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GPhC 2050927

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Superintendent Pharmacist

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Low Dose Naltrexone

Pharmacokinetics, Pharmacodynamics & Interactions and cautions in common practice.
Disclaimer

- I have no conflict of interest which would prevent me from presenting here today.
- This presentation is for general information only – and does not replace the need for a clinician.
- Patients should be treated holistically, clinicians should make prescribing decisions based upon their own knowledge and security of area of clinical practice.
Background

Pharmacy Superintendent, based in the UK.

Experience in LDN:

5000-6000 current patients

100,000+ Patient dispensing events in recent years

Work directly with the most experienced prescribers of LDN in the UK
Pharmacokinetics

L – Liberation of drug from pharmaceutical formulation

A – Absorption of the drug into the bloodstream
   (Bioavailability)

D – Distribution of the drugs in the body

M – Metabolism of the drug
   (Irreversible change to the molecule by a biological or chemical process.)

E – Excretion of the drug from the body.

Pharmacokinetics

L – Liberation of drug from pharmaceutical formulation

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid</td>
<td>Cream</td>
</tr>
<tr>
<td>Injection</td>
<td>Sublingual Drop</td>
</tr>
<tr>
<td>Wafer</td>
<td></td>
</tr>
</tbody>
</table>
Common Dosing formulations

- Tablets are not as commonly used for LDN dosing as capsules, but are cheaper to manufacture.

- Hardness
- Swelling
- Hydrophilic
- Excipient
- Glidant
Common Dosing formulations

- Tablets – Friability

“the condition of being friable, describes the ability of a solid substance to be reduced to smaller pieces with little effort. The opposite of friable is indurate.” (1)

- Massive effect on the dissolution rate.

- “Compounding pharmacists” are very aware of this – but experience is required to achieve consistent results.

- Common excipients are lactose, microcrystalline cellulose, calcium carbonate as “bulk fillers” and magnesium stearate as a glidant.

Common Dosing formulations

- Tablets – Disintegrants
- Hygroscopic – high affinity for water
- Swell
- Change shape
- Radical change
- Starch Glycolate
- Crospovidone
- Croscarmellose
Common Dosing formulations

- Capsules are the most common form of LDN dosing worldwide.
- Although multiple types of capsules are available, compounding pharmacies prefer manual fit, hard gelatin capsules.
  - Animal or vegetable origin gelatin
  - Shaped for fixed volume
  - Contents – similar to tablets – but uncompressed
Capsule Manufacture

- Generally filled by fixed volume.
- Quick, easy and simple for quality control (weight)
Further Reading on this process

Table 17.1  \( \text{CAPSULE SIZES AND APPROXIMATE FILL CAPACITIES} \)

<table>
<thead>
<tr>
<th>CAPSULE SIZE</th>
<th>APPROXIMATE VOLUME</th>
<th>APPROXIMATE POWDER WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>000</td>
<td>1.4 mL</td>
<td>430 mg–1.8 g</td>
</tr>
<tr>
<td>00</td>
<td>0.95 mL</td>
<td>390 mg–1.3 g</td>
</tr>
<tr>
<td>0</td>
<td>0.68 mL</td>
<td>325–900 mg</td>
</tr>
<tr>
<td>1</td>
<td>0.5 mL</td>
<td>227–650 mg</td>
</tr>
<tr>
<td>2</td>
<td>0.37 mL</td>
<td>200–520 mg</td>
</tr>
<tr>
<td>3</td>
<td>0.3 mL</td>
<td>120–390 mg</td>
</tr>
<tr>
<td>4</td>
<td>0.21 mL</td>
<td>100–260 mg</td>
</tr>
<tr>
<td>5</td>
<td>0.13 mL</td>
<td>65–130 mg</td>
</tr>
</tbody>
</table>

Table 17.1  \( \text{Capsule Sizes and Approximate Fill Capacities} \)

- https://www.inkling.com/read/pharmaceutical-calculations-howard-ansel-14th/chapter-17/special-calculations-capsule
Liquid formulations

- Oral Liquid formulations generally avoid the whole question of liberation, as the drug is already in solution – there is no release profile and dissolution is almost immediate.

- Formulations with liquid LDN can contain fewer of the excipients present in capsules or tablets, but more excipients to bulk up the liquid volume.

