for changes in symptoms, biomarkers of effect, or drug concentrations soon after prescription changes helps identify drug interactions early and can reduce harm.

Conclusion

Most potential drug interactions can be recognised by applying principles of clinical pharmacology and good clinical care. Increased vigilance by clinicians at the time of changing drugs improves the chance of identifying unwanted drug interactions before they cause significant harm. Knowing a few drugs well and making judicious use of available information is more effective for managing drug interactions than relying solely on electronic decision support.

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Drug-drug interactions: principles and practice

The pharmacological result (either desirable or undesirable) of drugs interacting with themselves or other drugs, with endogenous physiologic chemical agents (e.g. MAOI with epinephrine), with components of the diet such as food, nutritional supplements, with formulation excipients, with chemicals used in diagnostic tests or the results of such tests, with environmental factors or even with disease is known as **drug interaction**. When two or more drugs are involved in such drug interaction, it is known as **Drug-Drug Interaction (DDI)**.

The resultant effect of a DDI may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug. The interaction may be the result of

- a physico-chemical dealing of the two drugs, leading to
  - a change in the rate of absorption or the quantity absorbed in the body,
  - the binding ability of either drug, or
  - an alteration in the ability of receptor sites and cell membranes to bind either drug etc.

Epidemiology

Epidemiological data relating to the negative clinical outcome of DDIs has been rare and therefore the expression ***potential* DDI (pDDI)** is widely used. Even though many papers on drug interactions have been published in recent years from different countries, most of them focused on pDDIs rather than on actual interactions. The published incidence of actual DDIs is consistently lower than that of pDDIs.

Harmful DDIs account for about 10–20% of the adverse drug reactions requiring hospitalization and as they can be avoided, knowledge about DDI is very important.

The predictability of the DDI is largely derived from drug properties, method of drug administration, and patient-specific parameters. Consequently, adverse outcomes resulting from DDIs can be prevented by making patient- and situation-specific assessments and, if appropriate, **avoiding concomitant administration** by implementing **alternative therapeutic strategies**, or taking **precautionary measures** such as **dosage adjustments** and **increased monitoring**.

Types of drug-drug interactions

Interactions between drugs may be categorized by the underlying mechanism:

Behavioral DDIs occur when one drug alters the patient's behavior to modify compliance with another drug. For example a depressed patient taking an antidepressant may become more compliant with medication as symptoms improve.

Pharmaceutic DDIs occur when the formulation of one drug is altered by another before it is administered. For example precipitation of sodium thiopentone and vecuronium within an intravenous giving set.

Pharmacokinetic DDIs occur when one drug changes the systemic concentration of another drug, altering 'how much' and for 'how long' it is present at the site of action. This can be

an alteration in concentration of one drug by other through altering its absorption, distribution, metabolism, or excretion.

Pharmacodynamic DDIs occur when interacting drugs have either ADDITIVE effects, in which case the overall effect is increased; ANTAGONISTIC effects, in which case the overall effect is decreased or even 'cancelled out'; SYNERGISTIC effect in which pharmacologic effect is greater than the summation of each drugs effect.

Pharmacokinetic drug–drug interactions

Pharmacokinetics deals with the drug's journey through the body which includes absorption, distribution, biotransformation, storage, redistribution and elimination. During these processes, drug interactions occur when one drug (the perpetrator) alters the concentration of another drug (the object) with clinical consequences.

Altered bioavailability

When the amount of the object drug reaching the systemic circulation is affected by a perpetrator drug, e.g. when absorption or first-pass metabolism is altered in case of orally administered drugs, bioavailability gets altered. Drugs with low oral bioavailability are more frequently affected than those with high bioavailability. For example alendronate and dabigatran have low oral bioavailability. Co-administration with calcium can result in no alendronate being absorbed consequently decreasing the bioavailability while dabigatran co-administration with verapamil increases bioavailability and can result in an increased risk of bleeding.

Altered clearance

A perpetrator drug may affect metabolism or excretion of the object drug, particularly those with a narrow therapeutic index. Perpetrator drugs known to strongly affect drug metabolism, e.g. the perpetrators of the cytochrome P450 (CYP) DDI, are more likely to cause large concentration changes and in turn clinical consequences. Recognising these potential perpetrators of pharmacokinetic DDIs is important.

