DESIPRAMINE

01. Assay details

CH Labs Test Reference Guide

02. Therapeutic range

60-150 mcg/L (220-560 nmol/L) desipramine

How well established:
This range is not well established and the correlation between plasma concentration and effect is not strong (Friedel). Therefore routine drug concentration monitoring is not recommended for desipramine. Some patients respond at concentrations lower than 60mcg/L. Patients not responding at concentrations approaching 125ng/ml should be classified as non-responders. However, patients who have partially responded have been successfully treated with higher plasma concentrations. Note that at concentrations >150mcg/L desipramine, displays non-linear kinetics so 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 rapid metabolisers for whom standard doses are suboptimal. Some advocate drug monitoring 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 mcg/L 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 the therapeutic range is similar to that for the parent compound. It is not known which is the more pharmacologically active compound but similar activity has been observed for both in animal studies. This has particular implications for interpreting plasma concentrations in rapid metabolisers who will have relatively low concentrations of the parent compound.

03. Pharmacokinetics

F: 0.33-0.5	**Vd** (L/kg): 33-42	**Cl** (L/h/kg): 1.4-1.8*	**t½:** 17hrs (14-60)*
Fe: <0.05**	**Elimination route:** Dihydroxylation to the active metabolite 2-hydroxydesipramine which is renally eliminated.		
CYP: CYP2D6 (genetic polymorphism), 1A2		**Protein binding:** 90%	

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.
- Desipramine is 2-hydroxylated to an active metabolite 2-hydroxydesipramine with a half life of 22 hours.
- *There is a 10-fold variation in metabolism of desipramine due to genetic polymorphism of CYP2D6.
- **The active metabolite 2-hydroxydesipramine is renally eliminated, DOSE ADJUSTMENT IS REQUIRED IN RENAL IMPAIRMENT.
- Nonlinear (saturable) pharmacokinetics have been observed at concentrations >150ng/ml.
- Desipramine metabolite inhibits 2A6, 2B6, 2D6, 2E1, 3A4.

04. Indications

1. Treatment of depression
2. Analgesic adjunct in chronic pain and peripheral neuropathies
3. Attention-deficit/hyperactivity disorder (ADHD)
4. Bulimia

05. Loading dose

Not required. Start with a low dose (ie. 25 or 50 mg/day) and increase gradually according to clinical response and tolerance of adverse effects.

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

06. Maintenance dose

The usual adult dose is 100-200 mg as a single night-time dose or in divided daily doses. The required dose is variable depending on the individual pharmacokinetics.

07. Notes on administration

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 desipramine treatment, or after adding or removing a drug which may interact with desipramine.

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

09. Dose individualisation

The individual variability in metabolism and elimination (10-30fold) means that a wide range of drug concentrations can result for a given dose. The dose may need to be reduced in liver or renal disease.

10. Adverse effects

Adverse reactions: frequency not defined.
CNS: tremor (dose related), dizziness, drowsiness, headache, confusion, delirium, hallucinations, nervousness, restlessness, parkinsonian syndrome, insomnia, disorientation, anxiety, agitation, hypomania, exacerbation of psychosis, incoordination, seizures, extrapyramidal symptoms
CVS: arrhythmias, orthostatic hypotension (early in treatment at low doses) hypotension, hypertension, palpitations, heart block, tachycardia, myocarditis
DERM: alopecia, photosensitivity, skin rash, urticaria alopecia, photosensitivity, skin rash, urticaria
ENDO: breast enlargement, galactorrhoea, SIADH
EYES: blurred vision, disturbances of accommodation, mydriasis, increased intraocular pressure
GI: xerostomia, decreased lower oesophageal sphincter tone may cause GE reflux, constipation, nausea, unpleasant taste, weight gain/loss, anorexia, abdominal cramps, diarrhoea, heartburn
GU: difficult urination, sexual dysfunction, testicular oedema
HAEM: agranulocytosis, eosinophilia, purpura, thrombocytopenia
LIVER: cholestatic jaundice, increased liver enzymes, hepatitis
MUSC/SKEL: fine muscle tremors, weakness, numbness, tingling, paraesthesia of extremities, ataxia
MISC: diaphoresis (excessive), allergic reactions

11. Drug interactions

Desipramine 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 desipramine concentrations at "standard doses".

Drugs that may increase desipramine concentration (mostly by CYP2D6 inhibition)
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.

Desipramine may increase concentrations of the following drugs
Warfarin: Desipramine increases the half-life of Warfarin, increasing anticoagulant activity - monitor prothrombin ratios closely.

Pharmacodynamic interactions:

Via neurotransmitter effects:

Monoamine oxidase inhibitors - risk of serotonin syndrome: hyperpyrexia, hypertension, tachycardia, confusion, seizures and death have been reported. Desipramine 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 desipramine, which may cause severe headache or even death.

Antihypertensive drugs: Desipramine antagonises the hypotensive effects of clonidine, methyldopa, 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.

12. Factors that may give a false assay result

All tricyclic anti-depressants may interfere in assays involving other tricyclic anti-depressants. Concentrations 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

Desipramine acts primarily by noradrenaline selective reuptake inhibition.

16. Key references

1. Friedel RO. Relationship of desipramine plasma levels to therapeutic response: a critical reappraisal of the data. J Clin Psychiatry 45(10Pt2):46-9. Oct 1984
2. DRUGDEX Micromedex Inc., Denver,USA,2003
3. Medsafe - Desipramine data sheet, Mar 1999.

17. Last updated

June 2003