DOTHIEPIN

01. Assay details

No assay available

02. Therapeutic range

300-1200 nmol/L

How well established:

A number of studies have attempted to establish a relationship between plasma concentration and clinical effect for dothiepin. The majority have not shown any relationship in patients taking doses between 25mg and 225mg/day in a single dose. This is despite globally good clinical response in these patients. However there does seem to be a threshold plasma concentration (100ug/L, approx.300nmol/L) below which there is no reliable clinical effect. There was no good correlation between weight-corrected daily dothiepin dose and either dothiepin or nordothiepin (a metabolite) plasma concentrations. Weak correlations between daily weight corrected dose and plasma concentrations of two other active metabolites (dothiepin-S-oxide, nordothiepin-S-oxide) have been found. Monitoring drug concentrations may still be indicated to avoid toxic side effects at, or above, the upper limit of the quoted reference range, particularly given the poor correlation between drug dosage and plasma concentrations. The ratio of dothiepin to nordothiepin (ratio >1.1) has been used as a measure of compliance.

03. Pharmacokinetics

F: 0.3 (1st pass metabolism)	**Vd** (L/kg): 45	**Cl** (L/h/kg): 1.4	**t½:** 22hrs (range11-40 hrs)
Fe: <0.05	**Elimination route:** Extensive hepatic metabolism: N-demethylation, S-oxidation.		
CYP: unknown: probably 2D6 + 3A4		**Protein binding:** 0.8-0.9	

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:

- Dothiepin is readily absorbed. Peak plasma concentrations are achieved within 2-4 hours.
- Steady state concentrations are achieved within 12 days (either once-daily or three times daily administration).
- Elimination half lifes: 23-46 hrs for dothiepin metabolites.
- In the elderly, clearance is reduced, volume of distribution is diminished and AUC increased.

04. Indications

1. Depression (efficacy indistinguishable from amitriptyline)
2. Anxiety (efficacy similar to amitriptyline, alprazolam)

3. Analgesia: significantly greater than placebo in psychogenic facial pain, idiopathic fibromyalgia syndrome or rheumatoid arthritis

05. Loading dose

Not required. Commence with a low dose and increase gradually over 2-3 weeks according to clinical response and tolerance of adverse effects, ie. "start low, go slow".

06. Maintenance dose

The starting dose is 75mg daily in divided doses or a single dose at night, increasing to 150mg daily according to the severity of illness.
Doses of up to 225mg daily have been used in hospital inpatients.
Recommended starting dose in the elderly: 50-75mg daily and increasing with caution.

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 10-16 hours after the last dose. Samples should be taken at steady state, at least 12 days after commencing therapy, or changing the dose, or adding or removing a drug which may interact with amitriptyline

09. Dose individualisation

The wide range of interindividual variability in metabolism and elimination rates means that doses vary widely based on drug concentration monitoring. The dose may need to be reduced in liver disease (impaired metabolism)

10. Adverse effects

Adverse effects have been reported in 51% of patients (incidence of side effects lower than amitriptyline).

>10%

CNS: drowsiness 17%, dizziness 10%
GI: dry mouth 24%, gastrointestinal disorders (nausea, vomiting, diarrhoea) 11%

1-10%

CNS: tremor 8.5%, insomnia 5,7%, blurred vision 4.5%, headache 2%
CVS: palpitations 3.0%, hypotension 2%
MISC: sweating 6%, weight gain 3.5%

<1%

CVS: cardiac dysrhythmias 0.1%

11. Drug interactions

Dothiepin is structurally similar to amitriptyline and is probably metabolised predominantly by CYP 2D6, which is subject to genetic polymorphism - 5-10% of Caucasians and 1-2 % of Asian/ Polynesians are poor metabolisers which may result in increased drug concentrations at "standard doses".

Drugs that may increase dothiepin concentration

Phenothiazines, SSRI antidepressants - particularly fluoxetine and paroxetine, cimetidine, other tricyclic antidepressants, quinidine (via 2D6 inhibition), amiodarone, macrolides (3A4 and 1A2 inhibition), ketoconazole (3A4 inhibition), methylphenidate.

Drugs that may reduce dothiepin concentrations

Carbamazepine, phenytoin, nicotine, rifampicin- by inducing the metabolism of tricyclic via CYP 1A2 and 3A4.

Dothiepin may increase concentrations of the following drugs

Warfarin: Dothiepin 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. Tricyclic anti-depressants should not be used in conjunction with a MAOI, or within 14 days of stopping one.

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

Antihypertensive drugs: Dothiepin may antagonise the hypotensive effects of guanethidine and clonidine.

Sedation: Cumulative with alcohol and other sedatives.

Anticholinergic effects: cumulative with other anticholinergic drugs.

QT prolongation: additive with macrolides, antihistamines, antiarrhythmics, 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

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14. Dialysability

Not removed by dialysis because of large volume of distribution.

15. Comments

The efficacy and adverse effects for dothiepin offer no advantage over other tricyclic antidepressants when taken in therapeutic doses. The apparent excess mortality when taken in overdose has led to the suggestion that dothiepin should not be used as a first-line treatment.

16. Key references

1. Drugs. 1989, 38: 1-174.
2. Buckley NA, Dawson AH, Whyte IM, Henry DA. Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. Lancet 1994, 343: 159-162.
3. Ilett KF, et al. Plasma concentrations of dothiepin and its metabolites are not correlated with clinical efficacy in major depressive illness. Therapeutic Drug Monitoring 1993, 15; 351-357.

17. Date

Dec 2000