ACUTE PAIN MANAGEMENT IN METHADONE MAINTENANCE TREATMENT

by

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ABSTRACT

Pain is a very complex process and presents great challenges for modern medicine and pharmacology. There seems to be a general consensus that in the treatment of pain, patients with a prior history of substance abuse (particularly opioid dependent individuals) appear to be at increased risk for mismanagement problems. There are increasing numbers of people who are receiving opioids as substitution treatment for dependence. There have been many reasons postulated as to why this population is more likely to receive sub-optimal treatment, with further ad hoc suggestions as to their opioid analgesic needs. There are discrepancies in the literature about the pain sensitivity of methadone maintenance patients. Further, there are few and conflicting data about the antinociceptive, physiological and subjective effects of additional opioids in these patients. This thesis had one broad aim, to produce data that would eventually help in the formulation of prescribing guidelines, improved policies, and more importantly help direct optimal acute pain management for methadone maintenance patients.

The first study compared the responses to pain induced by a cold pressor test and electrical stimulation in 16 methadone maintained patients and 16 drug-free healthy volunteers. It reconciled the discrepancies in the literature by ascertaining that the relative pain sensitivity of methadone maintenance patients is determined by the nature of the nociceptive stimulus (e.g., cold pressor test vs. electrical stimulation), the concentration of methadone (trough vs. peak plasma concentration), and whether thresholds are determined for detection of pain or pain tolerance. Methadone maintenance patients are hyperalgesic to pain induced by the cold pressor test but not electrical stimulation. This hyperalgesia is particularly pronounced at times of putative trough plasma methadone concentrations. A low pain tolerance to detection ratio was highlighted as a marker of this hyperalgesia in methadone maintained patients.

In the second study, intravenous morphine was administered on two separate occasions to 4 methadone patients and 4 healthy volunteers to determine the antinociceptive effects. The data showed that methadone patients are cross-tolerant to the antinociceptive effects of morphine up to plasma concentrations of approximately 60\text{\textmu}g/mL. They are hyperalgesic to a cold pressor test but not electrical stimulation, confirming the findings of the first study. A low pain tolerance to pain detection ratio for the cold pressor test was confirmed as a sensitive marker of hyperalgesia in this patient population. These findings suggest that plasma morphine concentrations, which have previously been reported as being adequate for minimal to severe post-surgical pain relief, are likely to be ineffective in managing episodes.
of acute pain amongst this patient group, and that large doses of morphine may be required to manage episodes of severe acute pain amongst individuals maintained on methadone. Further research is urgently needed to determine whether other drugs are more effective than morphine in managing acute pain in this patient population.

Data from the first and second studies were combined to determine the physiological and subjective effects of methadone alone, and in combination with morphine. These data indicate that methadone patients have a significantly lower respiratory rate compared with healthy control subjects. Further, additionally administered morphine produced no clinically significant cardiovascular or respiratory effects in the methadone patients. The data also suggest that in the context of acute pain management, methadone patients are unlikely to experience a classic “high” from the administration of additional opioids.

The final study investigated the antinociceptive effects, physiological and subjective effects, of (+)-S-ketamine alone and in combination with morphine in a sample of methadone patients and healthy volunteers. The data indicate that low dose (+)-S-ketamine alone, or in combination with low dose morphine is likely to be ineffective in managing episodes of acute pain in methadone maintenance patients. Despite a lack of antinociceptive effects, the findings show that even at very low doses (and plasma concentrations), (+)-S-ketamine produces pronounced subjective effects amongst methadone patients, and is likely to have high abuse potential in this patient group.

It was concluded that these data consistently show that methadone maintenance patients are hyperalgesic to pain induced by a cold pressor test but not electrical stimulation; methadone maintenance patients are cross-tolerant to the antinociceptive effects of conventional doses of morphine. In addition, low dose (+)-S-ketamine, alone, or in combination with low dose morphine, did not produce any significant antinociceptive effects amongst this patient group. Further research is urgently needed to determine whether other drugs such as gabapentin, tramadol, clonidine, or non-steroidal anti-inflammatory drugs, alone or in combination with morphine, are effective in managing acute pain in this patient population. Clinicians should aggressively treat complaints of pain amongst patients in this population, remembering importantly to treat the pain not the addiction.
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