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Pharmacokinetic interactions1–4

Pharmacokinetics CHAPTER 11 Drug interactions with alcohol Drug interactions with alcohol are complex. Many patient-related and drug-related factors need to be considered. It can be difficult to predict outcomes accurately because a number of processes may occur simultaneously or consecutively. Pharmacokinetic interactions1–4 Alcohol (ethanol) is absorbed from the gastrointestinal tract and distributed in body water. The volume of distribution is smaller in women and the elderly where plasma levels of alcohol will be higher than in young males for a given intake of alcohol. Ingested alcohol is subject to metabolism by alcohol dehydrogenase (ADH). A small proportion of alcohol is metabolised by ADH in the stomach. The remainder is metabolised in the liver by ADH, and by CYP2E1. At low alcohol concentrations only ADH is active; CYP2E1 only begins to contribute when concentrations approach the legal driving limit of many countries (0.08%).5 CYP2E1 plays a minor role in occasional drinkers but is an important and inducible metabolic route in chronic, heavy drinkers. The induction of CYP2E1 accounts for the apparent tolerance of alcohol in heavy drinkers.6 CYP1A2, CYP3A4 and many other CYP enzymes also play a minor role in the metabolism of ethanol.7,8 CYP2E1 and ADH convert alcohol to acetaldehyde. This is both the toxic substance responsible for the unpleasant symptoms of the ‘Antabuse reaction’ (e.g. flushing, headache, nausea, malaise) and the compound implicated in hepatic damage. It may have psychotropic effects – ethanol is metabolised to acetaldehyde by CYP2E1 in the brain.9 The enzyme catalase is also known to metabolise alcohol to acetaldehyde in the brain and elsewhere.10 Acetaldehyde is further metabolised by aldehyde dehydrogenase to acetic acid and then to carbon dioxide and water (Figure 11.1).

- This is a minor route in occasional drinkers, and a major route in heavy drinkers and at higher blood alcohol concentration. The ubiquitous enzyme catalase is also able to metabolise ethanol but its overall contribution is not known. Alcohol dehydrogenase (ADH) CYP2E1* Aldehyde dehydrogenase Ethanol Acetaldehyde Ethanoic acid CYP3A4 CYP1A2 Water + CO2 CYP2B6 Figure 11.1 Metabolism of alcohol.

 All of the enzymes involved in the metabolism of alcohol exhibit genetic polymorphism. For example, the majority of people of

north Asian origin are poor metabolisers via aldehyde dehydrogenase.11 Enzyme function can change in response to alcohol. Chronic consumption of alcohol induces CYP2E1 and CYP3A4. The effects of alcohol on other hepatic metabolising enzymes have been poorly studied. Table 11.8 lists drugs that inhibit ADH and aldehyde dehydrogenase. Interactions are difficult to predict in alcohol misusers because two opposing processes may be at work: competition for enzymatic sites during periods of consumption/ intoxication (increasing drug plasma levels) and enzyme induction prevailing during periods of sobriety (reducing drug plasma levels10). In chronic drinkers, particularly those who binge-drink, blood levels of prescribed drugs may reach toxic levels during periods of intoxication with alcohol and then be sub-therapeutic when the patient is sober. Even in non-intoxicated individuals there is some evidence that co-administered alcohol confers competitive inhibition of CYP3A4, leading to increased exposure to drugs metabolised by this enzyme (Table 11.9).15 This makes it very difficult to optimise treatment of physical or mental illness. Table 11.8 Drugs that inhibit alcohol dehydrogenase and aldehyde dehydrogenase. Enzyme Inhibited by Potential consequences Alcohol dehydrogenase Aspirin H2 antagonists Reduced metabolism of alcohol resulting in higher plasma levels for longer periods of time Aldehyde dehydrogenase Chlorpropamide Disulfiram Griseofulvin Isoniazid Isosorbide dinitrate Metronidazole* Nitrofurantoin Sulphamethoxazole Tolbutamide Reduced ability to metabolise acetaldehyde leading to ‘Antabuse’ type reaction: facial flushing, headache, tachycardia, nausea and vomiting, arrhythmias and hypotension *Evidence that metronidazole has any effect on aldehyde dehydrogenase is surprisingly weak.12–14 Table 11.9 Co-administration of alcohol and substrates for CYP2E1 and CYP3A4.5,6,16 Substrates for enzyme (note: this is not an exhaustive list) Effects in an intoxicated patient Effects in a chronic, sober drinker CYP2E1 Isoniazid Paracetamol Phenobarbitone Warfarin Zopiclone Competition between alcohol and drug leading to reduced rates of metabolism of both compounds. Increased plasma levels may lead to toxicity Activity of CYP2E1 is increased up 10-fold Increased metabolism of drugs potentially leading to therapeutic failure

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