Pharmacokinetics

Trazodone is readily absorbed from the gastrointestinal tract although absorption is affected by food. When trazodone is taken shortly after a meal there may be an increase in the amount absorbed, a decrease in the maximum concentration, and a lengthening in the time to maximum concentration compared with the fasting state; peak plasma concentrations occur about one hour after a dose when taken on an empty stomach and after about 2 hours when taken with food. Protein binding is reported to be about 89 to 95%.

Trazodone is extensively metabolised in the liver and paths of metabolism include *N*-oxidation and hydroxylation. It is metabolised to its active metabolite *m*-chlorophenylpiperazine via the cytochrome P450 isoenzyme CYP3A4. Trazodone is excreted mainly in the urine almost entirely in the form of its metabolites, either in free or in conjugated form: some is excreted in the faeces via biliary elimination. The elimination of trazodone from the plasma is biphasic, with a terminal elimination half-life of 5 to 9 hours.

Small amounts of trazodone are distributed into breast milk.

◊ References.

1. Bayer AJ, *et al*. Pharmacokinetic and pharmacodynamic characteristics of trazodone in the elderly. *Br J Clin Pharmacol* 1983; **16:** 371–6.
2. Nilsen OG, Dale O. Single dose pharmacokinetics of trazodone in healthy subjects. *Pharmacol Toxicol* 1992; **71:** 150–3.
3. Nilsen OG, *et al*. Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. *Pharmacol Toxicol* 1993; **72:** 286–9.

Uses and Administration

Trazodone is a triazolopyridine antidepressant chemically unrelated to other classes of antidepressants. It blocks the reuptake of serotonin at presynaptic neurones and has an action at 5-HT_1 receptors. Trazodone is also an antagonist at 5-$HT_{2A/2C}$ receptors. Unlike the tricyclic antidepressants, trazodone does not inhibit the peripheral reuptake of noradrenaline, although it may indirectly facilitate neuronal release. Trazodone blocks central α_1-adrenoceptors and appears to have no effect on the central reuptake of dopamine. It does not appear to have very significant antimuscarinic properties, but has a marked sedative action.

For the treatment of **depression** trazodone hydrochloride is given in oral doses of 150 mg daily initially; total daily dosage may be increased by 50 mg every 3 or 4 days up to 300 to 400 mg daily if necessary. The daily dosage may be divided throughout the day after food or be given as a single dose at night. Divided daily dosages of up to 600 mg may be given in severe depression in hospitalised patients. A suggested initial dose in elderly and other susceptible patients is 100 mg daily, and total daily doses above 300 mg are unlikely to be needed in these patients.

In the treatment of **anxiety** (p.952), trazodone hydrochloride is given in an initial oral dose of 75 mg daily increasing to 300 mg daily if necessary.

As with other antidepressants, trazodone should be withdrawn gradually.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Trazodone has a different biochemical profile from both the tricyclics and the SSRIs.

References.

1. Weisler RH, *et al*. Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 1994; **14:** 170–9.

Disturbed behaviour. Trazodone has produced beneficial results[1-3] when tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (see p.954). Some[4] also consider that, in the management of dementia, trazodone might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant of or unresponsive to antipsychotics. However, the evidence for such use is poor; a systematic review on the use of trazodone in the treatment of behavioural and psychological symptoms of dementia found that the evidence from randomised, placebo-controlled studies was insufficient for any recommendations to be made.[5] The risk of adverse effects such as sedation and orthostatic hypotension, which may be particularly problematic in the elderly, should also be considered.[4]

1. Pasion RC, Kirby SG. Trazodone for screaming. *Lancet* 1993; **341:** 970.
2. Lebert F, *et al*. Behavioral effects of trazodone in Alzheimer's disease. *J Clin Psychiatry* 1994; **55:** 536–8.
3. Sultzer DL, *et al*. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am J Geriatr Psychiatry* 1997; **5:** 60–9.
4. Rabins PV, *et al*. APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
5. Martinon-Torres G, *et al*. Trazodone for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 24/11/05).

Sexual dysfunction. Priapism can occur as an adverse effect of trazodone (see Effects on Sexual Function in Adverse Effects, above) and this has led to trials of oral trazodone for the treatment of erectile dysfunction (p.2179). Positive responses have been reported, both with yohimbine[1] and alone.[2] However, there appear to have been few controlled studies and a systematic review[3] considered some of these to be either small, brief, or methodologically weak. Meta-analysis[3] of data from 6 studies did not find trazodone to be superior to placebo but subgroup analysis possibly suggested a better outcome in patients with psychogenic erectile dysfunction and in those given doses of 150 to 200 mg daily.

1. Montorsi F, *et al*. Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. *Urology* 1994; **44:** 732–6.
2. Lance R, *et al*. Oral trazodone as empirical therapy for erectile dysfunction: a retrospective review. *Urology* 1995; **46:** 117–20.
3. Fink HA, *et al*. Trazodone for erectile dysfunction: a systematic review and meta-analysis. *BJU Int* 2003; **92:** 441–6.

Substance dependence. The antidepressant, anxiolytic, and sedative properties of trazodone have been reported to have been useful when tried in patients having withdrawal syndromes from a variety of substances including alcohol (p.1626),[1] cocaine (p.1860),[2] and benzodiazepines (p.987).[3-5]

1. Le Bon O, *et al*. Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 2003; **23:** 377–83.
2. Small GW, Purcell JJ. Trazodone and cocaine abuse. *Arch Gen Psychiatry* 1985; **42:** 524.
3. Ansseau M, De Roeck J. Trazodone in benzodiazepine dependence. *J Clin Psychiatry* 1993; **54:** 189–91.
4. Rickels K, *et al*. Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology (Berl)* 1999; **141:** 1–5.
5. Petrovic M, *et al*. A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients: success rate and effect on subjective sleep quality. *Int J Geriatr Psychiatry* 1999; **14:** 754–60.

