INTERACTIONS BETWEEN ALCOHOL AND DRUGS

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SUMMARY

In western society alcohol consumption is common as is the use of therapeutic drugs. It is not surprising therefore that concomitant use of these should occur frequently. The consequences of this combination vary with the dose of drug, the amount of alcohol taken, the mode of administration and the pharmacological effects of the drug concerned. Interactions may be pharmacokinetic or pharmacodynamic, and while coincidental use of alcohol may affect the metabolism or action of a drug, a drug may equally affect the metabolism or action of alcohol. Alcohol-drug interactions may differ with acute and chronic alcohol ingestion, particularly where toxicity is due to a metabolite rather than the parent drug. There is both inter- and intra-individual variation in the response to concomitant drug and alcohol use. Interactions are also age-dependent and become more frequent in the elderly, a group who are often using several drugs simultaneously. This article aims to give an overview of the principles behind alcohol-drug interactions, and to discuss in more detail some of those most commonly seen in clinical practice.

GENERAL PRINCIPLES

Alcohol consumption is widespread in many countries where it is taken for its pleasant taste and mood-altering effects. Unfortunately abuse of alcohol is also common, making it the foremost drug of abuse worldwide. Alcohol-related problems are a frequent reason for consulting the doctor, and are a contributory factor in 20-40% of hospital admissions.[1] Alcohol-associated medical disorders are common in the elderly. In addition, alcoholics are often undiagnosed before admission to hospital. Indeed, unless the diagnosis is clear on admission, or unless acute alcohol withdrawal supervenes during the hospital stay, the diagnosis of alcoholism is frequently missed.

An interaction between pharmacologically-active compounds can be described as a combined action resulting from their concomitant use that deviates from the expected additive effect of the compounds. The result may be potentiation or antagonism of one or both.[2] Many people take prescription drugs; therefore interactions between alcohol and drugs occur commonly, and are seen frequently in clinical practice (Table 1). The consequences of accompanying alcohol and drug use vary with the dose of drug and amount of alcohol taken, with the mode of administration of the drug, and with the effects of the drug concerned. Alcohol may alter the effects of the drug; drug may change the effects of alcohol; or both may occur.

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The interaction between alcohol and drug may be pharmacokinetic, with altered absorption, metabolism or elimination of the drug, alcohol or both.[2] Alcohol may affect drug pharmacokinetics by altering gastric emptying or liver metabolism. Drugs may affect alcohol kinetics by altering gastric emptying or inhibiting gastric alcohol dehydrogenase (ADH).[3] This may lead to altered tissue concentrations of one or both agents, with resultant toxicity. The results of concomitant use may also be principally pharmacodynamic, with combined alcohol and drug effects occurring at the receptor level without important changes in plasma concentration of either. Some interactions have both kinetic and dynamic components and, where this is so, the final combined result may be difficult to predict.

Alcohol-drug interactions differ not only with amount of alcohol taken but also with pattern of alcohol intake. When intake is acute, there is usually inhibition of the enzymes of drug metabolism. Alternatively, chronic alcohol abuse may lead to enzyme induction, increasing drug metabolism. The clinical results may then vary depending on whether toxicity is due to the parent drug or one of its metabolites. The main problem in clinical practice is the unpredictability of the effect of alcohol on drug metabolism, particularly given the variable nature of alcohol ingestion by most patients. In addition, patients with heavy alcohol use often have unreliable drug compliance.

The elderly take more drugs than the young, have more coincidental pathology to their main illness, and also show age-related changes in pharmacokinetics and pharmacodynamics. They are thus at greater risk of alcohol-drug interactions. Community surveys of the elderly have shown that between 25% and 38% of those who responded used alcohol together with at least one drug with the known potential to produce adverse effects in combination.[4] The elderly often have impaired homeostatic responses, and may have reduced renal and hepatic function. They frequently have increased end-organ sensitivity to drugs and alcohol; this is particularly true of the central nervous system and combined use of CNS depressants and alcohol may be dangerous.[5] The elderly are at increased risk of hypotension when nitrates are taken in conjunction with alcohol, and at increased risk of over-anticoagulation from simultaneous use of warfarin and alcohol.[5] The effects on memory of alcohol use add further to the problems of compliance with therapy often seen in this patient group.

