

Drug Interactions:

A Method to the Madness

With many cardiac patients taking at least four or five medications, drug interactions are bound to occur. To ensure patient well-being, it is paramount to understand medications and predict interactions before they occur. Dr. Lin lends a hand by reviewing the underlying mechanisms behind drug interactions.

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Rick's case

Rick, 55, recently suffered a myocardial infarction.

He is currently on quadruple therapy of metoprolol, acetylsalicylic acid, angiotensin-converting enzyme inhibitor, and statin.

Three months into therapy, Rick develops depression. His family doctor prescribes fluoxetine.

Shortly thereafter, he develops syncopal episodes with marked bradycardia.

What's causing Rick's condition? For more, go to page 22.

Having an awareness of drug interactions is more important today than ever before. The aging population requires multiple medications as new guidelines recommend the use of multiple classes of medication to protect these patients.

As an example of polypharmacy, look at patients' post-myocardial infarction (MI). They should be taking antiplatelet therapy, a statin, angiotensin-converting enzyme (ACE) inhibitor, and beta blocker. This quadruple therapy forms the basis of state-of-the-art treatment.

We are constantly trying to treat patients earlier, meaning they will need multiple therapies for longer durations. With this new found polypharmacy philosophy comes the risk of drug interactions (DI). In fact, physicians today need to not only know about all the prescribed drugs a patient is taking, but also all the herbal medications they may be using as well.

Many cardiac patients are on at least four or five medications. It has been estimated that the risk of DI can increase from 6% in patients taking two medications, to 50% with five medications, and 100% with up to 10 medications.¹ In order to avoid interactions, it is important to review some basic concepts in pharmacology.

1 Pharmacodynamics

An example of a pharmacodynamic interaction is when an ACE inhibitor is combined with an angiotensin receptor blocker (ARB). Both medications block the renin-angiotensin-aldosterone system (RAAS), which can lead to increased potassium levels in the body. While the ACE/ARB combination has been shown to have significant benefits for heart failure patients, one must monitor for hyperkalemia because of this pharmacodynamic interaction.

The RALES study showed that spironolactone was useful in heart failure as well. However, it is an aldosterone antagonist and it too drives up potassium in the body. A combination of this plus an ACE inhibitor or ARB may result in significant hyperkalemia as well.

2 Pharmacokinetics

The body goes through four steps when processing all medications. It absorbs, distributes, metabolizes, and eliminates drugs. Each step is important. Anything affecting these four steps can affect the drug levels in the body: too low and there won't be any effect, and too high would create side-effects.

Absorption

Certain medications can have variable absorption. For example, digoxin absorption increases with less acidity in the stomach. Taking digoxin with antacids, H2 blockers, or proton pump inhibitors will increase digoxin levels in the blood. Physiologically, the elderly have less acid in their stomachs, and hence they have higher digoxin absorption, even when they have been taking the same dose for years.

Distribution

Distribution deals with where the drug goes within the body (*i.e.*, into fat stores or attaching to protein, *etc.*). Drugs that are highly protein-

Types of interaction

There are two key concepts in pharmacology:

1. **Pharmacodynamics:**
What the drug does to the body
2. **Pharmacokinetics:**
What the body does to the drug

Drug interactions can be split up into these two categories.

It has been estimated that the risk of DI can increase from 6% to 50% for those taking two and five medications, respectively.

About the author...

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Followup on Rick

The bradycardia points to an excess of metoprolol, a substrate of CYP 2D6, as the cause of syncope.

Fluoxetine is not only a substrate, but also an inhibitor of CYP 2D6 enzyme. Therefore, the fluoxetine blocked the CYP 2D6, and the metoprolol was not processed in the usual manner. The metoprolol levels rose, resulting in bradycardia and syncope.

This case illustrates how understanding the terminology can help detect and predict interactions.

bound have very little free medication. If another drug, having a higher affinity to the protein, comes in and displaces the drug, the free medication will dramatically increase and side-effects may ensue.

Metabolism

Metabolism refers to all the biotransformation a medication undergoes in the body. Clearly, drug levels would be altered if the pharmacokinetic processes are sped up or blocked.

Think about a patient taking warfarin for atrial fibrillation. If amiodarone is added to see if he can be converted to sinus rhythm, then the warfarin levels will rise because amiodarone blocks the metabolism of warfarin.

International normalized ratios (INRs) could be used to adjust the warfarin dosage. While the INR is in the appropriate range one month later (2 to 3), amiodarone has a very long half-life, therefore, even at the same daily dose of amiodarone, the blood levels of amiodarone will continue to change for many months. This will also cause a change in the amount of warfarin in the body. So a good INR at one month may not be acceptable in three months.

