THE CLINICAL PHARMACOLOGY OF METHADONE INDUCTION

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Abstract

- Methadone is the foremost, long-standing pharmacological treatment for opioid addiction. It has been shown to have considerable cost benefit to the community and to decrease mortality. Despite methadone's decades-long use, much is still unknown regarding its clinical pharmacology, particularly during the induction phase of Methadone Maintenance Treatment (MMT).
- Contrary to previous reports, I found systemic methadone clearance does not increase significantly between induction and steady state phases of MMT, and did not approach the previously reported 3-fold increase. Clinical dose prescription based on the premise of metabolism auto-induction could increase risk of respiratory depression.
- Significant differences between R- and S-methadone pharmacokinetics showed the importance of stereoselective measurement in a clinical situation and significant plasma concentration-effect relationships demonstrated their potential influence on induction pharmacodynamics.
- Small increases in CYP3A4 activity as measured by the Erythromycin Breath Test from Day 1 to Day 40 of MMT were not correlated with changes in methadone clearance. CYP3A4 activities were informative but would be insufficient for use as a sole predictor of methadone clearance during MMT.
- Clinically significant respiratory depression occurred in 20 % of subjects, at times of peak plasma R-methadone concentrations, after reports of withdrawal symptoms at pre-dose sampling times, and irrespective of illicit opioid use. Utilisation of both respiratory rate and blood oxygen saturation measurements provided a good indication of respiratory risk for individuals.

- Although prior opioid use was a strong predictor of continued use during MMT, adoption of a new equation ("abc") and comprehensive documentation of each individual's MMT may increase prediction of MMT success.
- Even in light of recent advances in opioid substitution therapies, MMT's advantages ensure it is still at the forefront of addiction treatment. Careful choice of methodology enabled narrowing of this investigation to those factors most relevant in methadone pharmacology and most responsible for MMT success or failure, and therefore extending previous knowledge of this area. Such data might be utilised to develop a clinically applicable model for MMT, and help provide clients with a safe and uncomplicated transition from heroin use to methadone induction in the future.

Some people dream of great accomplishments…

Others stay awake and get them done!

Successories, Illinois

heroin(e) - anonymous

stayed away my whole life long
for fear of getting burned
till that fateful night in smoke and song
my steadfast head was turned
a drug more potent than any other
an addiction truer than fact
it comes in many shapes and colours
this one in red and black
overcome by temptation
interest outweighs prudence
destined for lust upon creation
the drug welcomes my crudeness
defeated by its savoury smell
my pleasure-lust takes over
as effects take hold i can hardly tell
why i'd ever wish to be sober
i remember well, no need to try
why i found it so appealing
i still recall my first high
with vivid mem'ry of the feeling
for weeks it went on like this
i had to get my fix
and those weeks were nothing short of bliss
my mind played wond'rous tricks
but then one day it all ran out
no drug to fill my veins
and left me alone, empty, in doubt
no heroin(e) to soothe the pains
a year and one half has gone and came
and the addiction still remains
simple mention of the sweet substance' name
sends flashbacks 'cross my brain
and once every now and then
i'll try to get some more
but empty-handed again and again
i'm left hollow to the core

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.

Erin Brooke Morton, 17 January 2007

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Publications and presentations in support of this thesis

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Morton, E.B., Somogyi, A.A., Bochner, F., White, J.M., Foster, D.J.R. Disposition of Methadone between Induction and Maintenance Phases of Treatment. ASCEPT/APG Regional Conference, Adelaide, Australia, 26 November 2004

Morton, E.B., Somogyi, A.A., Bochner, F., White, J.M. The Clinical Pharmacology of Methadone Induction. CPT2004, Brisbane, Australia, 1-6 August 2004

Additional publications and presentations associated with the work contained in this thesis

Foster, D.J.R., Morton, E.B., Heinkele, G., Mürdter, T., and Somogyi, A. Stereoselective quantification of methadone and a d_6-labelled isotopomer using high performance liquid chromatography-atmospheric pressure chemical ionization mass-spectrometry: Application to a pharmacokinetic study in a methadone maintained subject. *Therapeutic Drug Monitoring* **28** (4), 559-567.

