

Review Article**Drug interactions: A review with protein displacement drug-drug interaction****Sreya Kosanam**

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Abstract

Drug interactions are an important segment of drug related problems. Evaluation of Drug interactions is necessary along with patient management, especially in children and elderly patients who often receive multiple medications. Severity of drug-drug interactions is one of the problems which are poorly understood within the clinical medicine. It is increasingly necessary to become acquainted with the workings of protein bound metabolism and associated drug interaction which leads to increased free concentrations of drug in the body. In this manuscript drug interactions with emphasis on their relevance and mechanism are reviewed. Additionally, as an example of protein displacement drug-drug interaction between valporate and aspirin is discussed.

Keywords: Drug interactions, mechanisms, protein bound, valporate, aspirin

Introduction

A drug interaction is a situation in which a substance (usually another drug) affects the activity of a drug when both are administered together. This action can be synergistic (when the drug's effect is increased) or antagonistic (when the drug's effect is decreased) or a new effect can be produced that neither produces on its own. These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances (National prescribing service, 2009). The risk of drug interactions is due to multiple drug therapy, multiple prescribers, poor patient compliance, patient risk factors such as predisposing factors, advancing illness.

Drug interactions may include: drug-drug interactions, drug-food interactions, drug-laboratory interactions, drug-chemical interactions. Drug interactions may be the result of various processes. These processes may include alterations in the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion (ADME) of a drug. Alternatively, drug interactions may be the result of the pharmacodynamic properties of the drug, e.g. the co-

administration of a receptor antagonist and an agonist for the same receptor.

Synergy and antagonism

When the interaction causes an increase in the effects of one or both of the drugs the interaction is called a synergistic effect. An "additive synergy" occurs when the final effect is equal to the sum of the effects of the two drugs. When the final effect is much greater than the sum of the two effects this is called enhanced synergy (Zuzunaga, 2009). The opposite effect to synergy is termed antagonism. Two drugs are antagonistic when their interaction causes a decrease in the effects of one or both of the drugs. Both synergy and antagonism can both occur during different phases of the interaction of a drug with an organism, with each effect having a different name.

For example, when the synergy occurs at a cellular receptor level this is termed agonise, and the substances involved are termed agonists. On the other hand, in the case of antagonism the substances involved are known as inverse agonists. The different responses of a receptor to the action of a drug has resulted in a number of classifications, which use terms such as "partial agonist", "competitive agonist" etc. These concepts have fundamental applications in the pharmacodynamics of these interactions (Díez and Pujol, 2002).

Underlying factors

It is possible to take advantage of positive drug interactions.

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However, the negative interactions are usually of more interest because of their pathological significance and also because they are often unexpected and may even go undiagnosed. By studying the conditions that favour the appearance of interactions it should be possible to prevent them or at least diagnose them in time. The factors or conditions that predispose or favour the appearance of interactions include (Díez and Pujol, 2002):

Old age: factors relating to how human physiology changes with age may affect the interaction of drugs. For example, liver metabolism, kidney function, nerve transmission or the functioning of bone marrow all decrease with age. In addition, in old age there is a sensory decrease that increases the chances of errors being made in the administration of drugs (Merle et al., 2005).

✍ **Polypharmacy:** The more drugs a patient takes the more likely it will be that some of them will interact (Morillo, 2004).

Genetic factors: Genes synthesize enzymes that metabolize drugs. Some races have genotypic variations that could decrease or increase the activity of these enzymes. The consequence of this would, on occasions, be a greater predisposition towards drug interactions and therefore a greater predisposition for adverse effects to occur. This is seen in genotype variations in the isozymes of cytochrome P450.

✍ **Hepatic or renal diseases:** The blood concentrations of drugs that are metabolized in the liver and / or eliminated by the kidneys may be altered if either of these organs is not functioning correctly. If this is the case an increase in blood concentration is normally seen.

✍ **Serious diseases that could worsen if the dose of the medicine is reduced.**

✍ **Drug dependent factors (Molina, et al., 2007):**

- o **Narrow therapeutic index:** Where the difference between the effective dose and the toxic dose is small. The drug digoxin is an example of this type of drug.
- o **Steep dose-response curve:** Small changes in the dosage of a drug produce large changes in the drug's concentration in the patient's blood plasma.
- o **Saturable hepatic metabolism:** In addition to dose effects the capacity to metabolize the drug is greatly decreased.

Serious and severity of drug interactions

The American food and drug administration define a serious adverse event as one when patient outcome is one of the following Elizabeth Lipp (2008-06-15):

- Death
- Life-threatening

- Hospitalization (initial and prolonged)
- Disability-significant, permanent change, impairment in the patient body, structure, quality of life.
- Congenital anomaly
- Prevent permanent impairment or damage

Mechanism of drug interactions

There are several mechanisms by which drugs interact with other drugs, food, and other substances. An interaction can result when there is an increase or decrease in:

1. The absorption of a drug into the body;
2. Distribution of the drug within the body;
3. Alterations made to the drug by the body (metabolism); and
4. Elimination of the drug from the body.

Most of the important drug interactions result from a change in the absorption, metabolism, or elimination of a drug. Drug interactions also may occur when two drugs that have similar effects or opposite effects on the body are administered together. For example, there may be major sedation when two drugs that can cause sedation are taken simultaneously, such as narcotics with antihistamines.

Another source of drug interactions occurs when one drug alters the concentration of a substance that is normally present in the body. The alteration of this substance reduces or enhances the effect of another drug that is being taken. The drug interaction between warfarin (Coumadin) and vitamin K-containing products is a good example of this type of interaction. Warfarin acts by reducing the concentration of the active form of vitamin K in the body. Therefore, when vitamin K is taken, it reduces the effectiveness of warfarin.

