AMITRIPTYLINE

01. Assay details

CH Labs Test Reference Guide

02. Therapeutic range

Sum of amitriptyline and nortriptyline (active metabolite) concentrations = 360-900 nmol/L

How well established:
The therapeutic range for the treatment of major depression with amitriptyline is not well established. Controlled studies and meta-analyses have yielded conflicting results and the exact limits are not well defined. The proposed lower limit for combined amitriptyline and nortriptyline (active metabolite) concentrations ranges from 250-500 nmol/L. The proposed upper limit ranges from 500-900 nmol/L. The American Psychiatric Association has set a therapeutic range of 430-900 nmol/L. Most serious CNS and cardiac side effects are dose-dependent and significant toxicity occurs at amitriptyline concentrations greater than 1500 nmol/L.

Amitriptyline is subject to highly variable metabolism and elimination, and it has a narrow therapeutic index, so that although the target range is not well-defined, drug concentration monitoring does optimise use and safety. TDM enables assessment of individual pharmacokinetics for dose titration (2D6 polymorphism, differences in clearance etc) and interpretation of an unexpected clinical response (inadequately treated depression vs CNS toxicity). It improves precision for a therapeutic trial, ensuring a patient has steady state concentrations within a defined range for an adequate period of time. TDM is also useful in assessing compliance, and quantifying significant drug interactions.

Researchers advocate measuring a single amitriptyline concentration at steady state soon after starting treatment to determine the patient's drug handling. As the pharmacokinetics of amitriptyline are linear, the dose needed to produce a desired concentration can then be extrapolated from the dose: concentration ratio, unless interacting drugs are added or discontinued or the patient's metabolic state changes.

03. Pharmacokinetics

<table>
<tr><td>F: 0.5 (first pass metabolism)</td><td>Vd (L/kg): 15 (12-18)</td><td>Cl (L/h/kg): 0.7 (0.5-0.9)</td><td>t½: Ami 21 (+/-5) hrs, Nor 31 (+/-13) hrs</td></tr>
<tr><td>Fe: <0.05</td><td colspan="3">Elimination route: Metabolism - N-demethylation to active metabolite nortriptyline, 10-hydroxylation and conjugation</td></tr>
<tr><td colspan="2">CYP: 2D6 (genetic polymorphism), 1A2, 2C9, 3A4</td><td colspan="2">Protein binding: 0.95</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 7 days, but clinical antidepressant effect not apparent for 2-3 weeks. Amitriptyline is demethylated to its active metabolite

nortriptyline, which has a longer half-life. There is a 10-fold individual variation in metabolism of amitriptyline and nortriptyline due to genetic polymorphism of CYP 2D6, and variations in clearance and volume of distribution

04. Indications

1. Major depressive episode
2. Nocturnal enuresis
3. Migraine prophylaxis
4. Tension headache
5. Neuropathic pain

05. Loading dose

Not required. Give low dose, ie. 25 mg daily, and increase gradually according to clinical response and tolerance of adverse effects, ie."start low, go slow"

06. Maintenance dose

The usual adult dose is 75-150 mg as a single night-time dose, but the dose varies depending on individual pharmacokinetics.
Lower doses and use of the lower part of the therapeutic range are recommended in the elderly because of reduced clearance and increased susceptibility to side effects.

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 10 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 (10-30 fold) 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

10%

CNS: dizziness, drowsiness, headache
GI: dry mouth, constipation, diarrhoea, dyspepsia, increased appetite, nausea, weakness, unpleasant taste

1-10%

CNS: restlessness, insomnia, sedation, weakness, fatigue, anxiety, impaired cognitive function, seizures, tremor, extrapyramidal symptoms
CVS: hypotension, postural hypotension, arrhythmias, tachycardia, sudden death
EYES: eye pain, blurred vision
MISC: sweating, impairment of sexual function, urinary retention

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<1%

DERM: alopecia, photosensitivity
ENDO: breast enlargement, galactorrhoea, SIADH
HAEM: leukopaenia, eosinophilia, agranulocytosis
LIVER: cholestatic jaundice, abnormal LFTs
MISC: testicular swelling, raised intraocular pressure, allergic reactions

11. Drug interactions

Amitriptyline is metabolised by CYP 2D6 which is subject to genetic polymorphism - 5-10% of Caucasians and 1-2 % of Asian/ Polynesians are poor metabolisers, resulting in increased Amitriptyline concentrations at "standard doses".

Drugs that may increase amitriptyline concentrations:

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 amitriptyline concentrations

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

Amitriptyline may increase concentrations of the following drugs

Warfarin: Amitriptyline 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. Amitriptyline 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 Amitriptyline, which may cause severe headache or even death.

Antihypertensive drugs: Amitriptyline antagonises 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.

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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 large volume of distribution

15. Comments

Nil.

16. Key references

1. Linder MW, Keck PE. Standards of laboratory practice: antidepressant drug monitoring. Clinical Chemistry 1998; 44(5): 1073-1084.
2. Preskorn S.H., Fast G.H., "Therapeutic drug monitoring for antidepressants: efficacy, safety, and cost effectiveness. Journal of Clinical Psychiatry 52:6 (suppl) June 1991.
3. Dollery et al. Therapeutic Drugs
4. Drugdex

17. Date

Jul 2000