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Research Article

Clinically Important Pharmacokinetic Drug-Drug Interactions: An Overview of Excretion, Factors Affecting Excretion, and Transporter Mechanisms.

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Abstract:

Given the rising incidence of polypharmacy, it is more crucial than ever to take medication interactions into account. A drug-drug interaction (DDI) occurs when one drug alters the pharmacokinetics or pharmacodynamics of another, affecting its function. Drugs and other compounds found in foods, supplements, herbs, and tobacco products can also interact. Drug–disease and drug–laboratory test interactions are examples of further drug interactions. Drug-drug interactions (DDIs), which occur 20–40% of the time, are among the most common causes of prescription mistakes in developed countries, particularly for elderly patients. who are receiving multiple medications. Specifically, poly-therapy makes therapeutic management more complicated and raises the possibility of clinically significant DDIs, which can either decrease clinical effectiveness or cause adverse medication responses. Substance-substance Specifically, by complicating therapeutic management. Pharmacokinetics and pharmacodynamics are the two primary categories into which drug-drug interactions fall. When one medication changes the pace or degree of another's absorption, distribution, metabolism, or excretion, this is known as a pharmacokinetic drug interaction. With a focus on their clinical implications, This review aims to provide an overview of clinically important pharmacokinetic drug excretion interactions and their implications that are clinically important.

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Introduction

It should be taken into account that a patient who is admitted for an urgent illness may also need medication for other comorbidities, such as infections. When making treatment plans, it's crucial to consider any potential interactions between these medications. When additional medications are added to individuals with polypharmacy, the chance of interactions rises. According to studies, between 37 and 60 percent of patients may have an interaction while in the hospital, which might result in a decrease in efficacy or an increase in side effects. **[1].**

DDIs typically involve a precipitant drug (perpetrator), which alters the pharmacokinetics or pharmacodynamics of an object drug (victim). In some cases, these interactions can be bidirectional, where both drugs influence each other's effects. **[2].**

pharmacokinetic (PK) interactions these interactions are those in which ADME properties of the object drug is altered by the precipitant and hence such interactions are also called as ADME interactions". The resultant effect is altered plasma concentration of the object drug. When the precipitant medication modifies the target drug's absorption, distribution, metabolism, or excretion, pharmacokinetic (PK) interactions take place.These interactions are usually controlled by monitoring medication levels or vital signs. **[3].**

Pharmacodynamic (PD) interactions Are those in which the activity of the object drug at its site of action is altered by interactions or the effect of one drug is changed by the presence of another drug acting at the same biochemical or molecular site (e.g., drug receptor or second messenger system), on the same target organ, or on a different target but one that is associated with a common physiological process essentially when one drug modulates the pharmacologic effect of another by producing additive, synergistic or antagonistic. Synergistic or antagonistic effects from medication interactions might change a drug's toxicity or efficacy and need changing doses. **[4].**

Little variations in medication concentrations or effects are particularly essential since medications with a low therapeutic index are the most frequently implicated in PK or PD interactions. Genetic polymorphisms, renal or hepatic diseases, and even individual variability are all examples of patient variables that might cause high inter-individual variability. **[5].**

Most medications are eliminated in the urine or bile, with the exception of inhalation anesthetics. The glomeruli of the tubules receive blood entering the kidneys through the renal arteries. Water, minerals, and some drugs that are small enough to pass through the pores of the glomerular membrane are filtered into the tubule lumen. The blood contains bigger molecules such blood cells and plasma proteins**.[6]**

Active energy-using transport systems can then take drugs and metabolites from the blood and release them into the tubular filtrate, while blood flow continues to the remaining renal tubules. Renal tubular cells contain both active and passive transport pathways for drug reabsorption. Medication can alter how other pharmaceuticals are excreted by affecting the pH of renal tubular fluid, active transport systems, and blood flow to the kidney. **[7].**

It is always important to evaluate DDI information in a therapeutic setting. Renal excretion of medications suffers interference that leads to drug interactions primarily due to two factors: competition for renal tubular secretion together with alterations in tubular reabsorption. After uptake by Organic Cation Transporter 2 across the basolateral membrane of proximal tubular cells follow fundamental phase of Multidrug and Toxin Extrusion transporters 1 and 2-K (MATE1/MATE2-K)-mediated efflux across the luminal membrane. Every interaction mediated through renal transporters generates weaker drug effects than hepatic transporter interactions but remains clinically important. Renal tubular secretion is generally mediated by a coordinate activity of transporter-mediated uptake across the basolateral

membrane of proximal tubular cells by OCT2 and of transporter-mediated export across the luminal membrane by multidrug and toxin extrusion 1 and 2-K (MATE1/MATE2-K). Renal transporter-mediated drug interactions tend to be more modest compared to those mediated by hepatic transporters.

