10 - E. Metabolism of drugs

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© SPMM Course for lithium carbonate or Clozaril vs. zaponex for clozapine. E. Metabolism of drugs: Xenobiotics refer to the mechanism by which a foreign agent such as a drug molecule is metabolized and eliminated from our body. The metabolism or biotransformation of a drug renders it less lipid-soluble and more water-soluble. Therefore, the products of such metabolism are more readily eliminated from the body. The liver is the principal site of metabolism, but metabolism can occur in the gastrointestinal tract, plasma, lungs, kidneys, suprarenal cortex, placenta, skin, and lymphocytes. The four major metabolic routes are oxidation, reduction, hydrolysis, and conjugation. There are 2 phases of drug metabolism. Phase 1 metabolism includes oxidation, reduction and hydrolysis (often mediated by CYP system, see below), as a result of which a molecule (could be active or inactive) suitable for conjugation is produced. It is not essential that a drug undergo phase 1 metabolism in order to undergo phase 2 metabolism e.g. lorazepam, temazepam and oxazepam undergo direct phase 2 reactions. (As a result, in patients with alcoholic liver disease, oxazepam is favoured for alcohol detoxification instead of chlordiazepoxide which requires intact liver enzymes for phase 1 clearance) Phase 2 metabolism involves conjugation reactions such as glucuronidation, as a result of which polar compounds (mostly inactive) that are excretable in bile or urine are formed. A drug or drug metabolite from a phase 1 reaction is conjugated to a polar (water soluble) group by phase 2 metabolism. The result of this would be a water-soluble conjugate that can undergo renal excretion easily if it has a relative molecular mass of less than 300. If the relative molecular mass is more than 300, then the excretion would take place through bile. Metabolism usually yields inactive metabolites that are more polar and are easily excreted. Metabolism could also transfer some inactive pro-drugs into therapeutically active metabolites. Cytochrome P450 enzymes: Most psychotherapeutic drugs are oxidized by the hepatic cytochrome P-450 enzyme system. The human CYP enzymes comprise several distinct families and subfamilies. The most studied is CYP2D6. Together with CYP3A4, this constitutes nearly 90% of all psychotropic metabolism. The CYP enzymes are responsible for the inactivation of most psychotherapeutic drugs. These enzymes act primarily in the endoplasmic reticulum of the hepatocytes and cells of the intestine. Therefore, any cellular pathophysiology caused by viral hepatitis or cirrhosis may affect the

© SPMM Course efficiency of drug metabolism by the CYP enzymes. There are 3 ways in which drug interactions may influence the CYP system. It includes induction, non-competitive inhibition, and competitive inhibition. Genetic variations in the hepatic enzymes affect the rate of metabolism. Between 5 and 10% of Caucasians lack the enzyme CYP2D6 and are poor metabolizers of corresponding substrates. Up to 15-20% of East Asians are poor metabolizers of CYP2C19 substrates. The table below gives the list of some psychotropics with CYP-mediated drug

interactions. Some of the important pharmacokinetic drug interactions involving psychotropics include SSRIs especially fluvoxamine and fluoxetine inhibit CYP system. Fluoxetine increases plasma tricyclic antidepressants via 2D6 and 2C19. Fluvoxamine increases plasma clozapine concentrations. Clozapine levels may be increased 10-fold by the addition of fluvoxamine, which can induce seizures. Carbamazepine decreases the plasma concentration of several drugs including contraceptive pills. Most antidepressants can inhibit the metabolism of warfarin via a complex mechanism resulting in potentially serious bleeding. Tricyclics and haloperidol compete with each other for same metabolic enzymes. Carbamazepine and phenobarbitone can induce their own metabolism. Alcohol, smoking and brussel sprouts are CYP inducers. Grapefruit juice and caffeine inhibit CYP system

CYP enzyme Major psychotropics metabolized Effects of psychotropics CYP2D6 All TCAs, fluoxetine, paroxetine, trazodone, nefazodone, valproate, all neuroleptics, risperidone. Paroxetine, to some extent fluoxetine, neuroleptics, amitriptyline and clomipramine inhibit 2D6. CYP3A4 (Most prominent in gut wall mucosa) Clomipramine, fluvoxamine, mirtazapine, nefazodone, Carbamazepine, most benzodiazepines. Stimulated by carbamazepine and barbiturates. Inhibited by calcium channel blockers, fluoxetine, and nefazodone. Smoking induces CYP1A2 via PAH.

© SPMM Course Autoinduction: Carbamazepine is metabolized by the hepatic CYP2D6, synthesis of which in turn is induced by carbamazepine. As a result of this autoinduction, the rate of metabolism of carbamazepine (and other P450 substrates) gradually increases over the first several weeks of treatment. The initial steady state may be attained within 4 to 5 days, but autoinduction may delay final steady state until 3 to 4 weeks after treatment initiation. Hence, the level of carbamazepine must be monitored, and its dose often needs to be raised during this early phase of treatment. Chlorpromazine can also induce its own metabolism to some extent. Effect of smoking and caffeine: Smoking and caffeine affect glucuronidation reaction via UGT enzyme and CYP1A2. Drugs which are not dependent on CYP1A2 or UGT for their metabolism are unaffected by smoking or caffeine consumption. For example, risperidone and aripiprazole (metabolized by CYP2D6 and CYP3A), quetiapine (mainly metabolized by CYP3A), and ziprasidone (mainly metabolized by an aldehyde oxidase and CYP3A) are unaffected. But the metabolism of clozapine and olanzapine is mainly dependent on CYP1A2 and UGTs. Because caffeine competitively inhibits CYP1A2, it increases the levels of clozapine and olanzapine while Polyaromatic Hydrocarbons (PAH) in cigarettes induce the enzyme. The effects of inhibitors (caffeine) are seen sooner than those of inducers (smoking), which require fresh synthesis of CYP1A2 enzymes to produce an effect (de Leon, 2004).

ALCOHOL BREAKDOWN

Four distinct pathways for ethanol degradation have been described - 3 oxidative pathways and 1 non-oxidative pathway.

Each of the oxidative pathways starts with the oxidation of ethanol to acetaldehyde, which is then oxidized to acetate for subsequent extra-hepatic activation to acetylCoA. The first pathway which contributes for

> 90% breakdown in Caucasians, utilizes cytoplasmic alcohol dehydrogenase, the second oxidative pathway uses the endoplasmic reticulum Microsomal Ethanol Oxidizing System (MEOS or CYP450 2E1) and the third pathway uses peroxisomal catalase.

The nonoxidative pathway for ethanol metabolism is less well characterized but produces fatty acid ethyl esters (FAEEs) as primary end products.

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