OPIOID MAINTAINED SUBJECTS
AND THE EFFECTS OF HIGH DOSE MORPHINE
AND ADJUVANT ANALGESICS

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Abstract

Research has shown that maintenance on methadone and buprenorphine for the treatment of opioid addiction can produce the effects of hyperalgesia. This presents difficulties in the management of moderate to severe acute pain in this population. The situation is complicated by a dearth of evidence-based guidelines for pain management.

The main aims of the four studies described in this thesis were to examine whether very high intravenous morphine doses alone (55.2 mg) (targeting plasma morphine concentrations of 180 ng/ml), or in combination with ketorolac (185.4 mg) (targeting plasma ketorolac concentrations of 4000 ng/ml), tramadol (229 mg) (targeting plasma tramadol concentrations of 1000 ng/ml) or S(+)-Ketamine (S-ketamine) (14.5 mg) (targeting plasma S-ketamine concentrations of 60 ng/ml) (opioid adjuvants) produced antinociception or respiratory effects in methadone maintained subjects (methadone subjects) and buprenorphine maintained subjects (buprenorphine subjects). The antinociceptive tests of the cold pressor and electrical stimulation were utilised. The effects of different maintenance doses of methadone and buprenorphine were also examined. Methadone maintained subjects were stratified into once daily dose groups of 11-45 (n=6), 46-80 (n=6) and 81-115 (n=6) mg per day. Buprenorphine maintained subjects were stratified into once daily dose groups of 2 to 8 (n=4), 9 to 15 (n=4) and 16-22 (n=4) mg per day.

A healthy control group was administered lower doses of morphine alone (11.95 mg), and with adjuvants. The same doses of adjuvants were used in each instance.

In the first study high dose morphine failed to provide antinociception for the methadone subjects. High dose morphine significantly decreased respiration rate, but only by an average of 2 breaths per minute. Methadone subjects were hyperalgesic in the cold pressor test. There were no differences in the antinociceptive responses of the different stratified methadone groups to the high dose morphine. Methadone subjects maintained on the highest doses had the highest respiratory depression.

In the second study buprenorphine subjects performed similarly to methadone subjects in at least three respects: firstly, high dose morphine had little antinociceptive effect; secondly, this dose significantly decreased respiration rate; and thirdly, buprenorphine and methadone subjects were similarly hyperalgesic in the cold pressor test. There were also no differences in the antinociceptive responses of the different buprenorphine groups to the high dose morphine.

In the third study tramadol and ketorolac, when combined with high dose morphine, failed to provide antinociception in either the cold pressor or electrical stimulation tests to methadone subjects. The combination of S-ketamine and high dose morphine provided statistically but not clinically significant improvement in antinociception in the cold pressor test.
In the fourth study ketorolac and high dose morphine did not provide antinociception in buprenorphine maintained subjects. While the combinations of S-ketamine or tramadol and high dose morphine provided statistically significant antinociception for buprenorphine maintained subjects in the cold pressor test, it was not clear whether this change represented a clinically significant improvement.

High dose morphine alone, or combined with opioid adjuvants at these concentrations is unlikely to provide pain relief in this population. The use of higher concentrations of adjuvants in combination with high dose morphine needs to be further evaluated. Other strategies should also be explored that may provide effective pain relief in patients maintained on opioids for the treatment of opioid dependence.
Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Peter Athanasos, May 2013
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My family, my world.
Publications and Presentations in Support of This Thesis

Publications

Conference Presentations


Athanasos P, Smith C, Hay J, White J, Somogyi A, Bochner F and Ling W. Opioid dependent patients are cross-tolerant to the antinociceptive effects of S (+) ketamine, ketorolac or tramadol and high dose morphine. 66th Annual Scientific Meeting of the College on Problems of Drug and Alcohol Dependence (2004) San Juan, Puerto Rico (Oral presentation).


Abbreviations, prefixes and symbols

(Morphine 1) (M1)
(Morphine 2) (M2)
5 hydroxytryptamine (5HT)
Analysis of variance (ANOVA)
Australian Professional Society for Alcohol and Other Drugs (APSAD)
Buprenorphine maintained subjects (buprenorphine subjects)
Calcitonin gene-related peptide (CGRP)
Electrospray (ESI)
High-performance liquid chromatography (HPLC)
Hydrochloric acid (HCl)
Liquid chromatograph mass spectrometer (LCMS)
Methadone maintained subjects (methadone subjects)
Post methadone dose (2 hours)
Pre methadone dose (0 hours)
Quality control (QC)
Residual standard deviation of the mean (RSD)
S(+)-Ketamine (S-ketamine)
Standard error of the mean (SEM)