- Water, Glycerol, Flavourings, Preservatives etc.
Making LDN liquid

- Measurement
- Homogenisation
- Volumetric titration by halves
- Verification and batch records
- Stability
- Quality control
- Preservation considerations
Cream formulations

- Becoming more commonly used.
- LDN creams were first used for treatment of autism in children.
- Dosing is usually by volume
  - mg/5ml
- Amount to pass through the skin is highly variable.
Therapeutic doses of Naltrexone are possible via the transdermal route. (1)

Higher concentrations of cream and larger amounts may be required.

Not really compatible with current best models of LDN pharmacology.

Not much evidence that any vehicle compoundable in community pharmacy has a large effect. (2)

Patients do report response!

Recent indications wound healing. Sterility!

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More skin graphs...

Sublingual Drops contain a concentrated liquid form of Naltrexone. Commonly 10mg/1ml.

Dosing is usually by the “drop” - each drop has a fixed volume.

In 10mg/1ml, 1 drop has a fixed volume of 0.05ml, giving 0.5mg.

As with liquids, the drug is already in solution.

Added advantages include the avoidance of first pass metabolism.
Sublingual Drops

- Sublingual drug delivery has many advantages. (Clinical Pharmacokinetics Volume 41, Issue 9, pp 661-680)
- The drug is absorbed directly by passage through thin membranes in the oral mucosa.
- It is not subjected to an aggressive pH environment.
- Clinical evidence shows efficacy, possibly due to avoidance of 1st pass metabolism.
### ADSORPTION INTO THE BLOODSTREAM (LDN)

<table>
<thead>
<tr>
<th>METHOD of administration</th>
<th>Speed of adsorption</th>
<th>Bioavailability</th>
<th>Available for LDN treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>Fastest – almost instant</td>
<td>unknown</td>
<td>No</td>
<td>na</td>
</tr>
<tr>
<td>IV/IM</td>
<td>Very Fast - minutes</td>
<td>~100%</td>
<td>Naloxone bolus for overdose too high, IM implants of 1000mg give steady state.</td>
<td></td>
</tr>
</tbody>
</table>
ADSORPTION into the bloodstream (LDN)

<table>
<thead>
<tr>
<th>METHOD of administration</th>
<th>Speed of adsorption / %</th>
<th>Bioavailability</th>
<th>Available for LDN treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Capsule</td>
<td>Fast (5-30 minutes) / 90%+</td>
<td>~40%</td>
<td>Yes</td>
<td>0.5, 1, 2 or 4.5mg</td>
</tr>
<tr>
<td>Sublingual Drops</td>
<td>Fast (5-10 minutes) / unknown</td>
<td>~18% (but no first pass metabolism)</td>
<td>Yes 10mg/ml</td>
<td>1 to 18 drops under tongue (0.5-9mg)</td>
</tr>
<tr>
<td>Cream</td>
<td>Slow / unknown</td>
<td>~5-10% (estimated, but no first pass metabolism in liver, however metabolism in skin)</td>
<td>Yes, but rarely appropriate.</td>
<td>1mg – 20mg via cream</td>
</tr>
</tbody>
</table>
## Distribution

- The volume of distribution (VD) of naltrexone is 1350 litres, following IV.

<table>
<thead>
<tr>
<th>Drug</th>
<th>$V_D$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>8L</td>
<td>Reflects a high degree of plasma protein binding.</td>
</tr>
<tr>
<td>Theophylline, Ethanol</td>
<td>30L</td>
<td>Represents distribution in total body water.</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>15000L</td>
<td>Shows highly <em>lipophilic</em> molecules which sequester into total body fat.</td>
</tr>
<tr>
<td>NXY-059</td>
<td>8L</td>
<td>Highly charged <em>hydrophilic</em> molecule.</td>
</tr>
</tbody>
</table>

- Naltrexone is $\sim$25% plasma bound, so the naltrexone is very freely distributed throughout the body and organs.
Metabolism

- Naltrexone (NTX) is rapidly metabolised to 6-β-Naltrexol (NTXOL) and 2-Hydroxy-3-O-methylnaltrexol (HMNTXOL).

- NTX an NTXOL are structurally similar and most likely bind to the same receptor sites.

- Metabolism is primarily by the liver, but is metabolised at a higher rate than hepatic blood flow – so other mechanisms must be in effect.

- No effect on Cytochrome P450

- Care in liver failure


The metabolism of naltrexone in man.
Elimination of Naltrexone

- ~60% of initial dose of naltrexone can be recovered in urine as metabolites within 48h.
- <2% unchanged naltrexone in urine
- Does not require loading dose, and does not build up over time – even at high dose.
- For normal LDN dosing, plasma levels are almost undetectable at 24h.

