Opioid Maintained Subjects

And The Effects Of High Dose Morphine

And Adjuvant Analgesics

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September 2013

A thesis submitted for the degree of Doctor of Philosophy

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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

Acknowledgements

I would like to acknowledge the excellent help, support and guidance of Professor Jason White, Professor Andrew Somogyi and Emeritus Professor Felix Bochner. They are the best of scientists and it has been a privilege to learn from them.

To those excellent fellows Mark Hutchinson, David Foster, Andrew Menelaou and Tim Mitchell, for their sharp minds, strength of purpose and endless good cheer. To the staff of the Discipline, Anne Tonkin, Abdullah Salem, Rod Irvine, Olga Lopatko, Debbie Wellington, Karen Nunes-Vaz and Erin Morton, thank you. Thanks to Ian Musgrave and his team on level 3, Kosta Farmakis and Francis Dehle for their support, much humour and importantly, a shared love of science. Thanks to Aaron Farquharson for all of his help. Much appreciated. Thanks to Lyell Brougham of Recovery in the Royal Adelaide Hospital.

I wish to thank the following people and organizations: Walter Ling as co-author and co-designer of this set of studies, for his kind hospitality and generosity of spirit, Pfizer Australia Pty Ltd for their generous supply of S-ketamine, and the National Institutes on Drug Abuse, USA for the grant to carry out the studies. I would also like to acknowledge C.S.L. and Roche for their supply of tramadol and ketorolac.

The assays in this thesis were not performed by the author. The assays were performed by other members of the Discipline of Pharmacology, University of Adelaide (Andrew Menelaou and Glynn Morrish). My thanks to them.

My thanks to all the clients and staff at Warinilla, especially Toni Hendry, for their support.

To Jodie Harrison, a lovely person and a dear friend. Particular thanks to David Newcombe. Your support and friendship are valued. Justin Hay, your laughter and companionship has been much appreciated. Charlotte Goess, thank you for your help and friendship.

Peggy Compton. Thank you for our long discussions, excellent guidance, laughter and friendship.

Thank you Meg.

To Michael, Alice and James.

And most importantly, to Michael and Deanna, Diane and Michael, Andrew

and Rose.

My family, my world.

Publications and Presentations in Support of This Thesis

Publications

Athanasos P, Smith C, White J, Somogyi A, Bochner F and Ling W. (2006) Methadone maintenance patients are cross-tolerant to the antinociceptive effects of high morphine concentrations. Pain; 120: 267-275

Conference Presentations

Athanasos P, Neild R. Clinical implications of the expanding understanding of hyperalgesia in chronic opioid administration. Australian Professional Society for Alcohol and Other Drugs (APSAD) (2012) Melbourne

McCarthur J, Kennedy T, Semple T, Brougham L, Compton P de Crespigny C and Athanasos P. Postoperative recovery of opioid tolerant patients. Australian Professional Society for Alcohol and Other Drugs (APSAD) (2008) Sydney

McCarthur J, Kennedy T, Semple T, Brougham L, Compton P and Athanasos P. Postoperative opioid loading requirements following major surgery for opioid tolerant and other drug dependent patients. Australian Professional Society for Alcohol and Other Drugs (APSAD)/ Cutting Edge. National Alcohol, Drug and Addiction Treatment Conference (2007) Auckland, New Zealand.

Athanasos P. Pain: The new comorbidity. Drug and Alcohol Nurses of Australasia National Conference (2007) Whyalla. (Oral Presentation)

Athanasos P and de Crespigny C. Opioid dependent patients: Specific nursing strategies for their pain management. Cutting Edge. National Alcohol, Drug and Addiction Treatment Conference (2006) Wellington, New Zealand. (Oral Presentation)

Compton P, Athanasos P and de Crespigny C. Opioid tolerance and effective management of acute pain. Drug and Alcohol Nurses of Australasia National Conference (2006) Sydney. Pre-conference keynote workshop.

Athanasos P and de Crespigny C. Specific nursing strategies for the pain management of opioid dependent patients. Drug and Alcohol Nurses of Australasia National Conference (2006) Sydney. (Oral Presentation).

Athanasos P, Smith C, Ling W, Bochner F, Somogyi A and White J. Morphine plus S (+) ketamine or tramadol elicit antinociception in opioid non-tolerant and buprenorphine maintained but not in methadone maintained subjects. International Association for the Study of Pain 11th World Congress (2005) Sydney, Australia.

Athanasos P, Smith C, Ling W, Bochner F, Somogyi A and White J. High dose morphine plus S (+) ketamine or tramadol elicits antinociception in buprenorphine maintained patients. 67th Annual Scientific Meeting of the College on Problems of Drug and Alcohol Dependence (2005) Orlando, Florida, USA (Oral presentation).

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Athanasos P, Smith C, White J, Somogyi A, Bochner F, Menelaou A, Edwards S and Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high morphine concentrations. Australian Professional Society for Alcohol and Other Drugs (APSAD) (2002) Adelaide, South Australia, Australia (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)