Metabolism

Changes in drug metabolism are the most important causes of unexpected drug interactions. These occur by changing drug clearance or oral bioavailability. There are several enzyme families involved in drug metabolism, the CYP enzyme family being the most important ones.

Inhibition of a CYP enzyme increases the concentration of some drugs by decreasing their metabolism. For example clarithromycin is a strong inhibitor of CYP3A-catalysed simvastatin metabolism, thus increasing the risk of myopathy. Drug inhibition of CYP enzymes is also used therapeutically. For example ritonavir, a strong inhibitor of CYP3A, reduces metabolism of other protease inhibitors thus increasing their effectiveness in treating HIV (so called 'ritonavir-boosted' regimens).

Induction of a CYP enzyme decreases the concentration of some drugs by increasing their metabolism. For example carbamazepine is a strong inducer of CYP3A that increases the metabolism of the combined oral contraceptive, thus increasing the risk of unwanted pregnancy.

Prodrugs

Some drugs rely on CYP enzymes for conversion to their active form by a process known as bioactivation. As this is usually dependent on a single enzyme pathway, prodrugs are particularly vulnerable to changes in metabolism. Inhibition of bioactivation may lead to inadequate concentrations of the active drug and therapeutic failure. For example, tamoxifen is metabolised by CYP2D6 to its active form endoxifen, and concomitant therapy with the strong CYP2D6 inhibitor paroxetine has been associated with increased mortality in breast cancer.

Excretion

Some drugs are excreted from the body unchanged in the active form, usually in the urine or via the biliary tract in the feces. Effects on renal tubular function or urine pH may alter renal drug clearance. For example probenecid reduces the renal clearance of anionic drugs such as methotrexate and penicillin.

Altered distribution

This occurs when the concentration of drug at the site of action is changed without necessarily altering its circulating concentration. This is particularly an issue for drugs with intracellular or central nervous system targets. Some drugs cause significant changes in the cell membrane transport of other drugs. For example verapamil inhibits efflux transporters (e.g. P-glycoprotein) increasing the concentrations of substrates such as digoxin and cyclosporin. Probenecid inhibits anion transporters (e.g. OAT-1) increasing the concentrations of substrates such as methotrexate and penicillins.

Pharmacodynamic drug–drug interactions

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and the mechanisms of their actions. These interactions occur between drugs with additive or opposing effects. The brain is the organ most commonly compromised by pharmacodynamic interactions.

Pharmacodynamic interactions between drugs with additive effects may be intentional (e.g. when combining antihypertensives) or unintentional (e.g. serotonin syndrome caused by adding tramadol to a selective serotonin reuptake inhibitor). Conversely, combining drugs with opposing effects can result in loss of drug effect, e.g. reduced bronchodilation by a β_2 agonist prescribed with a non-selective β blocker.

Considering drug effects by organ is a useful way to recognise pharmacodynamic interactions. Ask yourself – might any of these drugs affect the same organ (e.g. the brain)? This allows you to consider interactions between drugs with different modes of action, e.g. an anticholinergic and a benzodiazepine.

How to avoid unwanted drug–drug interactions in clinical practice

In order to reduce the number and to improve the management of pDDIs, physicians primarily have to be aware of the presence of the pDDI. Obtain a thorough drug history, including over-the-counter and herbal products. Pharmacodynamic DDIs can be anticipated based on knowledge of the clinical effects of the drugs involved. The better the pharmacological knowledge, the easier it is! Prescribe few drugs and know them well. Pharmacokinetic DDIs are more difficult to anticipate since they are not predictable from the clinical effects of the drugs involved. Recognition of drugs that have a narrow therapeutic index and the major perpetrators of pharmacokinetic interactions will help identify most of these.

Five 'rules' to manage potential DDIs in clinical practice is available:

- Any interactions between existing drugs in a given patient have already occurred. Hence they are part of differential diagnosis.
- Knowledge of the pharmacological effects of drugs and of patient physiology together allows recognition of potential pharmacodynamic DDIs.
- Drugs with a narrow therapeutic index are particularly susceptible to pharmacokinetic DDIs.
- A small number of drugs are important 'perpetrators' of pharmacokinetic DDIs.
- Starting or stopping a drug is a prescribing decision that may cause a drug interaction.

Monitoring patients for drug toxicity or loss of efficacy is part of routine care. Checking