Amitriptyline hydrochloride

CAS: 549-18-8
MF: C_{20}-H_{23}-N
MW: 313.87
pKa = 9.40
Solubility: Freely soluble in chloroform and alcohol. In water, 10.84 mg/l at 25 C° [1].

Major use
As an antidepressant drug [1].

Human toxicity
Coma, seizures, and cardiovascular effects are common after amitriptyline overdosage. Symptoms often appear within 4 hours of ingestion and are usually maximal at 24 hours; most patients regain consciousness within 36 hours, but, because of delayed absorption, long half lives and enterohepatic recycling, patients remain at risk for up to 4-6 days [3]. Cardiovascular effects include conduction abnormalities (prolonged PR interval, QRS widening, QTc prolongation, rightward shift in the terminal 40 milliseconds of the QRS axis), dysrhythmias (sinus tachycardia, AV block, torsades de pointes, ventricular tachycardia and fibrillation) and hypotension. Severe cardiac toxicity generally develops within six hours, although ECG changes may persist beyond 48 hours. Neurological effects - Mental status can deteriorate rapidly; effects include lethargy, confusion including anticholinergic delirium, coma and seizures. CNS effects generally develop within 6 hours and may persist 24 to 48 hours [2].

Respiratory depression, aspiration and ARDS may complicate severe overdoses. Anticholinergic effects (mydriasis, tachycardia, urinary retention, decreased gastrointestinal motility) are common, but may be masked in severe overdose. Rhabdomyolysis and renal failure may result from prolonged seizures or coma [2].

Respiratory depression may occur rapidly after overdose. Both hyperthermia and hypothermia have been reported. Hypotension occurs with severe overdose. Tachycardia is a common anticholinergic and early sympathomimetic effects [2].

Lethal symptoms: CNS excitation/depression, Heart arrythmias/arrest [4].

Therapeutic dose: Usual initial dose is 75 mg/day in divided doses. Dose can be increased to 150 mg/day in outpatients and 200 to 300 mg/day in hospitalized patients [2].

Poisonings with 2g of tricyclic antidepressants have a potentially fatal outcome and severe intoxication can be expected at doses above 1 g [2, 4].

Therapeutic, toxic, and lethal blood concentrations: 0.05-0.2 mg/l, >0.5 mg/l, and 10-20 mg/l, respectively [1].

Kinetic data
Absorption: Amitriptyline is completely but slowly absorbed from the gastrointestinal tract after oral administration [3]. Bioavailability is 30 to 60% [2]. Since amitriptyline slows gastrointestinal transit time, absorption can be delayed, particularly at an overdose [3].

Kinetics is biphasic [4].

Volume of distribution –11-18 l/kg [3, 4].

Distribution: Because of its high lipophilicity, amitriptyline is widely distributed throughout the body and extensively bound to tissue and plasma proteins [3]. Amitriptyline passages the blood-brain barrier freely [4]. Accumulates in liver, kidney, lung, heart and CNS [4].

The plasma half-life: 10-28 hours [3, 4].

Plasma peak concentration: 4-8 hours [3] and 20 h at overdose [4].

Protein binding: 96.4 +/- 0.8% [2].

Passage of brain-blood barrier: free [4].

Metabolism and excretion
Amitriptyline is extensively metabolized in the liver by N-demethylation, hydroxylation, and conjugation. The microsomal enzyme systems responsible for metabolism are enhanced by barbiturates, smoking, and alcohol. All tricyclic antidepressant drugs undergo enterohepatic circulation [2].

The following metabolites have been found:
a. Nortriptyline (active)
b. 10-hydroxy-nortriptyline
c. Z-10-hydroxy-nortriptyline
d. E-10-hydroxy-nortriptyline [2].

Metabolites more toxic than amitriptyline: Nortriptyline [4].

Excretion: Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either in conjugated or non-conjugated form. Acidification of the urine to a pH of 4 increased the urinary excretion of amitriptyline and its metabolite nortriptyline 1000-fold; however, urinary excretion accounted for only 5% of the dose in volunteers during 72 hours [3, 4].

Toxicological mechanisms
Blocks the neuronal reuptake of norepinephrine, serotonin, and dopamine and prevents reuptake of heart noradrenaline [3, 4].
It has also been postulated that tricyclics exert their major toxicity via a non-specific membrane-stabilizing effects, similar to other drugs such dextropropoxyphene, chlorpromazine, and the beta-blockers [2].

Target organs*:* CNS and heart [4].

References

1. HSDB, TOXNET (2005).
2. Poisindex, Thomson Micromedex (2005).
3. *Therapeutic drugs*, ed. C. Dollery, Churchill Livingstone (1991).
4. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, B., Hallander, S., Walum, E. & Bondesson, I. (1998) MEIC Evaluation of Acute Systemic Toxicity: Part V. Rodent and Human Toxicity Data for the 50 Reference Chemicals, ATLA 26, 571-616.

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