Abbreviations, prefixes and symbols

δ	Delta
κ	Kappa
μ	Mu
σ	Sigma
AAG	α_1-acid glycoprotein / Alpha-1-acid glycoprotein
ABCB1	Multi-drug resistance gene (current name)
AEs	Adverse Effects
AIDS	Acquired Immuno-deficiency Syndrome
AIHW	Australian Institute of Health and Welfare
Ala	Alanine
ALT	Alanine transaminase
Asn	Asparagine
Asp	Aspartic acid
ASPD	Antisocial Personality Disorder
AST	Aspartate aminotransferase-serum
AUC	Area Under the plasma concentration-time Curve
BD	Becton Dickinson
C	Cytosine
Ca^{2+}	Calcium Ion
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
cAMP	Adenosine 3',5'-cyclic monophosphate
CER	Percentage of ^{14}C-Erythromycin dose released per minute as labelled carbon dioxide
CER_{20min}	CER at, for example, 20 minutes after ^{14}C-Erythromycin dose
CLND	Chemiluminescent-nitrogen detector
CoA	Coenzyme A
CNS	Central Nervous System
CP	Cold Pressor (Test)
CV	Coefficient of Variation
CYP450	Cytochrome P450 enzymes
CYP3A4/CYP2D6 etc	Cytochrome P450 3A4/2D6 etc
CYP2D6	Cytochrome P450 2D6 gene
d0	Unlabelled methadone
d3	Deuterium labelled methadone (3 deuterium atoms)

d6	Deuterium labelled methadone (6 deuterium atoms)
D*	Day * of MMT
DAMGO	[D-Ala^2,*N*-MePhe^4,Gly-ol^5] enkephalin
DASC	Drug & Alcohol Services Council
DCS	Department of Correctional Services
DNA	Deoxyribonucleic Acid
DPHM	Diphenhydramine
dpm	Decay per minute
DRD2	Dopamine *D2* Receptor
DSM-III-R	Borderline Personality Disorder
EBT	Erythromycin Breath Test
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EMDP	2-ethyl-5-methyl-3,3-diphenpyrroline
EUT	Erythromycin Urine Test
GABA	Gamma Aminobutyric Acid
GC-MS	Gas Chromatography – Mass Spectrometry
GPCR	G-protein coupled receptor
GRK	G-protein coupled receptor kinases
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HQC	High Concentration Quality Control
IC_{50}	Concentration for 50 % inhibition
INR	International Normalized Ratio
IS	Internal Standard
iv	Intravenous
K^+	Potassium Ion
LAAM	*Levo-α*-acetylmethadol / *Levo-alpha*-acetylmethadol
LC-MS	Liquid Chromatography – Mass Spectrometry
LOQ	Limit of Quantification
LQC	Low Concentration Quality Control
MAPK	Mitogen-activated protein kinase
MDR1	Multi-drug resistance gene (old name)
MIA-	Methadone Induction Study A subject
MIB-	Methadone Induction Study B subject
MMT	Methadone Maintenance Treatment

MOP	Mu Opioid (Peptide) Receptor
MQC	Medium Concentration Quality Control
MSC	Methadone Symptoms Checklist
MSCWYN	Methadone Symptoms Checklist –Withdrawal subscale, categorical scoring
NAS	Neonatal Abstinence Syndrome
NMDA	N-methyl-D-aspartate
NTS	Tractus solitarius
OPRM1	Mu Opioid Receptor Gene
ORM	Orosomucoid
PAR	Peak Area Ratio
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
P-gp	P-glycoprotein
PhD	Doctorate of Philosophy
PK	Pharmacokinetics
PKA	Cyclic AMP-dependent protein kinase (protein kinase A)
PKC	Protein Kinase C
POMS	Profile of Mood States
QC	Quality Control
r^2	Coefficient of Determination
R-	Right
Rac-	Racemic
RAH	Royal Adelaide Hospital
RIA	Radioimmunoassay
RNA	Ribonucleic Acid
RP-HPLC	Reverse-Phase High Performance Liquid Chromatography
SA	South Australia
SAEs	Serious Adverse Effects
SAVIVE	South Australia Voice for IV Education
S	Sinister
S1/S2	Standard number 1/ Standard number 2
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
SROM	Slow Release Oral Morphine
Thy	Thymine

T_{max}	Time of Maximum labelled carbon dioxide exhalation
TH	Alpha-tocopherol
TMD	Total Mood Disturbance
TQ	Alpha-tocopherolquinone
UCR	Urinary Cortisol Ratio
US/USA	United States of America
UV	Ultraviolet
UV-HPLC	High Performance Liquid Chromatography with Ultraviolet Detection
VAS	Visual Analogue Scale
WHO	World Health Organisation