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Influence of Alcohol and Smoking on Drug Action: A Step for better utilization of drugs

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ABSTRACT

In the present health care scenario most of the health care personnel assume that the drug-drug interactions are the only interactions with clinical importance and are basically unaware of the fact that there are more potentially harmful drug interactions than drug-drug interactions. The knowledge of drug interactions that are likely to occur in the case of cigarette smoking and alcohol ingestion can empower a physician to avoid drug interactions that lead to deleterious outcomes. Both smoking and alcoholism can have several stimulatory and inhibitory effects on the several pharmacokinetic and pharmacodynamic properties of a drug.

Keywords: Alcohol, pharmacokinetic, pharmacodynamic, smoking.

INTRODUCTION

A drug interaction can simply be defined as an interaction between a drug and any other substance that prevents the drug from performing as expected. An interaction can usually alter the various physiological factors like the absorption, distribution, metabolism and elimination of the drug. The drug interactions due to changes in distribution are less pronounced than the other factors. A drug interaction can have synergistic or antagonistic effects, and could be even harmful at times. Very common drug interactions include drug-drug interactions, food and beverage interaction with drug, interaction of the medical condition of the person like a Cardiac arrest history, drug- laboratory test interactions, drug interactions caused by diseased state of the patient and even the environmental chemicals and smoking habits of the person also effect the physiological parameters that define a particular drug.

ALCOHOL-DRUG INTERACTIONS

People commonly report euphoria after drinking alcohol, although the extent depends on the social setting. This effect is frequently given as an important reason for the social use of alcohol. However the interaction between many medications and alcohol can lead to a significant increase

in one's risk of illness, injury, or even death[1]. Alcohol is a well-known mucosal irritant; it causes marked irritation of gastric mucosa if ingested in large quantities at concentration of 20% or more. Chronic alcoholism results in enzyme induction. Acute alcoholism intoxication tends to inhibit drug metabolism (whether alcoholic or not) [2]. Severe alcohol induced hepatic dysfunction may inhibit ability to metabolize drug. Some of the examples of these type of interactions are cited in table 1.

Table 1: List of various alcohol drug interactions

ALCOHOL DRUG INTERACTIONS		
Drug	Prescribed Purpose	Interaction
Anesthetics (ex: Diprivan, Ethrane, Fluothane)	Administered prior to surgery to render a patient unconscious and insensitive to pain	Increased amount of drug required to induce loss of consciousness - increased risk of liver damage
Antibiotics	Used to treat infectious diseases	Reduced drug effectiveness -nausea/vomiting -headache - convulsions
Antidepressants (ex: Elavil)	Used to treat depression and other forms of mental illness	Increased sedative effects - may decrease effectiveness of anti-depressant - potential for dangerous rise in blood pressure
Antidiabetic medications	Used to help lower blood sugar levels in diabetic individuals	Reduced drug effectiveness - Nausea - Headache
Antihistamines (ex: Benadryl)	Used to treat allergic symptoms and insomnia	-Intensified sedation -Excessive dizziness
Antipsychotic medications (ex: Thorazine) ⁵	Used to diminish psychotic symptoms such as delusions and hallucinations	Intensified sedation - impaired coordination - potentially fatal breathing difficulties
Antiseizure medications (ex: Dilantin)	Used to treat epilepsy	-Decreased protection against seizures - increased risk of drug-related side effects
Antiulcer medications (ex: Tagamet, Zantac)	Used to treat ulcers and other gastrointestinal problems	-Increased presence of drug - Increased risk of side affects
Cardiovascular medications (ex: nitroglycerin, Apresoline, Ismelin, Inderal)	Wide variety of medications used to treat ailments of the heart and circulatory system	-Extreme dizziness or fainting - reduced drug effectiveness
Narcotic pain relievers (morphine, codeine, Darvon, Demerol)	Used to alleviate moderate to severe pain	Intensified sedation - Increased possibility of a fatal overdose
Nonnarcotic pain relievers (aspirin, ibuprofen, acetaminophen)	Used to alleviate mild to moderate pain	Increased risk of stomach bleeding - increased risk of the inhibition of blood clotting -increased effects of consumed alcohol *acetaminophen (Tylenol) taken during or after drinking may significantly increase one's risk of liver damage
Sedatives and hypnotics (Valium, Dalmane, Ativan, sleeping pills)	Used to alleviate anxiety and insomnia	Severe drowsiness - depressed cardiac and respiratory functions - increased risk of coma or fatality

