminal cancer pain patients

	Glutamate (μM)	*Aspartate (μM)*
Baseline	2.7 ± 1.8	0.7 ± 0.2
ED	0.4 ± 0.2*	0.2 ± 0.1*
LOA	3.5 ± 2.7†	0.8 ± 0.2†
2 ED	2.8 ± 2.9†	1.1 ± 0.4†

ED = effective dose; LOA = loss of the analgesic; 2 ED = double the effective dose. *$P < 0.05$ (compared with baseline). †$P < 0.05$ (compared with ED). Data are expressed as the mean ± SD.

weeks) in the present study. On increasing the IT dose of morphine by 50 μg daily, even doubling the effective dose (857 ± 83 μg), morphine could not relieve pain (pain score = 7.1 ± 0.5), and glutamate and aspartate levels remained elevated compared to those at the ED (Table III).

Discussion

Surprisingly, before being referred to us, four of the 14 patients had received meperidine which should be avoided in cancer patients due to its short duration of action and its toxic metabolite, normeperidine. Furthermore, five of the 14 patients had received *im* opioids, a practice which is also not recommended for the management of cancer pain because of unreliable absorption and inconvenience. Moreover, some patients were receiving opioids on a *prn* basis, which could explain, in part, why their pain was not well controlled. Such inadequacy of cancer pain management has been reported by Ger *et al.* Most physicians with an inadequate knowledge of opioids hesitate to give the maximal dose for analgesia. The barriers to optimal cancer pain management were inadequate guidance from a pain specialist, inadequate knowledge of cancer pain management, and inadequate pain assessment.[12]

Cumulated evidence shows that NMDA antagonists inhibit morphine tolerance and suggests that activation of NMDA receptors may attenuate morphine's analgesic effect.[3–5] In our previous report, we demonstrated that the NMDA antagonists, MK-801 and D-AP5, attenuated morphine tolerance in a rat spinal model.[5] More recently, we further demonstrated that NMDA receptor binding activity was increased in the spinal cord of tolerant rats.[10] In the present study, we observed that IT morphine injection, at the effective dose, provided better pain relief and was associated with lower levels of EAA. However, after long-term IT administration, morphine lost its analgesic effect at this effective dose, and this was associated with increased glutamate and aspartate levels in the CSF. Once morphine has lost its analgesic effect, even doubling the effective dose did not provide satisfactory pain relief and high EAA levels were still observed in the CSF. In our previous report, we had found that the NMDA antagonist ketamine enhanced morphine's analgesic effect when co-administered intrathecally.[11] The results from both studies suggest that long-term IT morphine administration may activate the pain facilitatory system, increase the release of EAA, and thus reduce morphine's analgesic effect.[10,13] In a rat spinal model, Jhamandas *et al.* observed increased EAA release in the CSF after continuous IT morphine infusion for four days. However, the increase was not significant and the authors suggested that EAA might not play a role in morphine tolerance.[14] This discrepancy between their results and ours might be due to differences between cancer pain patients and naïve rats. Alternatively, only a small amount of EAA released after IT morphine infusion in the study by Jhamanda *et al.* may still have resulted in a reduction of morphine's antinociceptive effect.

In summary, glutamate and aspartate levels increased in the CSF after long-term IT morphine administration in terminal cancer pain patients and this increase was associated with loss of morphine's analgesic effect. A comparable study is currently being carried out in a rat spinal model. By studying both clinical cancer pain patients and the rat spinal model, we hope to clarify the role of EAA in morphine tolerance.[13]

References

1 *Wong CS, Su YF, Watkins WD, Chang KJ.* Continuous intrathecal opioid treatment abolishes the regulatory effects of magnesium and guanine nucleotides on mu opioid receptor binding in rat spinal membranes. J Pharmacol Exp Ther 1992; 262: 317–26.

2 *Wong CS, Su YF, Chang KJ, Watkins WD.* Intrathecal pertussis toxin treatment attenuates opioid antinociception and reduces high-affinity state of opioid receptors. Anesthesiology 1992; 77: 691–9.
3 *Trujillo KA, Akil H.* Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 1991; 251: 85–7.
4 *Gutstein HB, Trujillo KA.* MK-801 inhibits the development of morphine tolerance at spinal sites. Brain Res 1993; 626: 332–4.
5 *Wong CS, Cherng CH, Luk HN, Ho ST, Tung CS.* Effects of NMDA receptor antagonists on inhibition of morphine tolerance in rats: binding at μ-opioid receptors. Eur J Pharmacol 1996; 297: 27–33.
6 *Huang NK, Tseng CJ, Wong CS, Tung CS.* Effects of acute and chronic morphine on DOPAC and glutamate at subcortical DA terminals in awake rats. Pharmacol Biochem Behav 1997; 56: 363–71.
7 *Tracey DJ, De Biasi S, Phend K, Rustioni A.* Aspartate-like immunoreactivity in primary afferent neurons. Neuroscience 1991; 40: 673–86.
8 *Aanonsen LM, Lei S, Wilcox GL.* Excitatory amino acid receptors and nociceptive neurotransmission in rat spinal cord. Pain 1990; 41: 309–21.
9 *Cahusac PMB, Evans RH, Hill RG, Rodriguez RE, Smith DAS.* The behavioural effects of an N- methylaspartate receptor antagonist following application to the lumbar spinal cord of conscious rats. Neuropharmacology 1984; 23: 719–24.
10 *Wong CS, Hsu MM, Chou YY, Tao PL, Tung CS.* Morphine tolerance increases [^{3}H]MK-801 binding affinity and constitutive neuronal nitric oxide synthase expression in rat spinal cord. Br J Anaesth 2000; 85: 587–91.
11 *Yang CY, Wong CS, Chang JY, Ho ST.* Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth 1996; 43: 379–83.
12 *Ger LP, Ho ST, Wang JJ.* Physicians' knowledge and attitudes toward the use of analgesics for cancer pain management: a survey of two medical centers in Taiwan. J Pain Symptom Manage 2000; 20: 335–44.
13 *Hsu MM, Wong CS.* The roles of pain facilitatory systems in morphine tolerance. Acta Anaesthesiol Sin 2000; 38: 155–66.
14 *Jhamandas KH, Marsala M, Ibuki T, Yaksh TL.* Spinal amino acid release and precipitated withdrawal in rats chronically infused with spinal morphine. J Neurosci 1996; 16: 2758–66.