An examination of the pharmacodynamics and pharmacokinetics of Levo-alpha-acetylmethadol (LAAM), compared to methadone, in opioid maintenance patients

David A L Newcombe

Discipline of Pharmacology

School of Medical Sciences (Faculty of Health Sciences)

The University of Adelaide

A thesis submitted for the degree of Doctor of Philosophy

July, 2006

Table of Contents

List of Tables

List of Figures

List of Appendices

Abstract

Methadone is currently the most widely used agent to manage opioid dependence, but clinical experience has highlighted some limitations with its use. In particular, a relatively high proportion of patients complain of breakthrough withdrawal symptoms (non-holding) at apparently adequate methadone doses. Levo-alpha-acetylmethadol (LAAM) is a long acting opioid that is likely to benefit methadone non-holders; however, relatively little is known about its pharmacology at steady state. The primary aim of this thesis was to evaluate LAAM as an alternative maintenance pharmacotherapy to methadone for the treatment of non-holders; subsidiary aims were to elucidate the pharmacodynamics and pharmacokinetics of LAAM and its active metabolites (nor- and dinor-LAAM), and to examine the *in vitro* activity of LAAM, nor- and dinor-LAAM. Sixteen methadone maintenance patients (non-holders=8) were recruited to participate in a randomised, crossover trial of LAAM and methadone. At steady state there were two testing sessions (24 h for methadone and 48 h for LAAM) that featured the concurrent measurement of plasma drug concentrations and both subjective and physiological indices of opioid effect. Cognitive and psychomotor functions were also assessed once during each inter-dosing interval study. Ten age-and gender-matched controls were also tested. The peak magnitude of methadone's and LAAM's effects were similar. Compared to methadone, LAAM was associated with more stable and less severe withdrawal and mood disturbance. The general pattern of symptom complaints and cognitive function was similar for both drugs. Severity of mood disturbance and withdrawal was similar in holders on methadone and LAAM, but was greater in non-holders when they were taking methadone than LAAM. In comparison to plasma (R)-(-) methadone, plasma nor- and dinor-LAAM concentrations fluctuated little over the dosing interval. Furthermore, nor- and dinor-LAAM were both more potent in the guinea-pig ileum bioassay, and had greater affinity for mu opioid receptors in receptor binding studies, than LAAM. In conclusion, LAAM converted methadone non-holders into LAAM holders. It is proposed that it is the relatively flat plasma concentration-time profile for nor- and dinor-LAAM that confer stability of opioid effect, minimising withdrawal. Therefore, LAAM may have a role in selected patients, whose response to methadone is suboptimal.

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.

David A.L.Newcombe, 31 July, 2006

Acknowledgements

There are many people I would like to thank:

To my mentors and supervisors – Professors Jason White, Andrew Somogyi, and Felix Bochner, thank you for your patience, exemplary supervision, and continual belief in me. I must also thank Drs Rod Irvine and Abdallah Salem for their supervision of *in vitro* assay work.

Thanks must go to other students and departmental staff members whose work made it possible to undertake this research. In particular I would like to thank Andrew Menelaou and Dr David Foster for developing the LAAM assay; Andrew Menelaou, Betinna Christensen and Marie-Loiuse Brixen (visiting students from the Royal Danish School of Pharmacy) for undertaking plasma LAAM assays; Andrew Menelaou for undertaking plasma methadone and morphine assays, and urinary LAAM assays, and Gordon Crabb for technical support. In addition, part of the isolated guinea pig ileum work was undertaken by third year Bachelor of Science students (Karen Beard, Emma Clarke, Amanda Jackson, and Tracey Siebert).

I am indebted to my colleague, and friend, Dr Pat Kent (PhD, MPsych) for her invaluable assistance in devising the battery of neuropsychological tests used in this study, and for training me in the administration and scoring of the tests.

To the wonderful and supportful staff at Warinilla clinic (in particular Toni Hendy, Dr Tony Chadderton, Anne Fisk and Martin Hurley) without whom recruitment for this study would not have been possible. Thankyou also to Dr Ian Buttfield (Physician) for screening patient ECGs for the presence of cardiac dysrhythmias.