CLINICAL PHARMACOLOGY OF ALCOHOL

Alcohol is rapidly absorbed from the gastrointestinal tract. The small intestine is the main site of absorption, although there is also some absorption from the gastric mucosa. There is considerable inter- and intra-individual variability in absorption, particularly if there is concomitant ingestion of food.[6] Higher concentrations of alcohol irritate the gastric

TABLE 1
Drugs that commonly interact with alcohol.

Type of agent	Examples	Consequences of interaction with alcohol
CNS depressants	benzodiazepines, tricyclic antidepressants, sedative antihistamines	sedation, psychomotor impairment with concomitant use
Agents provoking disulfiram-like reactions	tolbutamide, metronidazole, sulfonamides, some cephalosporins	'antabuse' reaction; worse in heavier drinkers
Analgesics	paracetamol	increased hepatotoxity in heavy drinkers (may occur at therapeutic doses)
Vasodilators	methyldopa, nitrates, hydralazine	hypotension, unexpected collapse
Antidiabetic agents	long-acting oral hypoglycaemics	hypoglycaemia due to impairment of liver gluconeogenesis by alcohol
Coumarin anticoagulants	warfarin	hepatic enzyme induction interferes with anticoagulant control
NSAIDs	aspirin, others	synergistic effect on gastric mucosa with increased risk of bleeding
Anticonvulsants	phenytoin, (others)	enzyme induction with chronic alcohol excess may affect metabolism
H_2 blockers	cimetidine, ranitidine	inhibit gastric ADH, increasing blood alcohol (at low doses of alcohol only)

mucosa causing pyloric spasm and, consequently, slow down absorption of alcohol and drugs.

Alcohol (ethanol) is a small molecule that is both water and lipid-soluble and, once absorbed, easily permeates all organs, affecting their function. Initially alcohol is distributed throughout the body water. The apparent volume of distribution is reduced with age because of decreased total body water. Once absorbed there is redistribution into the cellular compartment; inebriation and, subsequently, sedation occur when blood alcohol concentrations (BACs) are already falling. In inebriating doses (BAC $\geq$ 0.5 mg/ml of blood), ethanol disorganises the lipid bilayers of neural cell membranes, interfering with synaptic function and impairing neurotransmitter release.[2] There is inhibition of cell membrane ATPase, impaired function of cholinergic muscarinic receptors, and a reduction in cytoplasmic calcium concentrations in certain regions of the brain. The sedative and anxiolytic effects of alcohol, as well as the motor incoordination seen with higher doses, are mediated via gamma-aminobutyric acid (GABA) type-A receptor activation.[7,8] Blockade of the GABA receptor by partial inverse agonists significantly attenuates the intoxicating effects of ethanol.[9] Genetic animal models of alcohol dependence have also identified GABA (A) receptors as likely mediators of the behavioural adaptations associated with ethanol dependence and withdrawal.[7]

Metabolism of alcohol is via the alcohol dehydrogenase pathway (Figure 1). The first-pass metabolism (FPM) of alcohol is extremely variable. When the dose of alcohol is small or when alcohol is taken after a meal, first-pass metabolism may be 75% or higher.[10-12] With larger doses of alcohol, the barrier to systemic toxicity provided by FPM can be overcome, and FPM falls to 10% or lower.[11,13,14] Whilst the majority of FPM occurs in the hepatocytes, a small proportion occurs at the level of the gastric mucosa. Cytoplasmic ADH in the hepatocytes and gastric mucosal cells oxidise ethanol to acetaldehyde with the loss of H+ which reduces NAD to NADH. When alcohol is used to excess, large amounts of reducing equivalents accumulate leading to a variety of metabolic derangements including hyperlactic-acidaemia and hyperuricaemia. Gastric ADH levels are lower in women than in men, lower in Orientals than in Caucasians, and lower in alcoholics than in non-alcoholics.[1,15] This may partly explain the higher BACs achieved for the same dose in alcoholics compared to non-alcoholics. The ADH activity of the stomach is 100 times less than that of the liver, and so the relatively small contribution of gastric ADH to the metabolism of alcohol suggests other causes for these differences.[3] Acetaldehyde is further converted to acetic acid by aldehyde dehydrogenase (AIDH). The rate of elimination of alcohol varies between individuals from 70-150 mg/kg/hr and is independent of dose. There is little intra-subject variability.