Preparations

USP 31: Trazodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Taxagon; ***Austria:*** Trittico; ***Belg.:*** Nestrolan; Trazolan; ***Braz.:*** Donaren; ***Canad.:*** Desyrel; Trazorel†; ***Chile:*** Diapresan; Trant; Trittico; Tronsalan; ***Cz.:*** Trittico AC; ***Fin.:*** Azona; ***Ger.:*** Thombran; ***Gr.:*** Trittico; ***Hong Kong:*** Trittico; ***Hung.:*** Depsan†; Trittico; ***Irl.:*** Molipaxin; ***Israel:*** Depyrel†; Trazodil; Trittico; ***Ital.:*** Trittico; ***Mex.:*** Sideril; ***Neth.:*** Trazolan; ***Pol.:*** Trittico; ***Port.:*** Trazone; Triticum; ***Rus.:*** Trittico (Триттико); ***S.Afr.:*** Molipaxin; ***Singapore:*** Trittico; ***Spain:*** Deprax; ***Switz.:*** Trittico; ***Thai.:*** Desirel; Trazo; ***Turk.:*** Desyrel; ***UK:*** Molipaxin; ***USA:*** Desyrel†; ***Venez.:*** Trittico.

Trimipramine *(BAN, USAN, rINN)*

IL-6001; 7162-RP; Trimeprimine; Trimipramiini; Trimipramin; Trimipramina; Trimipraminum. Dimethyl{3-(10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl-2-methyl)propyl}amine.

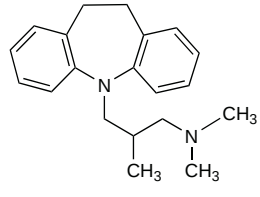
Тримипрамин

$C_{20}H_{26}N_2$ = 294.4.

CAS — 739-71-9.

ATC — N06AA06.

ATC Vet — QN06AA06.



Trimipramine Maleate *(BANM, USAN, rINNM)*

Maleato de trimipramina; Trimipramiinimaleaatti; Trimipramin maleinát; Trimipramine Hydrogen Maleate; Trimipramine, maléate de; Trimipramini maleas; Trimipraminmaleat; Trimipramin-maleát; Trimipramino maleatas.

Тримипрамина Малеат

$C_{20}H_{26}N_2,C_4H_4O_4$ = 410.5.

CAS — 521-78-8.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Trimipramine Maleate). A white or almost white crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

USP 31 (Trimipramine Maleate). A white to almost white crystalline powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Porphyria. Trimipramine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Trimipramine is readily absorbed after oral doses, peak plasma concentrations being obtained in 2 hours. It is metabolised in the liver to its major metabolite desmethyltrimipramine, which is active. Trimipramine is excreted in the urine mainly in the form of its metabolites. It is about 95% bound to plasma proteins. The plasma elimination half-life is reported to be about 23 hours.

◊ References.

1. Maurer H. Metabolism of trimipramine in man. *Arzneimittelforschung* 1989; **39:** 101–3.
2. Musa MN. Nonlinear kinetics of trimipramine in depressed patients. *J Clin Pharmacol* 1989; **29:** 746–7.

Uses and Administration

Trimipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It has marked antimuscarinic and sedative properties.

Trimipramine is given orally as the maleate although doses are expressed in terms of the base. Trimipramine maleate 34.9 mg is equivalent to about 25 mg of trimipramine. In the treatment of depression, the usual initial dose is the equivalent of trimipramine 50 to 75 mg daily, gradually increased as necessary to 150 to 300 mg daily. The recommended initial dose for the elderly in the UK is 30 to 75 mg daily, gradually increased as necessary. In the USA, the elderly and adolescents may be given 50 mg daily initially followed by gradual increments as necessary up to a maximum of 100 mg daily. Trimipramine may be given in divided doses during the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable and usually given at night.

Trimipramine has also been given orally as the hydrochloride and the mesilate; the mesilate has also been given intramuscularly.

Trimipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

BP 2008: Trimipramine Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Surmontil; ***Canad.:*** Apo-Trimip; Novo-Tripramine†; Rhotrimine; Surmontil†; ***Denm.:*** Surmontil; ***Fin.:*** Surmontil; ***Fr.:*** Surmontil; ***Ger.:*** Eldoral†; Herphonal; Stangyl; Trimidura; Trimineurin; ***Hong Kong:*** Surmontil; ***Hung.:*** Sapilent; ***India:*** Surmontil†; ***Irl.:*** Surmontil; ***Israel:*** Surmontil; ***Ital.:*** Surmontil; ***Neth.:*** Surmontil†; ***Norw.:*** Surmontil; ***NZ:*** Surmontil; Tripress; ***Philipp.:*** Surmontil; ***Port.:*** Surmontil; ***S.Afr.:*** Surmontil; Tydamine; ***Spain:*** Surmontil; ***Swed.:*** Surmontil; ***Switz.:*** Surmontil; Trimine; ***UK:*** Surmontil; ***USA:*** Surmontil; ***Venez.:*** Surmontil†.