Drug Interactions and Polypharmacy in the Elderly

With the seemingly constant flow of new therapeutic agents and new treatment indications for existing medications, polypharmacy is increasingly common, especially among elderly patients. While the benefits of comprehensive treatment are proven in well-designed trials, the risk of drug interactions (DIs) with each new combination in each patient must be carefully assessed. With a better understanding of pharmacodynamics and pharmacokinetics, these interactions can be predicted, prevented and minimized, allowing patients to benefit from a full spectrum of medical therapy.

by Peter Lin, MD, CCFP

Elderly patients often present with multiple medical conditions, and treating all of those conditions often necessitates polypharmacy. With each new guideline publication, increasing numbers of medications are shown to have benefits for our patients. In a post-myocardial infarction (MI) patient, for example, the current standard of care consists of using a statin, an angiotensin-converting enzyme (ACE) inhibitor, a beta-blocker and an antiplatelet agent. Each component of this quadruple therapy has been tested in large clinical trials and has been shown to have a significant benefit for the patient. In essence, this is the state-of-the-art, evidence-based medicine. But what about the risks of drug interactions (DIs) with polypharmacy?

As the number of medications being taken by a given patient increases, the risk of DIs in that patient also increases. The risk of DIs can increase from approximately 6% in patients taking only two medications to 50% in those taking five medications and 100% in those taking 10 medications.¹

Many DIs are avoidable, but those that are not require awareness of the interaction to allow for proper management and appropriate dosage adjustments. In reality, however, we must become knowledgeable not only about DIs; indeed, a broad understanding of how to use various drugs safely in our patients is essential. DIs comprise only one component of this complex issue.

For example, nonlinear pharmacokinetics may sound irrelevant to busy clinicians, but can have significant impact on their patients. Simply put, nonlinear pharmacokinetics means that doubling the dose of a given medication does not translate into just a doubling of the blood level or effect of the medication. For many medications, dose increases can produce exponential rises in blood levels, so even a small change in dose could mean a significant rise in the drug’s blood level and, hence, in potential side effects. This then becomes an important issue in prescribing safely to patients.

Similarly, it is important to be aware of medications employed in all therapeutic areas, because a medication prescribed by another physician or specialist can have effects on the medications a patient is already taking. This article focuses primarily on the DI aspect of these issues, with a particular emphasis on the cytochrome system. Examples are used to illustrate the method of the interactions discussed, and are not intended to provide an exhaustive list of all possible interactions.

Types of Interactions
In pharmacology, two key words that need to be understood are

Dr. Lin is Medical Director at the University of Toronto Health and Wellness Centre at Scarborough in Scarborough, Ontario.
“pharmacodynamics” and “pharmacokinetics.” Pharmacodynamics defines what a drug does to the body. Acetylsalicylic acid (ASA), for example, blocks platelet function, which results in increased bleeding time. Therefore, bleeding is the pharmacodynamic effect of ASA.

An example of a pharmacodynamic interaction is as follows: A patient takes over-the-counter ASA for his rheumatism and Ginkgo biloba for his memory. He develops atrial fibrillation (AF) and is prescribed warfarin by his cardiologist for stroke prevention. In this case, the ASA blocks the platelets and the warfarin affects the clotting factors. Both increase the risk of bleeding and, hence, the interaction is bleeding. Ginkgo biloba at high doses also increases bleeding. The pharmacodynamic interaction of all these medications would result in bleeding for the patient.

Pharmacokinetics, on the other hand, defines what the body does to the drug. The body absorbs the drug, distributes it, metabolizes it and then eliminates it. Anything that affects these four steps would affect the drug levels in the body; DIs can occur at any of these steps. For example, many elderly patients take bisphosphonates for osteoporosis. They also take calcium supplements. If they take these two medications together, the calcium binds onto the bisphosphonates and thereby reduces the absorption of the bisphosphonates. Bisphosphonates have low absorption to begin with, so this can almost eliminate any absorption of the drug. As a result, such patients are not getting the full benefit (or perhaps even any benefit) of their bisphosphonate treatment.