The microsomal ethanol oxidizing system (MEOS) is a cytochrome P450-linked metabolic pathway localised in the smooth endoplasmic reticulum of hepatocytes; it contributes to ethanol oxidation for larger doses, particularly where there is chronic alcohol excess. The MEOS is inducible by chronic alcohol consumption, and may metabolise up to 10% of the ingested ethanol.[16] The key enzyme involved is cytochrome P450 2E1 (CYP2E1), but other cytochromes, in particular CYP1A2 and CYP3A4,

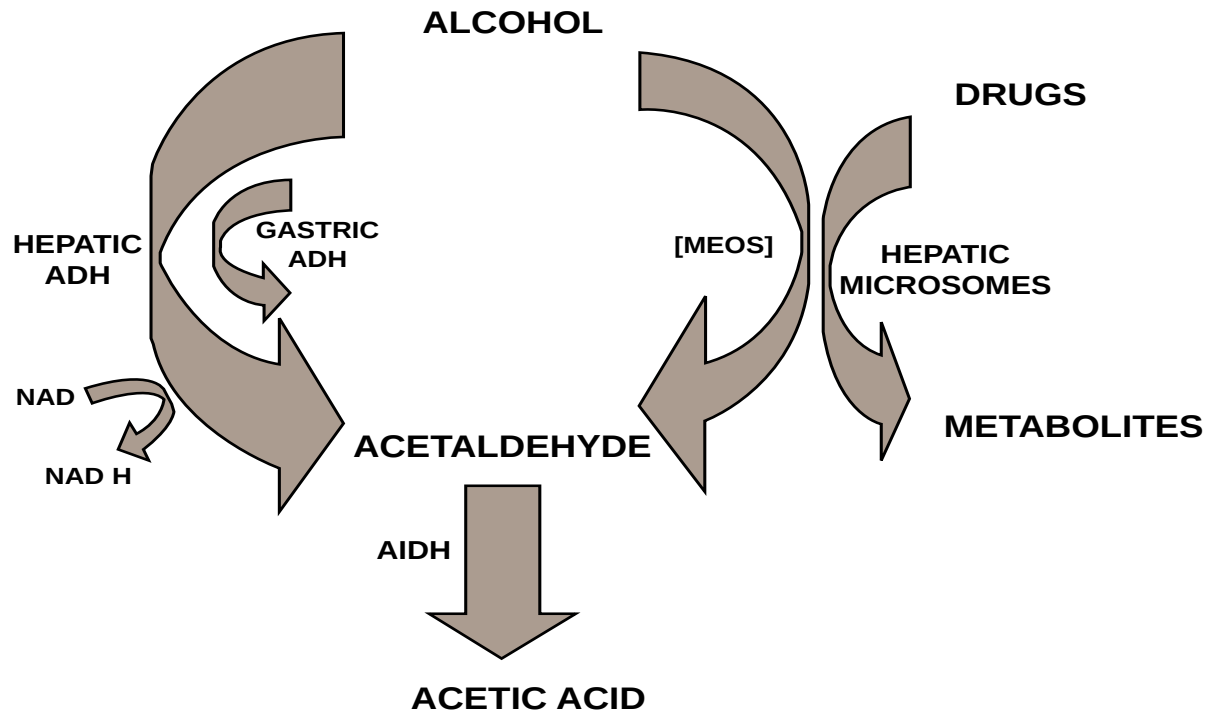

FIGURE 1
The metabolism of alcohol.
Under physiological conditions, approximately 90% of ingested alcohol is metabolised by the alcohol dehydrogenase (ADH) pathway. The great majority of this metabolism occurs in the hepatocytes, with a small proportion taking place in the gastric mucosa. During the oxidation of alcohol to acetaldehyde, nicotine adenine dinucleotide (NAD) is reduced to NADH. Approximately 10% of alcohol metabolism occurs in the MEOS (microsomal ethanol oxidising system), using cytochromes from the P450 group which also play a role in drug metabolism. The acetaldehyde produced by the oxidation of ethanol is further metabolised to acetic acid under the influence of the enzyme acetaldehyde dehydrogenase (AIDH). The MEOS is induced by alcohol excess.

may also contribute to alcohol metabolism.[17]

EFFECTS OF DRUG USE ON ALCOHOL

Inhibition of alcohol metabolism by drugs

Since ethanol and drugs are mainly metabolised by different enzyme systems, an inhibition of alcohol metabolism by therapeutic drugs is uncommon. Pyrazoles inhibit ADH, but are not generally used in clinical practice though 4-methylpyrazole is used in the treatment of ethylene glycol or methanol poisoning.[18] Chlorpromazine and chloral hydrate also inhibit alcohol dehydrogenase. Some drugs (aspirin, H_2-blockers) inhibit gastric ADH, and in individuals with a social pattern of drinking, i.e. ingestion of repeated small doses of alcohol, higher BACs are seen for a given alcohol intake.[19,20] Inhibition of AIDH results in the 'antabuse' reaction.

