ORIGINAL ARTICLE

Opioid-induced hyperalgesia after rapid titration with intravenous morphine: Switching and re-titration to intravenous methadone

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ABSTRACT

Background: Rapid titration with intravenous morphine (IV-MO) provides fast and efficient pain relief in cancer patients with severe-excruciating pain. However, some patients, after an initially favourable response, can develop an hyperexcitated state unrelieved or worsened by further dose increments.

Methods: Eighty-one patients admitted on emergency basis titrated with IV-MO were assessed.

Results: 12 patients were unsuccessfully titrated with IV-MO. Switching to intravenous methadone (IV-ME) and titrating the doses proved to be successfully.

Conclusion: In escalating opioid doses rapidly a recognition of the development of hyperalgesia should be suspected. Increasing doses of opioids may stimulate rather than inhibiting the central nervous system, with complex mechanisms already recognized in experimental studies. Switching to IV-ME and titrating the doses could be taken into consideration to break this vicious circle before pain conditions worsen irreversibly.

KEY WORDS

Cancer pain; opioid-induced hyperalgesia; opioid switching; opioid titration

Introduction

Opioid use has been increasing in the last years. The changing pattern in opioid use has resulted in the emergence of neurotoxicity as a major adverse effect of the treatment of cancer pain (1). Animal studies and clinical reports suggest that opioids, intended to abolish pain, can unexpectedly produce abnormally heightened pain sensations, which are characterized by a lowering of the pain threshold, commonly known as hyperalgesia (2,3). Such abnormal sensations could result in an exacerbation rather than an attenuation of excitatory behaviours.

The problem of hyperalgesia, tolerance, and nociception remains not clearly understood and quite difficult to interpret in the clinical setting of the cancer patients, where multiple factors are able to confound the picture (4-6).

Opioid induced hyperalgesia is a clinical paradox. It is possible to hypothesize an iatrogenic syndrome characterized initially by a declining analgesia, requiring further opioid escalation to maintain the previous level of analgesia, which is however fleeting, and then resulting in a worsening of pain and whole-body hyperalgesia. Alternately, patients on opioid therapy, who present long periods of breakthrough nociception due to an inadequate dosage, may require an aggressive treatment with increasing opioid doses. Titration with intravenous morphine (IV-MO) may provide fast and efficient pain relief, also providing information about the amount of opioids necessary for a subsequent treatment (7,8). According to the description of this iatrogenic syndrome described above, some patients, after an initially favourable response, can develop an hyperexcitated state worsened by further dose increments (9).

We here report the rapid establishment of morphine - induced hyperalgesia which was reversed by the administration of intravenous methadone in a sort of immediate opioid switching during rapid titration with intravenous morphine.

Patients and methods

In a period of one year we prospectively analysed patients admitted to an acute pain relief and palliative care unit with severe pain (intensity >7 on a numerical scale of 0-10) on an emergency basis. According to department policy patients underwent rapid titration with IV-MO. The protocol has been described elsewhere (9). Briefly, boluses of IV-MO were offered intensively, in doses of 5-10 mg every five minutes depending on the pain intensity and the previous opioid dosage. The effective dose of IV-MO is assumed to last approximately four hours (according to its duration and half-life) and calculated for the next 24 hours as a continuous infusion (the effective dose is multiplied for six), eventually supported by the same bolus dose for breakthrough pain.

Patients who did not responded favourably or showing a worsening pain despite increasing doses of morphine within 24 hours, even after an apparent pain relief of short duration, were switched to intravenous methadone (IV-ME). Thus, the clinical definition of hyperalgesia was the occurrence of increasing pain, diffuse in character, in patients who were titrated with IV-MO unsuccessfully (pain intensity ≥7, by using a numerical scale 0-10), despite an initial but short-lived analgesia, reflecting the iatrogenic syndrome describe above.

Doses of IV-ME were titrated again to relieve pain, at bedside and under medical supervision, regardless of prior morphine dose: IV-ME titration was stopped when patients reported an adequate pain relief. According to the efficacy of the bolus and patients' response, a continuous infusion of IV-ME was started in doses of approximately three times the dose of the effective bolus, as this doses was assumed to provide analgesia for about eight hours (while for IV-MO has been considered six times). This approach was suggested by initial clinical experience with dosing IV-ME after IV-MO. For example, if the patient responded positively to a bolus of 10 mg of IV-ME, a continuous infusion of 30 mg/day was started. In the subsequent days, doses were changed according to the need. After achieving a dose stabilization providing adequate analgesia and acceptable adverse effects, IV-ME was converted to the oral route (OR-ME), by using a ratio IV-OR of 0.8-1 (10). For example a patient receiving successfully 30 mg/day of IV-ME was converted to 36 mg of OR-ME. According to patient's preference ME could be switched to the initial drug prescribed at admission, using conversion ratios previously described (11).