Combining gemfibrozil and cerivastatin is not recommended as it increased cerivastatin levels by 559%.

Elimination

Elimination includes all the routes through which the drug can leave the body; it predominately occurs via the kidneys and feces. Renal or hepatic dysfunction will affect these routes and, subsequently, actual drug levels in the body.

Interactions involving cytochrome P450

Cytochrome (CYP) P450 are a set of enzymes found in the small intestine, liver, kidney, lungs, and brain. Their job is to make fat-soluble molecules more water soluble so they can be eliminated via the kidneys or feces.

Molecules that are processed are called substrates of the enzyme. For example, simvastatin is a substrate of CYP 3A4.² Inhibitors are chemicals that block the enzyme. Inducers are chemicals that speed up the enzyme activity.

Inhibitor interactions

Simvastatin is a substrate of CYP 3A4 and erythromycin is an inhibitor of that same enzyme. If simvastatin and erythromycin are used together, the CYP 3A4 would be blocked, preventing simvastatin from leaving the body in the usual way. As a result, the blood levels of simvastatin would rapidly increase, potentially leading to myopathy and rhabdomyolysis.

Gemfibrozil can also block statin metabolism and create complications. In particular, the combination of gemfibrozil and cerivastatin is not recommended because it has been shown to drive up cerivastatin levels by 559%.³

Furthermore, grapefruit juice blocks the CYP 3A4 in the intestine. This means that very little of the medication is processed as it crosses the gut wall, and so there is more drug available to enter the body.

7% to 10% of Caucasians, and 3% of the black and oriental populations, are known to be deficient in the CYP2D6 enzyme.

Inducer interactions

St. John's Wort is an inducer of CYP 3A4.⁴ Some calcium channel blockers (CCBs) are substrates of CYP 3A4. St. John's Wort increases the metabolism of the CCB, thus, there would be less CCB in the body, which may lead to worse blood pressure control.

Competitive interactions

Drugs can also interact based on competition. If too many drugs are sent toward the same enzyme, the medications may compete for the enzyme. Warfarin is a perfect example. Any other drug going through the same pathway will displace warfarin and the warfarin will not be processed, hence higher blood levels and side-effects.

By using the terminologies of substrate, inhibitor, inducer, and competition, it becomes possible to predict drug interactions that occur via the cytochromes.

Take-home message

- It is important to not only know all the prescribed drugs your patient is taking, but also all other medication (*i.e.*, herbals).
- Prescribed doses assume there will be normal metabolism in the patient. If they have faster or slower metabolism, dose adjustments are necessary.
- Drug response variations can be caused by genetics, age, inhibitors, inducers, *etc.* All factors that must be assessed prior to deciding which medication and what dose to prescribe.

What is the effect of genetic variation?

One final concept that is important in drug interactions is the effect of genetic variations. For example, some patients can only tolerate small doses of metoprolol, even in the absence of other medications. Could there be a genetic variation that explains this observation? The answer is, yes.


Approximately 40 years ago, it was noted that certain patients processed drugs quicker than others. Without a true understanding of the mechanisms involved, the

terms “extensive metabolizers” and “poor metabolizers” were coined to describe this phenomenon. Eventually, these differences were linked to the amount of cytochrome activity present in each patient; extensive metabolizers were patients with high cytochrome activity, while those with low activity were poor metabolizers.

CYP 2D6 is one such enzyme that exhibits polymorphism (*i.e.*, variation among people). Seven per cent to 10% of Caucasians, and 3% of the black and oriental populations, are known to be deficient in the CYP2D6 enzyme.⁵ Metoprolol is processed by this enzyme. Therefore, deficient patients would not be able to process metoprolol and, hence, even a small dose would result in very high blood levels of metoprolol.

Another example involves codeine. Codeine is a prodrug that requires CYP 2D6 to convert it into morphine. CYP 2D6 deficient patients would have no pain relief from codeine.

Essentially, every time a medication is prescribed, the dose chosen assumes there will be “normal” metabolism in that patient. If the patient has faster or slower metabolism, a dose adjustment is needed.

Drug response variations can be caused by genetics, age, inhibitors, inducers, *etc.*; these are the factors we must assess prior to deciding on the medication and dose. Interactions are only bad when we are unaware of them. Once we know about them, then we can make appropriate adjustments to ensure the well-being of our patients. 

References

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