Factor Affecting Renal Drugs Excretion

(a) Changes in urinary pH

The proportion of non-ionized drug form in the renal tubules determines passive reabsorption rates because the process depends on both pKa value and the urinary pH conditions. Urinary pH plays a crucial role in renal drug excretion by influencing drug ionization, as described by the Henderson Hasselbalch equation. Weak acids (pKa 3–7.5) are more ionized and excreted in alkaline urine, whereas weak bases (pKa 7.5–10.5) are more ionized and eliminated in acidic urine. Since ionized drugs are less lipophilic, they cannot diffuse back into renal tubules, increasing elimination In a way similar to drug absorption through the gastrointestinal tract passive reabsorption occurs in the renal tubules. Drugs pass through lipid tubular cell membranes only as their non-ionized lipid-soluble state exists. Acidic drugs focusing on pKa values between 3 to 7.5 exist mainly as ionized lipid-insoluble forms inside environments with high urinary alkalinity. The ionized forms fail to reenter the tubule cells because of their inability to diffuse through the membranes thus ending up in urine,Weak bases measuring between 7.5 and 10.5 pKa keep as ions in acidic urine conditions. Urine pH modifications play a key role in controlling drug ionization levels which subsequently determines the rates of drug reabsorbing and eliminating from the body. weak acids are more ionized in alkaline urine and weak bases are more ionized in acidic urine. The drug molecule stays ionized through pH changes which improves its urinary elimination while decreasing its reabsorption by the body. Conversely, shifting the pH in the other way would enhance drug retention.. ‘Fig. 1, illustrates the situation with a weakly acidic drug **[9]**

The clinical significance of this interaction mechanism is small, because although a very large number of drugs are either weak acids or bases, almost all are largely metabolized by the liver to inactive compounds and few are excreted in the urine unchanged. In practice therefore only a handful of drugs seem to be affected by changes in urinary pH (possible exceptions include changes in the excretion of ‘quinidine’, or ‘analgesic-dose aspirin’, due to alterations in urinary pH caused by antacids, and the increase in the clearance of ‘methotrexate’, with urinary alkalinisers). In cases of overdose, deliberate manipulation of urinary pH has been used to increase the removal of drugs such as methotrexate and salicylates **[10].**

Trimethoprim increased metformin AUC by 1.3 to 1.4-fold. Another example is that probenecid must be taken in order to avoid cidofoviir nephrotoxicity. Cidofovir's cytotoxic effects on the kidneys are controlled by the organic anion transporter 1 (OAT1), which probenecid inhibits.**[8].**

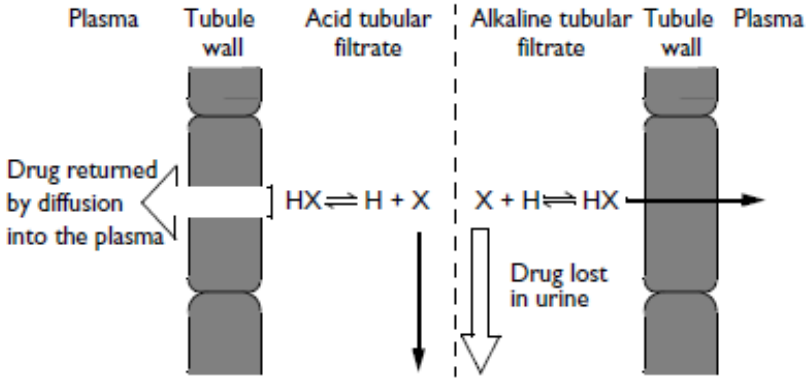

Fig. 1 An excretion interaction. If the tubular filtrate is acidified, most of the molecules of weakly acid drugs (HX) exist in an un-ionised lipid-soluble form and are able to return through the lipid membranes of the tubule cells by simple diffusion. Thus they are retained. In alkaline urine most of the drug molecules exist in an ionised non-lipid soluble form (X). In this form the molecules are unable to diffuse freely through these membranes and are therefore lost in the urine.