Further reading: http://www.drugs.com/pro/naltrexone.html
Elimination – clinical issues

- Anecdotal evidence of LFT and RENAL FUNCTION alterations after starting LDN.
- Previous liver/kidney problems require baseline and 1/12 + 3/12 monitoring.
- If liver problems, consider dosing to avoid first pass metabolism.
Pharmacodynamics

- Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.[1] One dominant example is drug-receptor interactions as modeled by

\[ L + R \rightleftharpoons L \cdot R \]

- where L=ligand (drug), R=receptor (attachment site), reaction dynamics that can be studied mathematically through tools such as free energy maps.

- Pharmacodynamics is often summarized as the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug.

Naltrexone/6-beta-naltrexol
Receptor attachment sites

- Reversible @ Opiate receptors, mu and kappa.
- Slight activity at delta.
- Competes with endogenous and exogenous opiates.
- Toll like receptors TLR4 (blocks signalling)
Biological outcomes

- Upregulation of Met-5-enkephalin production (OGF – Opiate Growth Factor)
- Increased expression of opiate/OGF receptors (sensitivity to opiates)
- Reductions in inflammation
- Reduced cell growth (Tumor)
- Upregulation of CD8+T cells

- “immunotherapy of cancer via mediation of cytotoxic T lymphocytes by methionine enkephalin”
- The opioid growth factor receptor axis: homeostatic regulator of cell proliferation and its implications for health and disease.
- “Low dose naltrexone targets the opioid growth factor receptor pathway to inhibit cell proliferation; mechanistic evidence from tissue culture model”
Common cautions

- Renal or hepatic failure
- Concurrent use of opioids
- Hashimoto’s Disease
- Immunosuppressants?
- Organ Transplantation
- Pregnancy / Breast Feeding
- Appropriate Dosing Route
# Painkillers

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Suitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine / Dihydrocodeine</td>
<td>Unless MR Formulation, leave 4 hour gap.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Partial agonist. Instant release tramadol less preferable to MR. Suggest MR formulation and morning dosing.</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Avoid if on instant release, 4-6h gap or MR formulation and give with morning dose. Evidence from compound preparations, Start slowly. 0.5mg slow initiation.</td>
</tr>
<tr>
<td>Morphine</td>
<td>Avoid if on instant release. Can precipitate withdrawal.</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>Avoid</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>OK</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>OK</td>
</tr>
<tr>
<td>Nefopam</td>
<td>OK – in fact good alternative. Potentiate?</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
### Other drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Suitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone / Methylprednisolone</td>
<td>Will not directly interact with LDN. However, may reduce effectiveness. Rule of thumb, initiate LDN 2-3 days after a short reducing course of steroids, or when on a daily dose &lt; 20mg. Withdraw gradually after LDN at full dose and results achieved.</td>
</tr>
<tr>
<td>Immunosuppressants, Sulphasalazine, Azathioprine</td>
<td>No direct interaction. Consider patient holistically. Withdraw slowly and symptomatically.</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Consider hasimotos. Regular levels. Counsel patient on symptoms of hyperthyroid.</td>
</tr>
<tr>
<td>Lyrica/pregabalin, gabapentin, amitriptiline, SSRIs, tricyclics etc</td>
<td>No interaction.</td>
</tr>
<tr>
<td>Benzodiazepines, hypnotics, Z-drugs</td>
<td>Consider holistically. LDN dosing mane.</td>
</tr>
<tr>
<td>Sativex</td>
<td>No interaction. Note psychiatric side effects.</td>
</tr>
<tr>
<td>Anti-psychotics</td>
<td>Careful monitoring required due to extra endorphin release. Special care in bipolar, or *zapines.</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>Monitor carefully. No direct interaction.</td>
</tr>
<tr>
<td>Anti-platelets / Coumadins</td>
<td>No interaction.</td>
</tr>
</tbody>
</table>
Dosing schedules – quick guide.

- **MS** – 1mg initially and increase by 1mg weekly until at 4.5mg. Assess at 3/12. Increased spasms.
- **CFS/ME** – 0.5mg, increase by 0.5mg. If flu symptoms appear, halve dose and repeat until at 4.5mg.
- **Cream**, as for MS but can double the dose due to low bioavailability.
- **Maximum dose** we see is 22mg.