Enhancement of alcohol metabolism by drugs

Drugs that increase the rate of gastric emptying, such as erythromycin or cisapride, increase the bioavailability of alcohol.[3] Some drugs enhance the rate of alcohol metabolism by inducing MEOS or increasing hepatic blood flow and liver weight. Phenobarbitone increases the rate of disappearance of ethanol, probably by both mechanisms.[21] For this to occur, phenobarbitone levels must be low enough to not interfere with binding of ethanol to cytochrome P450. Clofibrate increases alcohol metabolism by increasing both liver size and the hepatic capacity to utilise reducing equivalents such as NAD. Large doses of fructose (1-2 g/kg) increase elimination of alcohol by 30-100% but do not significantly modify the symptoms of hangover.[2]

EFFECTS OF ALCOHOL USE ON DRUGS

Drug use with acute alcohol intake

The principal effect of the acute ingestion of alcohol is the inhibition of drug metabolism.[22] Large amounts of alcohol taken acutely inhibit cytochrome P450-mediated drug metabolism by competing for a partially common detoxification process. There is competition for binding, with displacement of drug from enzyme and inhibition of cytochrome P450 reductase.[23,24] In addition to a lowered rate of Phase 1 oxidation reactions, glucuronide conjugation is also inhibited by 50%. Inhibition of some drug metabolising systems occurs at low concentrations of ethanol, whereas for others high concentrations are required. The simultaneous administration of alcohol and drugs not only inhibits drug metabolism but also slows the rate of alcohol metabolism.[22]

The consequence of the decrease in drug metabolism depends on whether drug toxicity is due to the parent drug or one of its metabolites. Reduced metabolism of a toxic parent drug or a toxic intermediate will increase toxicity, whereas reduced formation of a toxic metabolite may protect against toxicity. Increased toxicity is seen with methadone, tranquillisers and barbiturates which, if taken in conjunction with acute alcohol excess, achieve enhanced

brain and liver concentrations, with a marked increase in sedation and respiratory depression.[25] This is clinically relevant in the setting of methadone abuse which often occurs in combination with alcohol, and also in the context of many successful suicides which have involved this type of interaction.[1] Decreased toxicity is frequently seen in parasuicide by paracetamol overdose. This often occurs in the setting of alcohol excess. The acute alcohol intoxication reduces formation of the toxic metabolite of paracetamol.[26]

Beverages with a high ethanol concentration will delay gastric emptying and this may affect the absorption of some drugs.[3] There is some evidence that low-to-moderate doses of alcohol may increase hepatic blood flow, allowing more unchanged drug to pass through the liver, particularly in cirrhosis of the liver. Concomitant β-blockade use may prevent this increase in hepatic blood flow.

Drug use with chronic alcohol intake

Prolonged use of alcohol in substantial doses usually results in the development of tolerance. Additionally alcoholics tend to display tolerance to various other drugs. This may be attributed both to CNS adaptation with altered neural biochemistry, and to metabolic adaptation, with increased elimination of ethanol by the activated MEOS.[24] The serum albumin levels may be abnormally low in some chronic alcoholics, influencing the volume of distribution of those drugs which are highly protein-bound.[27]

Cytochrome P450 2E1 (CYP2E1) is induced by ethanol, and its activity increases five- to tenfold in alcoholics.[28] This does not affect metabolism of accompanying drugs if a continuous supply of alcohol substrate persists. The induction in the activity of the MEOS after chronic alcohol consumption contributes to the ethanol tolerance that develops in the alcoholic, and extends to various other drug metabolising systems in hepatic microsomes, thereby accelerating drug metabolism in general. Alcoholics are known to be tolerant to various psychoactive drugs, and while this has generally been attributed to CNS adaptation, metabolic adaptation also plays a role, with enhanced hepatic clearance of drug.[29] Studies have shown increased clearance of ethanol, phenobarbital, propranolol, tolbutamide, warfarin and diazepam in rats or man fed pure ethanol under controlled conditions for a prolonged period.[1,29-34]