Example of drug excretion interaction

Quinidine + Antacids or Urinary alkalinisers

Large rises in urinary pH due to the concurrent use of some antacids, diuretics or alkaline salts can cause quinidine retention, which could lead to quinidine toxicity, but there seems to be only one case on record of an adverse interaction (with an aluminium/magnesium hydroxide antacid). Aluminium hydroxide alone appears not to interact **[11].**

Mechanism

Quinidine is excreted unchanged in the urine. In acid urine much of the quinidine excreted by the kidney tubules is in the ionised (lipid-insoluble) form, which is unable to diffuse freely back into the cells and so is lost in the urine. In alkaline urine more of the quinidine is in the non-ionised (lipid-soluble) form, which freely diffuses back into the cells and is retained.

In this way the pH of the urine determines how much quinidine is lost or retained and thereby governs the serum levels. In *vitro* data suggest that changes in pH and adsorption effects within the gut due to antacids could also affect the absorption of quinidine **[12].**

Aspirin or other Salicylates + Antacids

The serum salicylate levels of patients taking large, anti-inflammatory doses of aspirin or other salicylates can be reduced to subtherapeutic levels by some antacids. The maximum plasma levels of aspirin may be increased by antacids, although the extent of absorption is unaltered.

Mechanism

Aspirin and other salicylates are acidic compounds that are excreted by the kidney tubules and are ionised in solution. In alkaline solution, much of the drug exists in the ionised form, which is not readily reabsorbed, and therefore is lost in the urine. If the urine is made more acidic (e.g. with ammonium chloride), much more of the drug exists in the un-ionised form, which is readily reabsorbed, so that less is lost in the urine and the drug is retained in the body. In vitro data show that magnesium oxide and aluminium hydroxide strongly adsorb aspirin and sodium salicylate. However, in three of the studies above aluminium hydroxide-containing antacids had no effect on

the extent of absorption of salicylate, although the rate of absorption may be increased as a result of an increase in the solubility of

salicylate in a less acidic gastric environment **[13,14].**

Methotrexate + Urinary alkalinisers

Alkalinisation increases the solubility of methotrexate in the urine and also increases its excretion. Methotrexate is much more soluble in alkaline than in acid fluids, therefore urinary alkalinisers such as sodium bicarbonate and acetazolamide are often given to patients receiving high-dose methotrexate to prevent the precipitation of methotrexate in the renal tubules, which would cause damage. However alkalinisation also increases the loss of methotrexate in the urine because at high pH values more of the drug exists in the ionised form, which is not readily reabsorbed by the tubules.

This increased loss was clearly shown in about 70 patients in whom alkalinisation of the urine (to pH greater than 7) with sodium bicarbonate and hydration reduced the serum methotrexate levels at 48 hours by 73% and at 72 hours by 76%.1 In this instance the interaction was being exploited therapeutically to avoid toxicity. This interaction has also been shown by others. The possible consequences should be recognised if concurrent use is undertaken Table 1.5', lists some possible interaction due to change in renal transport **[15].**

Table 1.5 Examples of interactions probably due to changes in renal transport

Drug affected	*Interacting drug*	*Result of interaction*
Cephalosporins Dapsone Methotrexate Penicillins Quinolones	Probenecid	Serum levels of drug affected raised; possibility of toxicity with some drugs
Methotrexate	Salicylates and some other NSAIDs	Methotrexate serum levels raised; serious methotrexate toxicity possible

(b) Changes in active renal tubular excretion

The renal tubular excretion pathways become targets for medication interactions because different drugs attempt to use similar active transport systems. The substance probenecid functions as a renal secretion inhibitor of penicillin and other drugs through its mechanism of hindering active transport. Testimonies from recent research confirm the mechanism of action for probenecid as the substance impedes organic anion transporters (OATs) while these transporters control tubular excretion of anionic medications in the kidneys. The simultaneous competition for the transporters caused by probenecid leads to reduced drug elimination which contributes to elevated plasma drug levels and affected pharmacokinetics. This mechanism demonstrates how renal transporter proteins influence the assessment and administration of drug-drug interactions especially among drugs which heavily depend on renal elimination processes. Additionally, several of the kidney's ABC transporters may be inhibited by probenecid. P-glycoprotein and the ABC transporter are also found in the kidneys, and treatments that alter them might affect how effectively the body gets rid of them.. **[16].**