Change in absorption

Most drugs are absorbed into the blood and then travel to their site of action. Most drug interactions that are due to altered absorption occur in the intestine. There are various ways that the absorption of drugs can be reduced. These mechanisms include:

1. An alteration in blood flow to the intestine;
2. Change in drug metabolism (breakdown) by the intestine;
3. Increased or decreased intestinal motility (movement);
4. Alterations in stomach acidity, and
5. A change in the bacteria that normally reside in the intestine.

Drug absorption also can be affected if the drug's ability to dissolve (solubility) is changed by another drug or if a substance (for example, food) binds to the drug and prevents its absorption.

Changes in transport and distribution

The main interaction mechanism is competition for plasma protein transport. In these cases the drug that arrives first binds with the plasma protein, leaving the other drug dissolved in the plasma, which modifies its concentration. The organism has mechanisms to counteract these situations (by, for example, increasing plasma clearance), which means that they are not usually clinically relevant. However, these situations should be taken into account if there other associated problems are present such as when the method of excretion is affected.

Changes in Metabolism

Many drug interactions are due to alterations in drug metabolism. Further, human drug-metabolizing enzymes are typically activated through the engagement of nuclear receptors. One notable system involved in metabolic drug interactions is the enzyme system comprising the cytochrome P450 oxidases (Lipp, 2008).

CYP450

Cytochrome P450 is a very large family of haemoproteins (hemoproteins) that are characterized by their enzymatic activity and their role in the metabolism of a large number of drugs Danielson PB (December 2002). The most important enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 (Nelson, 2003). The majority of the enzymes are also involved in the metabolism of endogenous substances, such as steroids or sex hormones, which is also important should there be interference with these substances. As a result of these interactions the function of the enzymes can either be stimulated (enzyme induction) or inhibited (enzyme inhibition).

Enzymatic inhibition

If drug A is metabolized by a cytochrome P450 enzyme and drug B inhibits or decreases the enzyme's activity, then drug A will remain with high levels in the plasma for longer as its inactivation is slower. As a result, enzymatic inhibition will cause an increase in the drug's effect. This can cause a wide range of adverse reactions.

Enzymatic induction

If drug A is metabolized by a cytochrome P450 enzyme and drug B induces or increases the enzyme's activity, then blood plasma concentrations of drug A will quickly fall as its inactivation will take place more rapidly. As a result, enzymatic induction will cause a decrease in the drug's effect.

Excretion interactions

Renal excretion

Only the free fraction of a drug that is dissolved in the blood plasma can be removed through the kidney. Therefore, drugs that are tightly bound to proteins are not available for renal excretion, as long as they are not metabolized when they may be eliminated as metabolites (Bádenas, 2017-2018). Creatinine clearance is used as a measure of kidney functioning but it is only useful in cases where the drug is excreted in an unaltered form in the urine. The excretion of drugs from the kidney's nephrons has the same properties as that of any other organic solute: passive filtration, reabsorption and active secretion. In the latter phase the secretion of drugs is an active process that is subject to conditions relating to the saturation of the transported molecule and competition between substrates. Therefore, these are key sites where interactions between drugs could occur. Filtration depends on a number of factors including the pH of the urine, it having been shown that the drugs that act as weak bases are increasingly excreted as the pH of the urine becomes more acidic, and the inverse is true for weak acids.

Bile excretion

Bile excretion is different from kidney excretion as it always involves energy expenditure in active transport across the epithelium of the bile duct against a concentration gradient. This transport system can also be saturated if the plasma concentrations of the drug are high. Bile excretion of drugs mainly takes place where their molecular weight is greater than 300 and they contain both polar and lipophilic groups. The glucuronidation of the drug in the kidney also facilitates bile excretion.

Example studies

Valproate toxicity developed in three patients given large and repeated doses of aspirin. Increased levels of free valproate were found in 5 children within hours of them taking aspirin. Conversely, a slightly reduced valproate level was reported in one patient who took ibuprofen. Modestly altered protein binding has been shown when sodium valproate was given with diflunisal or naproxen, but this appears unlikely to be clinically important.

Clinical evidence, mechanism, importance and management

A 17 year old girl taking valproate 21 mg/kg daily was prescribed aspirin 8 mg/kg daily for lupus arthritis. Within a few days she developed a disabling tremor which disappeared when the aspirin was stopped. Total serum valproate levels were not significantly changed but the free fraction fell from 24% to 14% when the aspirin was withdrawn (Goulden et al., 1987).

Aspirin displaces valproate from its protein binding sites Farrell, Intern Med (1998) and also alters its metabolism by the liver (Farrell et al., 1982), so that the levels of free (and pharmacologically active) valproate rise. This could temporarily increase both the therapeutic and toxic effects of the valproate. However, there is evidence that increased hepatic elimination of valproate counterbalances this effect. Valproate and aspirin are highly bound to plasma proteins, such as albumin (Goulden, 1987; Abbott et al., 1986; Pisani, 1992). Thus when they are co-administered at sufficient doses, there is mutual displacement and a rise in the free fraction of each drug. Moreover, aspirin is an inhibitor of beta-oxidation, and this process is responsible for roughly 40% of valproate's metabolism. These two factors combine to produce modest increases in total valproate levels and it leads to significant increase in valproate concentrations.

Direct information seems to be limited to the studies cited. Clinically relevant interactions appear rare, probably because in most cases the effects of aspirin on free valproate levels cancel each other out. The combination need not necessarily be avoided, but it would seem prudent to be aware of this interaction if valproate and high aspirin are used.

Conflicts of interest: None

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