CLOMIPRAMINE

01. Assay details

CH Labs Test Reference Guide

02. Therapeutic range

How well established:
This range is not well established with poor correlation between plasma concentration and therapeutic index. Some patients respond at low doses, trough plasma concentrations >125ng/ml represent a maximal dose. Patients not responding at this concentration should be classified as non-responders. However, patients who have partially responded have been successfully treated with higher plasma concentrations. Note that at concentrations >150ng/ml desipramine displays non linear kinetics so caution and close monitoring is required

The adverse effects that correlate most closely with plasma concentrations are symptomatic postural hypotension and tremor. Other adverse effects correlate more closely with the patient's clinical state than drug concentrations.

Desipramine is metabolised by CYP2D6, which is subject to genetic polymorphism. There is large inter-individual pharmacokinetic variability, and drug concentration monitoring is useful in identifying slow metabolisers to minimise toxicity at conventional doses and fast metabolisers for whom standard doses are suboptimal. Some advocate TDM at the beginning of therapy to guide dose adjustment, and avoid toxicity. It is also useful for assessing compliance.

The therapeutic range of 60-150 ng/ml was developed in patients less than 71 years of age. Older patients are more prone to adverse effects and less likely to benefit from treatment, however benefit occurs in a similar therapeutic range. Therefore we recommend closer monitoring for adverse effects in the elderly during upward titration of dose.

2-hydroxydesipramine plasma concentrations have been less well studied but with similar results. There is a poor correlation between plasma concentration and effect but with a suggestion that similar plasma concentrations to the parent compound are effective. It is not known which is the more pharmacologically active compound but similar activity has been observed in animal studies. This has particular implications for interpreting plasma concentrations in fast metabolisers who will have relatively low concentrations of the parent compound.

03. Pharmacokinetics

<table>
<tr><td>F: 0.5 (0.2-0.8)</td><td>Vd (L/kg): 14 (12-17)</td><td>Cl (L/h/kg): 0.5 (0.3-0.86)</td><td>t½: 19-37</td></tr>
<tr><td>Fe: <0.05</td><td colspan="3">Elimination route: Demethylation to the active metabolite desmethylclomipramine which is hydroxylated to inactive metabolites.</td></tr>
<tr><td colspan="3">CYP: Predominantly either CYP1A2 or CYP2C19, and to a minor extent CYP2D6</td><td>Protein binding: 97%</td></tr>
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F = Bioavailability, Vd = volume of distribution, Cl = clearance, t½ = terminal half-life of elimination, Fe = fraction excreted unchanged in the urine, CYP = cytochrome P450 enzyme/s

Other PK data:

- Steady state concentrations are achieved within one week, but the antidepressant effect is not apparent for two to four weeks.
- Clomipramine is demethylated to an active metabolite desmethylclomipramine with a half life of 69 hours.
- Desmethylclomipramine is hydroxylated via CYP2D6.
- Nonlinear (saturable) pharmacokinetics have been observed at concentrations >150ng/ml.

04. Indications

1. Depression
2. Obsessive compulsive disorder
3. Phobic states
4. Cataplexy accompanying narcolepsy

05. Loading dose

Not required. Start with a low dose ie 25mg 2-3 times daily for depression, obsessive compulsive syndromes, and phobias, or 10 mg 2-3 times daily for panic attacks and agoraphobia. Increase gradually according to clinical response and tolerance of adverse effects.

Closer monitoring recommended in the elderly because of decreased clearance and increased susceptibility to adverse effects.

06. Maintenance dose

The usual adult dose is 100-250 mg taken as a single daily dose on retiring to bed. The required dose is variable depending on the individual pharmacokinetics.

07. Notes on administration

The established practice is to commence people on divided daily doses then rationalise to a single daily dose. There is no particular reason why this needs to be so and the pharmacokinetics would suggest once daily dosing is adequate. Food does not alter the extent of absorption, but the peak concentration is decreased. Usually administered on retiring to bed.

08. When to monitor

At the trough concentration, just before the next dose, or at least 16 hours after the last dose.

Samples should be taken at steady state: at least one week after commencing or changing clomipramine treatment, or after adding or removing a drug which may interact with clomipramine.

As well as monitoring for clinical effect, adverse effect monitoring should include postural blood pressure and ecg monitoring (for widened QRS complex or increased QT interval).

09. Dose individualisation

The individual variability in metabolism and elimination means that given doses may result in a range of drug concentrations. The dose may need to be reduced in liver disease.

10. Adverse effects

> 10%

CNS: dizziness, drowsiness, headache, weakness
GI: xerostomia, constipation, increased appetite, nausea, unpleasant taste, weight gain

1-10%

CNS: confusion, delirium, hallucinations, restlessness, parkinsonian syndromes, insomnia, fine tremor
CVS: arrhythmias, hypotension
GI: diarrhoea, dyspepsia
GU: dysuria, sexual dysfunction

<1%

CNS: anxiety, seizures, tinnitus
DERM: alopecia, photosensitivity
ENDO: breast enlargement, galactorrhoea, SIADH
HAEM: agranulocytosis, leukopenia, eosinophilia
GI: cholestatic jaundice, increased liver enzymes
MISC: allergic reactions

11. Drug interactions

Clomipramine is metabolised by CYP1A2 and 2C19 to the active metabolite desmethylclomipramine. Desmethylclomipramine is metabolised by CYP2D6 which is subject to genetic polymorphism - 5-10% of Caucasians and 1-2% of Asian/ Polynesians are poor metabolisers, resulting in increased desmethylclomipramine concentrations at "standard doses".

<u>Drugs that may increase desipramine concentration (mostly by CYP2D6 inhibition)</u>

Phenothiazines, SSRI antidepressants - particularly fluoxetine and paroxetine, cimetidine, other tricyclic antidepressants, quinidine, haloperidol, metoprolol, flecainide propafenone. High doses of alcohol inhibit first pass metabolism and increase oral availability of Desipramine.

<u>Desipramine may increase concentrations of the following drugs</u>

Warfarin: Desipramine increases the half-life of Warfarin, increasing anticoagulant activity - monitor prothrombin ratios closely.

<u>Pharmacodynamic interactions:</u>

Via neurotransmitter effects:

Monoamine oxidase inhibitors - risk of serotonin syndrome: hyperpyrexia, hypertension, tachycardia, confusion, seizures and death have been reported. Clomipramine should not be used in conjunction with a MAOI, and a 14 day washout period should be observed if changing between a TCA and a MAOI.

Ritonavir - risk of serotonin syndrome at higher doses of TCAs: monitoring is required.

Sympathomimetic amines: the pressor effects of directly acting sympathomimetic amines are potentiated by clomipramine, which may cause severe headache or even death.

Antihypertensive drugs: clomipramine antagonises the hypotensive effects of clonidine, methyl dopa, guanethidine.

Sedation: Cumulative with alcohol and other sedatives

Anticholinergic effects: Cumulative with other anticholinergic drugs (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine, biperiden)

QT prolongation: Additive with macrolides, some quinolones, antihistamines, antiarrhythmics (type Ia and type III), cisapride etc.

12. Factors that may give a false assay result

All tricyclics may interfere in assays involving other tricyclic anti-depressants. Levels may be elevated or diminished depending on the drug being assayed. Assays in patients on two tricyclic antidepressants (or in overdose) may be inaccurate.

13. Overdose

TOXINZ

14. Dialysability

Not removed by dialysis because of the large volume of distribution

15. Comments

Clomipramine acts by Responders have a trend towards lower desmethylclomipramine/clomipramine ratios.

16. Key references

Nil.

17. Last updated

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