(c) Modifications to renal blood flow

Blood flow via the kidney is partially controlled by renal vasodilatory prostaglandin production. If the generation of these prostaglandins is inhibited, some medications may be excreted less often by the kidneys. This is the suggested mechanism for the interaction between various NSAIDs and the

rise in serum lithium that has been reported.. **[17].**

'Lithium + NSAIDs',

The use of Nonsteroidal anti-inflammatory drugs (NSAIDs) elevates lithium levels within the serum which might result in lithium toxicity for patients. The interaction between lithium and NSAIDs shows wide-ranging effects which differ among various drugs in addition to variations between individual patients who take the same medication. Celecoxib leads to an average 17% lithium level rise per research but reports show this NSAID can elevate lithium levels as much as 344% in specific cases. Research evidence indicates that NSAIDs as a group show similar effects on lithium levels because these medications share pharmacodynamic and pharmacokinetic processes. The kidney vasodilatory effect of prostaglandins gets inhibited by NSAIDs primarily because they lead to decreased renal blood flow and glomerular filtration rate (GFR). When this occurs lithium absorption in the proximal tubules rises which causes serum lithium levels to become higher. **[18].**

Mechanism

Not clear. It has been proposed that the NSAIDs that interact with the kidneys prevent the production of renal prostaglandins (PGE2), which lowers renal blood flow and, consequently, lowers the amount of lithium excreted by the kidneys. Furthermore, higher reabsorption of lithium and sodium may be linked to decreased renal PGE2 levels. However, this does not explain why serum-lithium levels are often unaffected by aspirin, which suppresses renal prostaglandin production by 65 to 70%. **[18].**

(D) Biliary excretion and the entero-hepatic shunt

(i) Recirculation of the enterohepatic

Many medications, either unaltered or conjugated (such as glucuronide) to increase their solubility in water, are eliminated by the bile. The gut flora converts some of the conjugates into their parent molecule, which is then reabsorbed. Even while this recycling mechanism lengthens the medication's duration in the body, an antibiotic that reduces the gut flora is not recycled and is eliminated from the body more quickly. This may also help to explain why concurrent use of tetracyclines or penicillins might occasionally lead to oral contraceptive failure. **[19].**

Contraceptives + Antibacterials; Penicillins

The antibiotics ampicillin, amoxicillin, flucloxacillin, oxacillin, phenoxymethylpenicillin, pivampicillin, and talampicillin have all been implicated with combined oral contraceptive failure. But the interaction—if there is one—seems to be quite uncommon. Ampicillin has not been shown to have any effect on ovarian suppression or contraceptive steroid levels in controlled investigations.**[20].**

Mechanism

The body system of enterohepatic recirculation significantly supports the metabolism and sustains the active concentration of estrogen in oral contraceptive medications. The contraceptive formula containing estrogen releases this hormone in the bile as sulfate and glucuronide

derivatives. The intestine bacteria break down the intestine-intaken conjugates to generate free forms that reconnect to the bloodstream. The overall purpose of this process keeps estrogen levels at sufficient amounts for effective contraception prevention. Science indicates that antibacterial medications like antibiotics can reduce the bacterial presence essential for deconjugating steroid compounds. Non-absorption of conjugated forms becomes more pronounced following the decrease of enterohepatic recirculation process due to their inefficient reuptake. The contraceptive becomes less effective when women experience subpar levels of circulating estrogen due to this effect. The interaction demonstrates that doctors need to evaluate how antibiotics affect gut bacteria while determining suitable contraception methods when patients take antibiotics.

(ii) Drug transporters

Increasing research indicates that a variety of drug transporter proteins, such as those

belonging to the ABC and SLC families, are involved in the hepatic extraction and release of medications into the bile. Numerous drugs, including bosentan, glibenclamide, and ciclosporin, are known to inhibit the bile salt export pump (ABCB11), however it is yet unclear how many of them are related to drug interactions. The maker of bosentan advises patients using the medication to avoid inhibiting this pump as it may raise their chance of developing cholestasis. **[21]**.

Drug transporter proteins

In addition to passive diffusion, drugs and endogenous chemicals can also flow through biological membranes through carrier-mediated mechanisms, commonly referred to as transporters. Though it is yet unknown how many of them contribute to drug interactions specifically, significant progress has been made in identifying different transporters. The ATP-binding cassette (ABC) transporter P-glycoprotein (P-gp) represents a prominent member of multimembrane transporters which acts to eject drugs from cells while its genetic basis stems from the MDR1 gene (ABCB1 gene). The bile salt export pump (BSEP) stands as an important ABC transporter that also goes by the name sister P-glycoprotein (ABCB11). The bile acid secretion function of BSEP stands essential for bile flow since its inhibition or malfunction has been linked to an increased chance of developing cholestasis.Several critical drug transport functions during membrane transit occur through the essential solute carrier (SLC) superfamily members alongside ABC transporters. The SLC transporters comprise three major groups known as OCTs, OATs and OATPs which collectively enable drug absorption and distribution and excretion from the body. The drugмегgenecid blocks transport activities of OATs by vying for use of these transport systems which results in modified drug clearance levels and possible changes in plasma drug amounts. **[23].**

glibenclamide' and 'ciclosporin'

Glibenclamide and bosentan tend to enhance the risk of liver damage, thus it is best to avoid taking them together. Bosentan lowers glibenclamide's plasma levels, whereas glibenclamide lowers bosentan's plasma levels.