CYP2E1 also has a pronounced capacity to activate many xenobiotics to highly toxic metabolites including industrial chemicals such as vinyl chloride and xylene, anaesthetics such as enflurane and halothane, and commonly-used medications such as isoniazid, phenylbutazone and paracetamol.[1,28,35-37] Heavy drinkers are thus at an increased risk of toxicity when exposed to these substances. If alcohol is discontinued, CYP2E1 is freed to use the drug as a substrate, significantly increasing the rate of the drug's metabolism, and reducing tissue concentrations of the drug. This increased metabolism may cause adverse effects if it leads to the increased formation of a toxic metabolite (paracetamol is a good example), or loss of essential endogenous substances such as vitamins or steroids.[26] Even after withdrawal, alcoholics need doses different from those required by non-drinkers to achieve therapeutic levels of some drugs.[22] This metabolic tolerance persists for several days to weeks after cessation of alcohol abuse, and varies with different drugs.

THE ANTABUSE REACTION

This peculiar reaction is a symptom complex comprising marked facial flushing, intense throbbing in the head and neck, headache, vomiting, dyspnoea, sweating, hypotension, thirst and confusion. It occurs with varying severity in subjects drinking alcohol while taking a drug that inhibits AIDH, such as disufiram or calcium carbimide. The pathogenesis of the disulfiram reaction is complex and remains poorly understood. Within an individual, the blood concentration of acetaldehyde correlates with the severity of the antabuse reaction;[38] intravenous administration of exogenous acetaldehyde reproduces the cardiovascular effects in man.

Prior intake of enzyme-inducing drugs reduces sensitivity to disulfiram, while heavy metals may cancel the inhibition of AIDH. In addition, the disulfiram block is less effective at higher concentrations of acetaldehyde, so that after a few drinks the reaction may become tolerable or can be avoided. In cirrhosis, the antabuse reaction is less severe as the impaired liver is unable to produce much acetaldehyde. Antabuse-like reactions may be provoked by several drugs other than disulfiram and carbamide, including oral sulphonylureas, metronidazole, griseofulvin and cephalosporins with a N-methylthioterazole side-chain.[3] These antabuse-like reactions, however, are less consistent in their occurrence than the disulfiram reaction.

SPECIFIC ALCOHOL-DRUG INTERACTIONS

Sedatives

While acute alcohol ingestion in conjunction with a sedative agent usually results in increased sedation, chronic alcohol abuse may decrease the action of a sedative due to enhanced first-pass metabolism by induced liver microsomes. In chronic alcoholics, the dose of propofol required to induce unconsciousness is increased.[39] On the other hand, acute oral administration of alcohol inhibits the enzymes which metabolise barbiturates, resulting in prolongation of the plasma half-life of phenobarbital and meprobamate. The lethal dose of barbiturates is nearly 50% lower in the presence of alcohol than when used alone, and completed suicides have frequently involved this combination.[40,41] Death results from respiratory depression.

The hypnotic chloral hydrate competes with ethanol for metabolism by hepatic ADH. The combined sedative effect of chloral hydrate and alcohol, sometimes called 'knock-out drops', is anecdotally strong and is thought to follow both pharmacokinetic and pharmacodynamic interactions.[42] Clinical studies have been confusing, however, and this interaction is yet to be fully understood.

The sedative agent chlormethiazole has been used in the treatment of alcohol withdrawal. Under normal conditions oral chlormethiazole has a bioavailability of 8-10%. In patients with cirrhosis of the liver, bioavailability and exposure (area-under-the-curve) are increased considerably. Acute concomitant alcohol use also increases the bioavailability of chlomethiazole. There is thus the risk of increased sedation and respiratory depression. The tendency of alcoholics to return to the bottle, coupled with the possible fatal effects of this interaction, makes chlomethiazole an unsuitable agent to treat alcohol withdrawal except under careful supervision.