By comparison, other pharmacokinetic interactions could cause significant problems. Take, for example, the case of cisapride (used to treat gastroparesis, ileus, chronic constipation and gastroesophageal reflux disease). This medication has a useful dosing of 40 mg per day. In some cases, an interaction may occur when another medication (e.g., erythromycin) blocks the metabolism pathway of cisapride, which results in the accumulation of cisapride in the body. At high levels, cisapride causes prolongation of QT intervals, which could lead to Torsade de pointes.

Pharmacokinetics will ultimately determine the amount of medication in the body. Affecting any of these steps changes the drug levels in the body by making them either too high or too low. An important concept to remember is that for all medications there is a useful dosing window and a toxic dosing window. In fact, this is true for any chemical that enters the body. Even oxygen has useful and toxic “windows” (i.e., toxic effects are produced if a patient receives 100% oxygen over a prolonged period of time). The goal in prescribing safely is to keep our patients in the useful window and avoid the toxic window.

Unfortunately, however, not all medications are created equal. Some medications, like amoxicillin, can be given in doses of up to 2 g at once without any toxic effects. With medications like warfarin, on the other hand, even a 1-mg change in dosage could be disastrous. This is because each medication has its own unique set of useful and toxic windows. How close these two windows are to each other is known as the therapeutic index (TI). A narrow TI means the two windows are close together, so even a small change in drug levels can send the patient from the useful window into the toxic window. A wide TI means the dose can be increased significantly before toxic effects are produced.

The TI for each medication is important in predicting DIs, as medications with narrow TIs are at higher risk for DIs. Hence, appropriately guiding the dosing of medications such as digoxin, theophylline, and warfarin requires careful blood monitoring. However, even with medications with wide TIs (e.g., cisapride), an interaction that blocks the elimi-

Many DIs are avoidable, but those that are not require awareness of the interaction to allow for proper management and appropriate dosage adjustments. In reality, however, we must become knowledgeable not only about DIs; indeed, a broad understanding of how to use various drugs safely in our patients is essential.
nation of a drug can drive blood levels up high enough to hit the toxic window. Therefore, care and knowledge must guide the use of any medicine.

**Cytochrome P450**

The cytochrome P450 is a set of enzymes found in the small intestine, liver, kidney, lungs and brain. They process a variety of chemicals and play a role in the metabolism step of the pharmacokinetic profile. Their job is to make fat-soluble molecules more water-soluble so they can be eliminated via the kidneys. Molecules that bind to these enzymes and are processed are called substrates of the enzyme. For example, cisapride is a substrate of the CYP 3A4 enzyme.6

Chemicals also can affect how the enzyme system functions. Some chemicals can block the enzyme. They enter the system and bind permanently to the enzyme so the enzyme no longer is able to process any other chemicals or medications. These are known as “inhibitors.” For example, erythromycin is an inhibitor of CYP 3A4.7 Cisapride needs CYP 3A4 to leave the body. When erythromycin blocks that enzyme, cisapride is unable to leave the body and the blood levels rise and cause the above-mentioned side effect (prolonged QT intervals).

“Inducers” are chemicals that accelerate the cytochrome function. St. John’s Wort, for example, is an inducer of CYP 3A4,2 through which some calcium channel blockers (CCBs) are metabolized. The addition of St. John’s Wort speeds up the metabolism of such CCBs and, hence, the blood-pressure control of the CCBs may be adversely affected.

Finally, an interaction based on “competition” can occur. If too many drugs are sent to the same enzyme, the medications may compete for use of that enzyme. Warfarin is a perfect example. Any other drug that goes through the same pathway will displace warfarin and the warfarin will not be processed (resulting in higher levels of warfarin and associated side effects).

With the four words, “substrate,” “inhibitor,” “inducer” and “competition,” it is easier to describe the effects of medications on the cytochromes. For example, consider the possibility that a novel treatment becomes available for Alzheimer’s disease (AD), but no DI trials have been done with the agent in question. Some basic tests show that the medication is a substrate of CYP 2C9. This would mean that any medication that blocks CYP 2C9 will slow down the clearance of this new drug and, predictably, the drug’s blood levels will increase. This would imply that inhibitors of CYP 2C9 should not be used together with this new drug. More important, if the combination must be used, the doses need to be lowered to avoid any toxic effects. The knowledge of pharmacokinetics and pharmacodynamics outlined above allows the safe use of this new, fictitious medication.

