

The double cross of morphine: Stopping OIH in its tracks

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Ann Palliat Med 2012;1(1):4-5. DOI: 10.3978/j.issn.2224-5820.2012.03.04

The likelihood of suffering most chronic pain conditions increases with age. Thus, as the elderly population of the world expands, and as the incidence of pain goes up with age, it is necessary to place an increased emphasis on the importance of pain relief as a vital standard of care. Opioid medications remain not only the gold standard analgesic against which all others are compared, but also the primary source of analgesia for chronic cancer and non-cancer pain. In line with this, the licit global consumption of morphine increased by a factor of 7 between 1989 and 2009 (International Narcotics Control Board, INCB). Unfortunately, the success of morphine-induced pain relief may be limited according to the time required for treatment. Clinically, chronic opioid treatment can lead to diffuse paradoxical pain sensations that manifest in locations distinct from the original pain complaint. This is referred to as opioid induced hyperalgesia (OIH), a phenomenon whereby analgesia requires increased doses of opioidergic drugs.

Whether or not OIH is a clinical reality is an ongoing debate. The majority of clinical studies investigating the development of OIH have been conducted in opioid addicts (1,2), patients maintained on methadone or non-opioids (3,4) and human volunteers receiving acute morphine infusions (5), often with contradictory results. It is generally accepted that the expression of OIH is dependent on multiple confounders and that the most reliable source of information regarding its aetiology will come from prospective controlled studies (6). Unfortunately prospective studies are limited by ethical constraints and in the

past they have offered small sample sizes (7) or result discrepancies most likely due to incomparable opioid dosing (8,9).

With their paper in the current issue of *Annals of Palliative Medicine*, Mercadante *et al.* not only provide prospective analysis of a relatively large cohort of severe pain patients but also, after morphine analgesia, address the clinically relevant question: Is there evidence of the development of OIH, and is there a benefit to opioid-switching after the onset of OIH in susceptible individuals? In a series of thorough tests Mercadante *et al.* describe eighty one patients who had been admitted to acute pain and palliative care units on an emergency basis with a pain intensity of >7 on a numerical scale of 1-10. As per instructions relating to the department policy and using a protocol that had been described previously, the patients underwent rapid titration with intravenous morphine (IV-MO) (10). After an initially favourable analgesic response twelve patients described worsening pain and were switched to intravenous methadone (IV-ME), which was successfully titrated to an acceptable dose to achieve stable analgesia. The authors propose a very interesting explanation for this difference between morphine and methadone based on differential endocytosis.

There is continuing discourse within clinical and scientific circles over whether OIH is a condition relevant to chronic pain patients. Mercadante *et al.* present persuasive evidence for the development of OIH in a population of susceptible patients who thereafter respond positively to morphine cessation and analgesic switch with re-titration. Emerging studies like this one coupled with the fact that opioids are the front-line treatment of moderate to severe pain remind us that backward translation i.e. trying to understand the basis of clinical findings regarding OIH in animal studies, remains a matter of great importance. Fortunately, pre-clinical research has produced a wealth of data regarding the neuronal mechanisms underlying OIH. Neuroadaptive alterations in the pain modulatory circuitry including alterations of the central glutaminergic system and spinal dynorphins are well documented in animal models of OIH, as is enhanced descending facilitation to the spinal cord from higher brain centres (11-13). Overall, it appears that

No potential conflict of interest.

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Submitted Mar 12, 2012. Accepted for publication Mar 19, 2012

Available at www.amepc.org/apm

ISSN: 2224-5820

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maladaptive increases in activity in those neuronal systems being suppressed by the opioid are behind the manifestation of OIH. Alongside opioid switching and re-titration the clinical problem of OIH might be tackled by combination therapy; a recent study from our group has shown that pregabalin, a drug traditionally used to treat neuropathic pain, reduces neuronal hyperexcitability and visceral hypersensitivity induced by chronic morphine exposure in rats (14).

Mercadante *et al.* only appear to score patient pain using the numerical scale throughout the study. This may be relevant for those patients who did not report worsening pain with IV-MO. Previously it has been shown that opioid addicts have an altered sensitivity to pain that is modality dependent; in particular their threshold for thermal pain is lowered (1). It is possible that the percentage of severe-pain patients who developed OIH was higher than reported simply because this modality was not tested. Further, it would be of interest to know whether or not the susceptible versus non-susceptible patients were previously opioid-naïve. This might be relevant as it may offer more insight to the basic scientist about the underlying molecular factors that contribute to the development of OIH.

In summary this paper provides an elegant and rare example of the prospective analysis of a large number of chronic pain patients prior to treatment with morphine. Whilst the authors concede that the switching and re-titrating approach is complex and requires an expert knowledge of adequate dose provision as well as the continual monitoring of patients, Mercadante *et al.* discuss findings that would hopefully influence clinical practice whilst encouraging basic scientists to understand the complex central changes that manifest leading to hyperalgesia. That chronic opioid treatment is clinically associated with the onset of diffuse paradoxical pain sensations renders this treatment suboptimal. The need to clarify the mechanisms and integrate pre-clinical and clinical knowledge continues to be paramount to optimizing opioid use in the clinic.

Acknowledgements

Kirsty Bannister is supported by NIH c/o F. Porreca, Tuscon.

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Cite this article as: Bannister K, Dickenson AH. The double cross of morphine: Stopping OIH in its tracks. *Ann Palliat Med* 2012;1(1):4-5. DOI: 10.3978/j.issn.2224-5820.2012.03.04