Benzodiazepines

Alcohol is a widely-used social drug, and benzodiazepines

are frequently-prescribed therapeutic agents: not surprisingly, concurrent use is common. Interactions of major consequence are infrequent, and are usually pharmacodynamic. Both pharmacological agents act by enhancing GABAergic transmission in the human CNS.[8,9] Alcohol potentiates the effects of long-acting benzodiazepines such as diazepam and chlordiazepoxide more than the shorter-acting compounds, for example oxazepam and lorazepam. Benzodiazepines which are N-demethylated or hydroxylated are potentiated more than those which are conjugated. Alcohol ingestion decreases the clearance of benzodiazepines taken orally.[43]

Patients who abuse benzodiazepines also frequently abuse alcohol, and the two drugs show cross-dependence.[44] Clinicians should avoid prescribing these agents to known alcoholics. Benzodiazepines may depress respiration after intravenous injection, and in combination with alcohol may cause death.[2] This interaction should be remembered when treating alcoholic seizures. The specific benzodiazepine antagonist flumazenil effectively cancels the share of benzodiazepines in mixed intoxications.

In general, the combined pharmacodynamic actions of alcohol and benzodiazepines outweigh any altered kinetics of the latter due to the former. Alcohol and benzodiazepines have additive effects on psychomotor performance, in particular sedation, and this has been a concern with regard to driving motor vehicles and operating heavy machinery.[44] More than 50% of fatal road traffic accidents in the USA are associated with elevated BACs.[22] Given the widespread use of benzodiazepines, their concomitant use must frequently occur in this setting. Recent evidence from Tayside highlights this danger.[45] However, when low doses of alcohol and benzodiazepine have been given in combination under experimental conditions, tolerance develops to the benzodiazepine minimizing or eliminating the combined effects.[2]

Opioids

Opioids are potent respiratory depressants, reducing both the rate and volume of respiration, and desensitising the respiratory centre to a rise in PCO_2. Alcohol is also a respiratory depressant, and the concomitant use of morphine and alcohol potentiates the effects of both drugs. Acute administration of ethanol increases brain and liver concentrations of unmetabolised methadone and decreases hepatic metabolism and biliary excretion of this heroin substitute.[25] Users of methadone often take alcohol in order to experience a 'high' that methadone alone does not provide.[46] Chronic alcohol abuse, on the other hand, increases metabolism by inducing liver enzymes and increases N-demethylation of methadone.[25] This can lead to a vicious cycle of increasing alcohol and methadone use. Ethanol-opioid interactions are unpredictable and potentially lethal, as both agents readily provoke vomiting while simultaneously suppressing the cough reflex and depressing respiration. It is thus not surprising that their concomitant use is a common precipitant of premature death in substance abusers.

There is at least one reported case of a death following a dose of 0.8-1 g of dextropropoxyphene (previously taken at a dose of 0.6 mg daily) in combination with an amount of alcohol giving BACs below 2 mg/ml.[2] In this case respiratory depression was not identified, and so the opioid antagonist naloxone was withheld with fatal effects. Concomitant alcohol abuse was identified in 20 of 48 dextropropoxyphene-related deaths in Scotland.[47]

Antidepressants

When used in conjunction with alcohol, the metabolism of tricyclic antidepressants is retarded, increasing the area under the plasma concentration-time curve (AUC), and hence exposure to the drug.[22,48] The combined pharmacodynamic effects of the two adversely influence motor skills, and this may be a problem when driving. There is an increased risk of hypotension and of cardiac arrhythmias.

Newer antidepressants do not appear to have significant interactions with alcohol. Mianserin may increase the sedative effect of alcohol. The selective serotonin reuptake inhibitors (SSRIs) do not have any effects on psychomotor performance in conjunction with alcohol. Mono-amine oxidase inhibitors (MAOIs) may provoke toxicity or a hypertensive crisis if taken with wines rich in tyramine.

Neuroleptics

Therapeutic levels of a neuroleptic combined with moderate-to-large quantities of alcohol have been seen frequently in long-term psychiatric patients on weekend breaks, but clinically significant interactions have rarely been reported. Associated alcohol use causes the decreased clearance of chlorpromazine. Chlorpromazine may also decrease alcohol metabolism by inhibiting ADH. The principal effects of combined use are pharmacodynamic, however, with the enhancement of sedative effects, hypotension and respiratory depression.[22] The akathisia and dystonia induced by neuroleptics may be triggered by relatively low doses of alcohol.[49] Neuroleptics should preferably be avoided in the treatment of alcohol withdrawal.

