A comparison of methadone and slow-release oral morphine as maintenance pharmacotherapies for opioid dependence

Timothy B. Mitchell
BPsych (Honours 1st Class)

Department of Clinical and Experimental Pharmacology
University of Adelaide

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Declaration

I hereby declare that this thesis is my own work and contains no material that 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 that has been previously published or written by another person, except where due reference has been made in the text. Any contribution made to the research by others is explicitly acknowledged in the thesis.

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Tim Mitchell

November 6th, 2003

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Abstract

Methadone is highly effective as a maintenance pharmacotherapy for opioid dependence but also exhibits several shortcomings. Of particular concern is the frequency with which patients report inadequate suppression of withdrawal symptoms or adverse effects despite seemingly adequate doses and the application of an individualised approach to dosing. The principal aim of this thesis was to evaluate slow-release oral morphine (SROM) as an alternative maintenance pharmacotherapy to methadone for the treatment of opioid dependence. Eighteen methadone maintenance patients reporting adequate (holders) or inadequate (non-holders) withdrawal suppression between doses were recruited to participate in an open-label, randomly-ordered crossover clinical trial of methadone and SROM. The study featured the concurrent measurement of plasma drug concentrations and both subjective and physiological indices of opioid effect throughout a 24-hour inter-dosing interval on one occasion for methadone and SROM after at least 4 weeks on a stable dose of each drug. Other foci included comparisons of clinical efficacy and acceptability and assessments of opioid withdrawal during the transition between medications. Compared to methadone, SROM was at least as effective overall in suppressing opioid withdrawal between doses and was associated with improved social functioning, fewer and less severe side effects, greater drug liking, reduced heroin cravings, and an enhanced sense of feeling 'normal', and yielded similar outcomes for measures of drug use, depression and health. The majority of patients stated a preference for SROM (78%) over methadone (22%), including 89% of the non-holders and 69% of the holders. The most frequently cited reasons for preferring SROM included fewer side effects, better withdrawal suppression, improved sleep, feeling more normal, improved health, and improved energy. Transfer from methadone to SROM was not associated with a prohibitive degree of opioid withdrawal, providing that an appropriate dose conversion ratio was applied. These findings suggest that SROM is a safe and efficacious maintenance pharmacotherapy for opioid dependence that may be particularly advantageous as an alternative for patients responding poorly to methadone. Further large-scale clinical

trials using double-blind methodologies and standard treatment outcome indicators are warranted.

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List of Abbreviations

6MAM	6-mono-acetylmorphine
AAG	Alpha-acid-glycoprotein
AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
AUD	Australian dollar
BDI	Beck Depression Inventory
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
Css	Average steady-state plasma concentration
DAM	Diacetylmorphine
DASC	Drug and Alcohol Services Council
Df	Degrees of freedom
ECG	Electrocardiogram
EDDP	2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
Id. no.	Identification number
IMOR	Immediate-release oral morphine
LAAM	Levo-alpha-acetylmethadol
LSEQ	Leeds Sleep Evaluation Questionnaire
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
MBG	Morphine Benzedrine Group scale
MG	Morphine Group scale
MSC	Methadone Symptoms Checklist
NAS	Neonatal abstinence syndrome
NMDA	N-methyl-D-aspartate
OTI	Opiate Treatment Index
P/T	Peak to trough plasma concentration ratio
POMS	Profile of Mood States
RAH	Royal Adelaide Hospital
RR	Relative risk ratio
SD	Standard deviation
SE	Standard error of the mean
SROM	Slow-release oral morphine
T>75%Cmax	Time plasma concentration exceeded 75% of Cmax
$T_{1/2}$	Half-life
Tmax	Time to reach maximum plasma concentration
TMD	Total mood disturbance
VAS	Visual analogue scale
Vd	Volume of distribution

Publications Related to This Thesis

Journal articles and reports

Mitchell, T.B., White, J.M., Somogyi, A.A., and Bochner, F. (2003). Comparative pharmacodynamics and pharmacokinetics of methadone and slow-release oral morphine as maintenance pharmacotherapies for opioid dependence. Drug and Alcohol Dependence, 72, 85-94.

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