A favourable response was defined as the achievement of a stable and acceptable analgesia (pain intensity ≤4, by using a numerical scale 0-10). Data were collected and analysed by the SPSS Software 14.0 version (SPSS, Inc., Chicago, Ill, US).

Statistical analysis of quantitative and qualitative data, included descriptive statistics, was performed for all the items.

Results

Eighty-one patients admitted to the unit on emergency basis who were titrated with IV-MO during the period taken into consideration were surveyed. 69 patients responded favourably to IV-MO titration and were normally converted to oral opioids, as per protocol. The median dose of the effective bolus was 10 mg (range, 4-18 mg).

Twelve patients were switched and re-titrated with IV-ME, because the previous titration with IV-MO failed and produced worsening pain rather than pain relief. No traditional adverse effects were noticed, except a mild myoclonus in three patients (n.1,2,3 in Table 1).

Characteristics of patients, initial bolus doses of IV-MO, the effective initial bolus dose IV-ME, and the final doses of OR-ME prescribed at time of discharge are presented in Table 1. The dose ratio between the initial bolus of IV-MO and the initial bolus of IV-ME was 2.24. All patients responded to opioid switching-titration with IV-ME, achieving stable analgesia (pain intensity ≤4, by using a numerical scale 0-10) except one patient who required a more complex treatment, including intrathecal administration of morphine and bupivacaine. One patient preferred transdermal therapy. When excluding the patient who required the spinal treatment, patients were discharged at home after a mean of 5.5 days (range, 3-9 days) after starting IV-ME.

Discussion

In the last years, experimental and clinical studies have pointed out the possible hyperalgesic effect of high doses of opioids. Intense opioid receptor activation, such as that occurring with a short-lived opioid like remifentanyl, induces rapid and extensive tolerance which has been shown in humans and perhaps manifesting as dramatic hyperalgesia (12,13). This may corresponds to a therapeutic paradox where the consequence (increasing pain), is treated by favouring its cause (opioid escalation).

Thus, in escalating opioid doses rapidly a recognition of the development of hyperalgesia should be suspected, as higher or rapid increases in doses of opioids may stimulate rather than inhibiting the central nervous system, with different mechanisms, well recognized in experimental studies (2).

Opioid switching is increasingly used in patients with a poor opioid response. The presumed offending drug should be stopped, and a rapid opioid substitution should be started (14,15).

In this circumstances methadone could be an optimal choice

Table 1. Characteristics of patients, previous treatment, initial IV-MO titration unsuccessful dose, IV-ME titration effective dose and opioids prescribed at discharge (mg).

	Age	Sex	Primary tumor	Cause of pain	Previous analgesic treatment before IV-MO titration	Initial IV-MO (mg)	Initial IV-ME (mg)	IV-ME infusion in the first 24 hrs	Opioid doses at discharge
1	65	M	Lung	Bone mts	OR-MO 200	20	5	15 mg/day	OR-ME 60
2	62	M	Head-neck	Bone mts Neuropathic pain post-dissection	OR-OX 60 Pregabalin 75	20	10	30 mg/day	OR-ME 45
3	58	M	Pancreas	Locally advanced	OR-MO 900	50	20	60 mg/day	OR-ME 180
4	50	F	Breast	Bone mts	OR-MO 120	20	7	21 mg/day	OR-ME 50
5	55	M	Lung	Nerve compression	OR-OX 20	20	6	18 mg/day	OR-ME 36
6	75	F	Pancreas	Locally advanced	OR-OX 60	20	8	24 mg/day	OR-ME 36
7	55	M	Bladder	Locally advanced Bone mts	OR-OX 800	60	20	60 mg/day	OR-ME 30 IT-MO 12 IT-BU 15
8	47	M	Unknown	Bone mts	TD-FE 1.2/day (50 µg/h)	20	10	30 mg/day	TD-FE 5.4
9	62	F	Breast	Bone mts	TD-FE 1.6/day (75 µg/h)	30	12	36 mg/day	OR-ME 90
10	76	F	Pancreas	Locally advanced	OR-OX 80	25	15	45 mg/day	OR-ME 120
11	64	M	Lung	Nerve compression	OR-MO 150	18	4	12 mg/day	OR-ME 35
12	51	F	Uterum	Locally advanved Nerve compression	OR-OX 30	20	5	15 mg/day	OR-ME 24
Mean	7 M 5 F				Mean OR-MO equivalents: 290 (384)	27.5(14.1)	10.6(5.6)	33 mg/day	OR-ME: 72(50)