Aspirin and NSAIDs

The combination of aspirin and alcohol induces an increase in the bleeding time. The mechanism for this is unknown.[50] Epidemiological data indicate an increased risk of gastrointestinal haemorrhage when aspirin or NSAIDs are taken together with alcohol. The risk is highest where all three are used together, and is due to a synergistic effect of the agents on gastric and duodenal mucosal damage.[51]

When alcohol and aspirin are taken together with food, there is an increase BACs.[19] This is thought to be due to inhibition of gastric ADH by aspirin, and has provoked interest because of the possible implications for patients on aspirin who may wish to drive after one or two drinks. As most studies suggest that the contribution of gastric ADH to alcohol metabolism is very small, and other findings have been conflicting, this work needs confirmation.

Paracetamol

Patients who attempt to overdose frequently combine alcohol and paracetamol. Ironically, the acute intake of alcohol protects the liver from paracetamol toxicity because the competition for cytochrome P450 results in less production of the paracetamol metabolite responsible for hepatotoxicity. Unfortunately this is not true in chronic alcohol abuse, and the literature contains many reports of hepatic injury following therapeutic doses of paracetamol in patients with a heavy alcohol intake.[52] In these patients, hepatic injury associated with paracetamol has been

described following repetitive intake for headache (including alcohol withdrawal headache), dental pain or pancreatitis, and has occurred with doses as low as 2.5-4 g.[53] In one recently-reported series, patients hospitalised with paracetamol toxicity related to accidental misuse had higher rates of morbidity and mortality than those who attempted suicide, even though the latter had taken more paracetamol.[54]

The mechanism behind the enhanced hepatotoxicity is an increased production of reactive metabolites of paracetamol by liver microsomes that have been induced by alcohol. Toxicity is also partly due to the malnutrition associated with alcoholism, which results in depleted glutathione stores. Under normal circumstances, glutathione is conjugated with the toxic paracetamol metabolite, preventing hepatotoxicity. Animal experiments show peak paracetamol toxicity after ethanol withdrawal, when there is no competition for the induced microsomes from ethanol.[55] Perversely, it is often during alcohol withdrawal that paracetamol is used to counteract the associated headache.

Antidiabetic agents

Alcohol blocks hepatic gluconeogenesis and the concomitant use of alcohol and oral hypoglycaemics may result in hypoglycaemia.[3] This risk is greater for long-acting sulphonylureas, and where the use of alcohol is accompanied by inadequate intake of food. The induction of hepatic enzymes seen with chronic alcohol abuse reduces the half-life of chlorpropamide and tolbutamide. Heavy drinking also increases the risk of lactic acidosis for patients on metformin.[56]

Warfarin

Warfarin metabolism is reduced in the context of concomitant alcohol use with a resultant increased anticoagulant effect and danger of haemorrhage. Blood warfarin levels are higher than might be expected from a given dose.[57] In chronic alcohol excess, enhanced enzyme activity leads to a decreased anticoagulant effect. Careful monitoring of the prothrombin time is required if warfarin is administered to these patients.

H_2 antagonists

A few studies have suggested that there is a potentiation of BACs when small doses of alcohol are taken in conjunction with H_2 antagonists.[3] This issue is of both clinical and medicolegal interest, as the use of H_2 blockers is widespread and any interaction may have implications for social drinkers who intend to drive after a few drinks. Most studies of this phenomenon have been confounded by failure to adjust for differences in food intake and alterations in gastric emptying. The majority of evidence, however, does not support a BAC potentiating effect of H_2 blockers. Debate continues in the literature.

CONCLUSION

Several pharmacokinetic and pharmacodynamic pitfalls await the clinician who prescribes drugs for his or her patients without concern for factors such as age, sex, weight, concomitant disease, the possibility of pregnancy, the possible interaction between agents, and the possibility that the patient may be poorly compliant with therapy. To this list should be added the possibility of alcohol use. The prescriber should be aware both of important interactions associated with acute alcohol intake, and those associated with chronic alcohol abuse. Where appropriate, it may be necessary for the clinician to warn patients to avoid alcohol, to withhold prescribing certain drugs, or to consider attending to a particular patient's drinking problem. Finally, doctors treating patients with acute drug overdose should always consider the possibility of concomitant alcohol ingestion, and be on the lookout for possible interactions.

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