

20 - A. Tricyclic antidepressants

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© SPMM Course 4. Clinically relevant kinetics and interactions: A. Tricyclic antidepressants: □ The tricyclics are orally well absorbed but have variable time to achieve peak plasma concentration (1 to 12 h). □ Many of them have active metabolites – see table below. □ Nearly 7-9% Caucasians are slow metabolizers (measured by debrisoquin hydroxylation) of tricyclics due to CYP2D6 polymorphism (Up to a 40 times difference in plasma TCA concentrations can occur as a result). □ Children clear more tricyclics from their body whereas the elderly clear less. □ Most tricyclics have a long half-life (close to 24 h) that allows once-daily dosing. They readily cross lipid barriers such as blood-brain barrier and placenta. □ They are extensively bound to plasma proteins e.g. Imipramine 80-95%. □ For TCAs plasma (not serum) levels are measured to assess therapeutic dosing. The levels are determined after 5-7 days when steady state is reached, and 8-12hrs after last dose to avoid false peaks earlier when absorption is occurring. A sigmoidal curve where proportional doseresponse plateaus at a particular dose is noted for imipramine and desipramine. For nortriptyline a clear therapeutic window is seen between 50 to 150ng/ml. This inverted U is not due to decreased responsivity secondary to side-effects.

□ Amitriptyline and clomipramine decrease the metabolism of morphine and may contribute to opioid toxicity through UDP glucuronyl transferase interaction. (Chadwick 2005)

Antidepressant Active metabolite Imipramine desipramine Amitriptyline nortriptyline Trazodone, nefazodone mCPP Fluoxetine norfluoxetine Sertraline desmethylsertraline

© SPMM Course Drugs Mechanism Effect Quinidine, cimetidine, fluoxetine, paroxetine, phenothiazines, disulfiram, methylphenidate Inhibit TCA metabolism Increase plasma TCA levels Smoking, phenytoin, carbamazepine, OC pills and barbiturates Induce metabolism Reduce TCA levels Phenothiazines Mutual inhibition of metabolism Both antipsychotic and TCA levels increase Anticoagulants TCAs increase warfarin levels High risk of bleeding Clonidine TCAs reduce clonidine levels Hypertensive crisis MAOIs Synergistic serotonergic enhancement esp. clomipramine TCAs reduce tyramine entry via monoamine reuptake channels Higher risk of serotonin syndrome Lower risk of cheese reaction L-dopa TCAs reduce absorption of L-dopa Lowers L-dopa efficacy in Parkinsonism Morphine Amitriptyline and clomipramine decrease the metabolism through UDP glucuronyl transferase interaction Increased opioid toxicity

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