Cyclosporin raises bosentan levels, whereas bosentan slightly lowers ciclosporin levels. The combination is contraindicated by the bosentan manufacturer because to the potential elevated risk of liver damage. **[22].**

(a) P-glycoprotein interactions

There is mounting evidence that some medication interactions happen as a result of the drugs interfering with P-glycoprotein function. This efflux pump, which is present in some cell membranes, possesses the capacity to expel drugs and metabolites from cells.. It can affect how much a drug is absorbed by the gut, distributed to the brain, testis, or placenta, and eliminated through the urine and bile. For instance, some drug molecules that have already been absorbed may be ejected back into the intestine by the P-glycoprotein in the gut lining cells, which would lower the overall quantity of medication absorbed. P-glycoprotein functions as an absorption barrier in this manner. Certain medications can also be expelled from the brain via P-glycoprotein activity in the blood-brain barrier's endothelial cells, which restricts their ability to enter the central nervous system and have an impact **[24].**

Drugs can affect P-glycoprotein (P-gp) operational levels since this important transport protein is involved in drug uptake from the body and drug release from the body. As an effective P-gp inducer rifampicin (rifampin) makes P-glycoprotein in gut lining cells work with accelerated efflux potential. The elevated activity produces better substrate elimination from the gastrointestinal space including digoxin. Lower plasma concentrations of the drug occur because the intestinal absorption of digoxin decreases.

Patients taking both digoxin and rifampicin experience diminished therapeutic benefits of digoxin due to reduced bioavailability which the medical community summarizes as "Digitalis glycosides + Rifamycins".

The pharmaceutical agent verapamil functions as a P-glycoprotein inhibitor which blocks normal protein export activity. The administration of verapamil prevents P-gp from eliminating digoxin from cell walls allowing the drug to accumulate in bloodstreams. Other medications affect how the body absorbs digoxin so plasma levels rise which increases the risk of medical side effects when no proper monitoring and management strategies are used. **[25].**

glycosides + Calcium-channel blockers; Verapamil

It has been demonstrated that ketoconazole raises CSF levels of ritonavir, potentially by blocking its efflux from the central nervous system. It also exhibits P-glycoprotein inhibitory actions. Therefore, the pharmacokinetics of several medications may be impacted by the activation or inhibition of P-glycoprotein. It should be noted that P-glycoprotein inhibition could affect medication distribution (like into the brain) more than drug absorption (like plasma levels). **[26].**

CYP3A4 and P-glycoprotein substrates, inducers, and inhibitors have similarities. Therefore, many of the medication interactions that are generally attributed to CYP3A4 alterations may include both pathways.. 'Table 1.6', lists some possible P-glycoprotein inhibitors and inducers.

Table 1.6 Some possible inhibitors and inducers of P-glycoprotein shown to alter the levels of P-glycoprotein substrates in clinical studies[1]

Inhibitors		*Inducers*
Atorvastatin	Ketoconazole	Rifampicin
Clarithromycin	Propafenone	St John's wort (*Hypericum perforatum*)
Dipyridamole	Quinidine	
Erythromycin	Valspodar	
Itraconazole	Verapamil	

Some cancer cells also express P-glycoprotein, which is where it was initially discovered. In order to improve the capacity of cytotoxic drugs to penetrate cancer cells, a number of P-glycoprotein inhibitors, including valspodar, have been developed.

Risk factors for patients who are more susceptible to adverse interactions

Adverse Drug interaction ADRs are caused by a variety of variables, some of which are associated with the patient, the medication, or society. For example, age has a significant influence on the incidence of adverse drug reactions (ADRs); patients of all ages are more susceptible to these responses than those of other age groups. ADRs are significantly impacted by alcohol use as well. Gender, ethnicity, pregnancy, breastfeeding, liver function, renal issues, frequency and dosage of medications, and many other characteristics are also considerations. The medical literature has extensively established the impact of these variables on adverse drug reactions. Medical professionals can select the most effective medication regimen by taking these aspects into account during medical examination **[27].**

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