Drug interactions are often categorized as pharmacodynamic or pharmacokinetic in nature.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction is related to the drug's effect on the body[3]. Surprisingly, there is a marked increase in the activity of several drugs owing to alcohol and drug interactions. An additive or synergistic effect is observed in the case of interaction of alcohol with CNS drugs. An enhanced, hypoprothrombinemic effect of oral anti-coagulants and hypoglycaemic effect of insulin with acute alcohol intoxication was witnessed. Alcohol increases the sedative effects of narcotic analgesic. Interaction of alcohol with β -blockers such as propranolol lowers the blood pressure to a very low level causing hypotension. A similar effect is also observed in the case of an alcohol nitrate interaction where alcohol adds to the blood vessel relaxing effect of nitrate and results in dangerously low blood pressure. Some of the antihistamines like brompheniramine chlorpheniramine, diphenhydramine, clemastine, fexofenadine, loratidine, cetirizine and astemizole increase drowsiness and slow mental and motor performances in alcoholics[4].

Pharmacokinetic drug interactions:

A pharmacokinetic drug interaction is related to the body's effect on the drug. A pharmacokinetic drug interaction can be caused by an alteration in absorption, distribution, metabolism, or elimination of a drug[5].

Effects on metabolism:

Effects of alcohol-drug interactions on metabolism are both stimulatory and inhibitory. Several cases of stimulatory effects of alcohol-drug interactions such as the reduction of half-lives of meprobamate from 17hrs to 7hrs and from 14hrs to 8hrs in non-alcoholic subjects after regular administration of ethanol for 1 month to alcoholic and non-alcoholic subjects are reported. Increased formation of hepatotoxic acetaminophen metabolites was also observed in chronic alcoholism[6].

Increased conversion of acitretin to etretinate seen in alcoholic subjects, resulted in teratogenic action can also be cited as a good example for the stimulatory effects of alcohol-drug interactions. NSAIDS like aspirin, ibuprofen, naproxen, ketoprofen, and nabumetone when taken with alcohol increase the risk of liver damage or stomach bleeding. The increased metabolism of HMG-Co reductase inhibitors like atorvastatin, cerivastatin, fluvastatin, pravastatin and simvastatin due to this interaction increases the risk of liver damage in alcoholic subjects.

Acute ethanol intoxication can also inhibit drug metabolism[7]. This effect is clearly seen in the fall of plasma clearance levels of Chlordiazepoxide administered intravenously during ethanol intoxication. Disulfiram-alcohol interaction is a typical example of the inhibitory metabolic effects caused by a Drug-alcohol interaction[8]. Disulfiram inhibits the activity of aldehyde dehydrogenase, thus inhibiting oxidation of acetaldehyde, an oxidation product of alcohol which resulted in accumulation of excessive quantities of acetaldehyde and development of unpleasant effects characteristic of disulfiram reaction. Disulfiram like reaction is observed in patients receiving cephalosporins like cefotetan, cefamandole, cefmetazole and cefoperazone following consumption of alcohol. Methylthiotetrazole a main substituent of all these four antibiotics is the main cause of such reaction[9]. Chloral hydrate, metronidazole, sulfonylureas are some of the drugs that exhibit disulfiram like reaction.

Other examples of inhibitory metabolic effects observed are increased incidence of side effects like nausea, vomiting when theophylline was administered to alcoholics. The interaction of Anthelmintics like metranidazole and antifungals like fluconazole, griseoflavin, ketocanazole etc with alcohol causes nausea, abdominal cramps, vomiting, headaches and flushing due to the inhibition of alcohol dehydrogenase by metranidazole, which causes severe alcohol intoxication

reaction. Therefore, these alcohol-containing products should not be taken at least 3 days after finishing the medication[10].