To all my friends and fellow PhD students, past and present thankyou all for your support, good humour, and pale *ales* at the Essex on Friday afternoon – I hope to have the honour of working with each of you in the future. Special thanks to Karen Nunes-vaz, and Dr Linda Gowing for their continual support over the years.

To my parents, Hazel and Len, who have always supported and encouraged my many endeavours over the years – a big thankyou. Special thanks to my father for proof reading drafts.

This journey would not have been possible without the love and support of my family – My beautiful wife Ruth, and my two boys James and Alistair, thanks guys you sacrificed so much to allow me to complete this PhD – this thesis is for you.

Throughout my candidature I was supported by an Australian Post Graduate Research Award.

Publications in support of this thesis

Newcombe, D.A.L, Bochner, F., White, J.M., & Somoggyi, A.A (2004). Evaluation of levo-alpha-acetylmethadol as an alternative treatment for methadone maintenance patients who regularly experience withdrawal: a pharmacokinetic and pharmacodynamic analysis. *Drug and Alcohol Dependence, 76,* 63-72.

Presentations to learned societies.

Newcombe, D.A.L., White, J.M., Menelaou, A.M., Brixen, M-L., Christensen, B., Mikhail, S., Somogyi. S.S. (2000). A comparison of the pharmacodynamics and pharmacokinetics of methadone and LAAM in maintenance patients, *Drug and Alcohol Dependence: Supplement, Abstracts from the Sixty-Second Annual Scientific Meeting of the College on Problems of Drug Dependence, 60 (Suppl. No.1)*

Newcombe, D.A.L., Irvine, R.J., Salem, A (2000). *In Vitro* Characterisation of the Relative Potency of Levo-Alpha-Acetylemthadol (LAAM) and its Nor-Metabolites, *Proceedings of the Joint meeting of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists and the British Pharmacological Society, 7, 111*

Abbreviations, prefixes and symbols

AAG	α_1 acid glycoprotein
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve (AUC) / area under the effect versus time curve during the dosing interval
ARCI	Addiction Research Centre Inventory
B.D	Administered twice daily
BDI	Beck Depression Inventory
C_{max}	Maximum plasma concentration
$C_{min\ (first)}$	Minimum plasma concentration pre-dose
$C_{min\ (last)}$	Minimum plasma concentration post dose
CL	Total systemic plasma clearance
CL/F	Apparent plasma clearance at steady state
CL_R	Renal clearance
CI	Confidence interval(s)
C_{ss}	Steady state plasma concentration
CV	Coefficient of variation (%)
dinor-LAAM	dinoracetylmethadol
EC_{50}	Concentration eliciting 50% of effect
FDA	Food and Drug Administration
HPLC	High performance liquid chromatography
IC_{50}	Concentration inhibiting 50% of ligand binding
i.m	Intramuscular administration
i.v	Intravenous administration
Ki	Inhibition constant
LAAM	Levo-alpha-acetylmethadol
LMP	LAAM maintenance patients
MBG	Morphine Benzedrine Group scale of the ARCI
MG	Morphine Group scale of the ARCI
MMP	Methadone maintenance patients
MMT	Methadone maintenance treatment
MSC	Methadone symptom checklist
NMDA	N-methyl-D-aspartate
nor-LAAM	noracetylmethadol
P	Statistical significance
p*Ka*	Ionisation constant
p.o	Oral administration

POMS	Profile of Mood States
P/T	Peak to trough plasma concentration ratio
r	Correlation coefficient
r^2	Ceofficient of determination
s.c	Subcutaneous administration
sd	Standard deviation
SEM	Standard error of the mean
SOWS	Short Opiate Withdrawal Scale
STAI	State Trait Anxiety Inventory
t½	Half life (distribution phase=t½α: terminal elimination phase=t½β)
t_{max}	Time to reack maximum plasma concentration
Vd	Volume of distribution
q.i.d	Administered four times a day