OR-MO=oral morphine; OR-OX=oral oxycodone; TD-FE=transdermal fentanyl; OR-ME=oral methadone; IV-MO=intravenous morphine; IV-ME=intravenous methadone; IT-MO=intrathecal morphine; IT-BU=intrathecal bupivacaine. Doses are expressed as mg/day. In brackets SD.

for switching, due to the different receptor activity, particularly in promoting receptor internalization. Morphine, in comparison with other opioids has an high activity-endocytosis ratio, and has an enhanced propensity to prolonging signals with prolonged drug exposure. Molecular events, such as desensitization and endocytosis would reduce this response. It has been experimentally demonstrated that endocytosis-promoting agonists may reduce the compensatory adaptive cellular changes that lead to upregulation of the cAMP pathway (16).

Of concern, opioids switching often deserves particular cautions, particularly when switching to methadone. Regardless of the different modalities proposed in literature, all these calculations do not take into account the modality of the previous opioid escalation from a dynamic point of view, that is the short time used to increase the dose of the previous opioid, or other causes as driving force for opioid escalation, for example the development of opioid-induced hyperalgesia (17).

An initial bolus of IV-ME, based on the response to IV-MO and the previous dosage of opioids, and evaluation of the clinical response under a strict surveillance, are clinically the guides for the subsequent treatment with an intravenous continuous infusion. This was an effective and safe treatment, as dosing is determined clinically, regardless of possible calculations, which are unreliable in such a clinical situation.

In a previous experience we reported how difficult can be switching patients in the presence of opioid-induced hyperalgesia (3). In such circumstances, it is difficult to calculate any approximate dose conversion rate. For example, in a case reported of many years ago, it has been reported a patient receiving parenteral morphine in doses of 21.600 mg/day which were converted to about 1% of the calculated equianalgesic dose of another opioid (18). In the series presented here, the clinical situation was quite complex because switching was performed in patients who were unsuccessfully titrated IV-MO. In unresponsive patients selected for this study, the mean dose of IV-MO which were clinically judged as producing

worsening pain was 22.1 mg (range, 18-60 mg). Patients were re-titrated with IV-ME with a mean dose of 10.1 mg (range 4-20) successfully in almost patients. The final mean dose of OR-ME before discharge was 67.6 mg. According to the methadone IV-OR conversion ratio adopted (10), this means that further refinements in methadone doses were needed in the following days to produce an adequate analgesia. Moreover the dose ratio between the initial bolus of IV-MO and the initial bolus of IV-ME was 2.24, which is very low in comparison with calculated equianalgesic methadone dose. Regardless of the final doses and the ratios found in this study, no data exists on direct ratios between IV-MO and IV-ME, given that oral availability ofmethadone is higher than that of oral morphine, but IV availability is similar. In patients who were titrated with IV-MO successfully (that is, patients who subsequently maintained analgesia after starting infusion) the median effective bolus of IV-MO was 10 mg, which is significant lower in comparison with unsuccessfully treated patients and similar to that reported in a previous study of IV-MO titration (9). Thus, the clinical judgement and the clinical impression guided the decision to switch to IV-ME, because there are no proofs that further increases in doses of IV-MO would produce a further analgesia, also considering that the majority of patients did not have other adverse effects limiting further dose escalation.

In conclusion, in escalating opioid doses rapidly, particularly IV-MO, a recognition of the development of hyperalgesia should be suspected. Opioid switching to IV-ME after unsuccessful titration with IV-MO, likely due to the occurrence of rapid opioid-induced hyperalgesia, could be effective in regaining analgesia. However, this approach is complex and requires an appropriate setting for monitoring patients and providing adequate dose changes subsequently according to the clinical response.

The should be taken with caution, given the paucity of clinical data assessing this topic. Unfortunately, the setting of poorly controlled pain is often unfit for appropriate controlled studies. The problem of hyperalgesia, tolerance, and nociception remains not well understood and quite difficult to interpret in the clinical setting of the cancer patients, where multiple factors are able to confound the picture. An integration of basic knowledge and clinical aspects may help assist clinicians to apply specific alternative approaches, such as those proposed in this study, in daily activity when such difficult conditions occur.

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