Effects on distribution:

Ethanol decreases the plasma protein binding of chlordiazepoxide. Hence percentage unbound after intravenous administration of the drug was found to rise from 5.3% to 6.6%. Therefore, plasma clearance of unbound drug decreased almost 50%, from 468ml/min to 264ml/min.

SMOKING-DRUG INTERACTIONS:

Many people who smoke become addicted to chemical called nicotine in cigarettes and other tobacco products. The health risks of tobacco smoking are well known with regard to diseases of the heart, lungs, and blood vessels. Tobacco smoke though essentially constitutes a gaseous phase, it also contains a portion of particulate matter containing nicotine and other polycyclic aromatic hydrocarbons (PAHs) which are products of incomplete combustion and are also carcinogenic. Nicotine can interact with several medications but most likely with those containing nicotine. But many other interactions between tobacco smoke and medications have been identified. Polycyclic aromatic hydrocarbons which are potent inducers of hepatic cytochrome P450 enzymes like aryl hydrocarbon hydroxylase (primarily CYP1A2) account for the occurrence of several such pharmacokinetic interactions.

Even Oxygen free radicals could be the cause for the detrimental effects of smoking on health. A study conducted by A.Hemalatha and co associates to examine the oxidant and antioxidant system among smokers and non smokers supported the above hypothesis. From the plasma excretion studies conducted on 14 smokers and 11 non smokers it was found that the protein carbonyl levels were found to be significantly higher in smokers than in non-smokers and the levels of plasma ascorbic acid, free sulfahydryl group and erythrocyte reduced glutathione were lower in smokers compared to non-smokers. There was also a decrease in the activities of catalase and glutathione peroxidase found in the erythrocytes of smokers which suggests the presence of oxidative stress in smokers.

Pharmacokinetic interactions:**Effects on metabolism:**

Vestal and co-workers who studied the systemic clearance levels in subjects both smokers and non smokers suggested that there is a profound increase of about 77% in the clearance levels of propranolol owing to the induction of hepatic microsomal enzymes by the cigarette smoke[11]. Higher quantities of pentazocine are required as a supplement to nitrous oxide anaesthesia in smokers also owing to the stimulation of metabolism caused due to smoking[12]. Studies conducted on the effect of smoking on oestrogen metabolism in postmenopausal women also revealed the stimulatory effect of smoking on metabolism. Another interesting aspect revealed in this study was that there was a reported increased risk of osteoporosis among postmenopausal smokers due to the lowered oestrogen levels. Another good example for the stimulatory effects of smoking on metabolism is the higher consumption of caffeine by smokers than non smokers. This can be attributed to the acceleration of demethylation pathways of caffeine metabolism by smoking.

The studies conducted on the clearance levels of theophylline in smokers and non smokers revealed several interesting aspects. There was a two-fold difference in theophylline dosage requirements between smokers and non-smokers. However there is a reduced toxicity during its clinical use in the case of smokers[13]. This effect was observed to be independent of age and the inhibited or accelerated metabolisms of the drugs brought about by cimetidine and phenytoin

respectively. The plasma levels of phenacetin after its oral administration are much lower in smokers when compared to non-smokers probably due to the increased presystemic gastrointestinal or hepatic metabolism. The half-life of alprazolam was also found to be reduced by 35% in smokers. The AUC of chlorpromazine was found to be decreased by 36% and the serum concentration by 24% suggesting that smoking also enhances the metabolism of chlorpromazine. The plasma concentration is observed to be decreased by 18% in smoking subjects due to the induction of CYP1A2 enzyme leading to its increased metabolism. Smokers might need increased doses of flecainide for the required therapeutic effect due to its increased clearance with a 25 % decrease in the trough serum concentrations.

