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

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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
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Publications in support of this thesis


Presentations to learned societies.


**Abbreviations, prefixes and symbols**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>AAG</td>
<td>α₁ acid glycoprotein</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the plasma concentration-time curve (AUC) / area under the effect versus time curve during the dosing interval</td>
</tr>
<tr>
<td>ARCI</td>
<td>Addiction Research Centre Inventory</td>
</tr>
<tr>
<td>B.D</td>
<td>Administered twice daily</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>C&lt;sub&gt;min (first)&lt;/sub&gt;</td>
<td>Minimum plasma concentration pre-dose</td>
</tr>
<tr>
<td>C&lt;sub&gt;min (last)&lt;/sub&gt;</td>
<td>Minimum plasma concentration post dose</td>
</tr>
<tr>
<td>CL</td>
<td>Total systemic plasma clearance</td>
</tr>
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<td>CL/F</td>
<td>Apparent plasma clearance at steady state</td>
</tr>
<tr>
<td>CLR</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval(s)</td>
</tr>
<tr>
<td>C&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>Steady state plasma concentration</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation (%)</td>
</tr>
<tr>
<td>dinor-LAAM</td>
<td>dinoracetylmethadol</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Concentration eliciting 50% of effect</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Concentration inhibiting 50% of ligand binding</td>
</tr>
<tr>
<td>i.m</td>
<td>Intramuscular administration</td>
</tr>
<tr>
<td>i.v</td>
<td>Intravenous administration</td>
</tr>
<tr>
<td>Ki</td>
<td>Inhibition constant</td>
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<tr>
<td>LAAM</td>
<td>Levo-alpha-acetylmethadol</td>
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<td>LMP</td>
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<tr>
<td>MBG</td>
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</tr>
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<tr>
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</tr>
<tr>
<td>MSC</td>
<td>Methadone symptom checklist</td>
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<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>nor-LAAM</td>
<td>noracetylmethadol</td>
</tr>
<tr>
<td>P</td>
<td>Statistical significance</td>
</tr>
<tr>
<td>pKa</td>
<td>Ionisation constant</td>
</tr>
<tr>
<td>p.o</td>
<td>Oral administration</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>POMS</td>
<td>Profile of Mood States</td>
</tr>
<tr>
<td>P/T</td>
<td>Peak to trough plasma concentration ratio</td>
</tr>
<tr>
<td>r</td>
<td>Correlation coefficient</td>
</tr>
<tr>
<td>r²</td>
<td>Coefficient of determination</td>
</tr>
<tr>
<td>s.c</td>
<td>Subcutaneous administration</td>
</tr>
<tr>
<td>sd</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
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<tr>
<td>SOWS</td>
<td>Short Opiate Withdrawal Scale</td>
</tr>
<tr>
<td>STAI</td>
<td>State Trait Anxiety Inventory</td>
</tr>
<tr>
<td>t½</td>
<td>Half life (distribution phase=(t_{\alpha}); terminal elimination phase=(t_{\beta}))</td>
</tr>
<tr>
<td>t_max</td>
<td>Time to reach maximum plasma concentration</td>
</tr>
<tr>
<td>Vd</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>q.i.d</td>
<td>Administered four times a day</td>
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