Insulin absorption may be decreased due to smoking and it may even cause release of endogenous substances that antagonize the effects of insulin[14]. Greater maximal insulin concentration (nearly 3 to 5 fold) is seen and the AUC is also increases by 2 to 3 fold. Insulin (inhaled) is contraindicated in smokers and those who have discontinued smoking for less than 6 months. In smokers the clearance of haloperidol is increased by about 44% and a 70% decrease in its serum concentration is also observed. The increase in the fluvoxamine metabolism in smokers can be attributed to the induction of CYP1A2 enzyme. There is also a 24% increase in the clearance and the AUC and plasma concentration are reduced by 31% and 34 % respectively. The clearance of olanzapine was found to be decreased by 98% due to the induction of CYP1A2 enzyme in smoking subjects. So there is a much need for the administration of an increased dosage of Olanzapine to smokers. Tacrine is used to treat Alzheimer's disease and is in a class of drugs known as acetyl cholinesterase inhibitors. Smoking cigarettes increases the elimination of tacrine from the body. This may be a problem for people who either start or stop smoking while taking the drug. Those who start smoking may experience a reduction in the beneficial effects of tacrine, while those who stop smoking might experience more side effects.

Pharmacodynamic interactions:

The stimulation of central nervous system by nicotine decreases the hypnotic activity of benzodiazepines like diazepam, chlordiazepoxide etc[14]. Smoking also induces nicotine mediated sympathetic activation which decreases the antihypertensive and heart rate control effects of several Beta blockers. The response levels of asthmatic smokers to inhaled corticosteroids are decreased due to increase in their metabolism of the steroids. The ineffectiveness of Propoxyphene to relieve mild to moderate headache or pain is observed in 10% of non-smokers, 15% of light smokers and 20% of heavy smokers. However the incidence of adverse effects of several drugs in smokers was found to be decreased when compared to non smokers[15]. Of the Reported 7 adverse reactions of Propoxyphene 6 were reported in non-smokers and only about 3% of smokers reported drowsiness with diazepam whereas 8% of non smokers reported it. Similar observations were noted in the incidence of drowsiness with chlordiazepoxide.

There is an increased risk of cardiovascular adverse effects in women who smoke and use oral contraceptives.

Smoking is also said to cause both pharmacokinetic and pharmacodynamic interactions in insulin and heparin. With heparin though the mechanism remains unclear a decrease in the half life and increase in the clearance levels of heparin is observed in smokers due to both pharmacokinetic and pharmacodynamic interactions[16]. Though these interactions are not clinically significant in the case of insulin may lead to increased dosages because smoking causes release of endogenous substances that cause insulin resistance.

A study conducted by Vani gupta and co associates examined the effect of short term cigarette smoking on insulin resistance and lipid profile in asymptomatic healthy adults. This study comprise of 44 healthy male subjects in the age group of 18 to 40 years (having BMI 25+3 and WHR less than 1). Of these 22 smokers were included in the study group and 22 smokers in the control group. Subject selection was done such that 1 smoker and 1 nonsmoker sibling or first degree male relative were selected from the same family. Fasting plasma glucose, insulin, lipid profile and homeostatic model assessment index (HOMA index) were compared as a measure of insulin resistance between both the groups[17].

Observations showed the significantly higher values of serum glucose (133.36+23.45mg/dl), serum insulin (32.04+6.02mcg/ml) and HOMA index (3.62+. 21) in smokers as compared to nonsmokers (serum glucose 86.95+19.32mg/dl), insulin (20.09+4.8mcg/ml) and HOMA index (3.29+.3). No significant difference was observed for number of subjects having insulin resistance (HI greater than 3.8) and lipid profile in both the groups. Thus it appears that smokers are prone to develop hyperinsulenemia, hyperglycemia and the metabolic syndrome.

CONCLUSION

Despite several efforts to reduce the incidence of several adverse medical events that are caused due to interaction of the drugs with several other agents, they continue to be an important problem in the efficacy of a drug formulation. The reduction of the risk of drug interactions is a challenge that embraces a number of considerations. Although they could be applied to drug therapy in general, following some guidelines to reduce and manage drug interactions is the responsibility of the health professionals who are involved in the process of selecting and monitoring therapeutic regimens. However severe the food drug interactions might be they cannot be avoided may be due to the lack of awareness among the people and several members of the health care system, therefore measures should be taken to educate them.

Identification of patient risk factors such as age, the nature of the patients medical problem (e.g.; impaired renal function), dietary habits, smoking and problems like alcoholism influences the effect of certain drugs and should be considered during the initial patient interview.

From the entire information available one can also understand the need for individualization of dosage regimens.

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