Continuing with this example, suppose this new drug is an inhibitor of CYP 3A4. This means it will block CYP3A4 so all the drugs that normally go through CYP 3A4 will be processed slower and all of their blood levels will rise. If this medication is an inducer of CYP 2C19, then all the medications that normally go through CYP 2C19 will go through much more quickly. Hence, their blood levels will all fall. Phenytoin, for example, goes through CYP 2C19. This new medication would speed up phenytoin’s metabolism and, hence, the phenytoin levels would fall and loss of seizure control would be a side effect of the combination.

Clearly, with an understanding of this terminology (substrates, inhibitors, inducers, competition), it is possible to predict DIs before they occur.

**Genetic Variation**

Approximately 40 years ago, it was noted that the hydrolysis of the muscle relaxant succinylcholine by butyrylcholinesterase (pseudocholinesterase) was abnormal in some patients. It turned out that 1 in 3,500 white subjects had an atypical form of butyrylcholinesterase,8 and that this form was unable to hydrolyze succinylcholine (thus prolonging the drug’s effects on muscle relaxation). This discovery eventually evolved into the concept that there are genetic variations in basically, the four steps in pharmacokinetics ultimately will determine the amount of medication in the body. Affecting any of these steps changes the drug levels in the body, making them either too high or too low.
different patient populations which would cause some patients to metabolize some drugs at different rates. Since then, there have been well-documented variations in several of the cytochromes, one of which is CYP 2D6.

CYP 2D6 is a very well studied enzyme. Its story began when researchers observed that some patients would metabolize certain drugs rapidly while other patients would metabolize those same drugs slowly. This greatly affected the blood levels of the drugs in these patients. Without any obvious explanation for this phenomenon, patients were classified as being fast metabolizers or slow metabolizers. This classification was not very useful, because it depended on the patient and on the specific drug. In other words, knowing that a patient was a fast metabolizer of metoprolol gave no insight into what other drugs he or she may be able to metabolize quickly.

With further research, and the advent of molecular genetics, it was discovered that there were different copies of the gene that codes for the CYP 2D6 enzyme. Some alleles made functional enzymes while other variants produced non-functional ones. Poor metabolizers had nonfunctional copies, while fast metabolizers had multiple copies of the functional gene. This discovery made it much simpler to predict interactions. All that was needed was a list of all the medications that use the CYP 2D6 enzyme. Patients with multiple copies of the gene for CYP 2D6 would metabolize all of these medications faster, so higher doses would be needed to maintain the same blood levels. On the other hand, in patients with the defective allele, even a small dose could result in toxic blood levels. Seven percent to 10% of white people and 3% of black and oriental people are known to be deficient in the CYP 2D6 enzyme. This is an example of how genetics may play a significant role in determining drug metabolism.

**AD Treatments**

Because AD is predominantly found in the elderly, the issue of polypharmacy and DIs in this population group is very important. Still, it is important not to discard good medications because of the potential risk of DIs. Instead, knowledge of the interactions should be employed so that appropriate steps can be taken to manage those interactions. Awareness and knowledge of DIs are key in helping to manage our patients. If the interaction in question raises the drug levels, the dosage needs to be reduced. If the interaction decreases drug levels, more medication is required. Such attention allows for the safe use of various medications in useful combinations.

In terms of cholinesterase inhibitors (ChEIs), donepezil, galantamine and rivastigmine are currently available in Canada for the treatment of AD. To use any medication properly, one has to be familiar with its characteristics, and all aspects of the medication have to be considered before it is used in a given patient.

For example, donepezil is 100% absorbed and is not associated with any food interactions. It has a half-life of 70 hours, which makes it a true once-daily medication. Also, because of its long half-life, no discontinuation-type symptoms are expected if the drug is stopped abruptly. All of these are important points, especially in this elderly population who may forget a dose and who may not remember to take medications more frequently than once per day. Galantamine and rivastigmine both have shorter half-lives and therefore need to be dosed twice per day.

Donepezil and galantamine are metabolized by CYP 3A4 and CYP 2D6. This means that inhibitors of these enzymes could theoretically increase the blood levels of these medications.

The common inhibitors of CYP 3A4 and CYP 2D6 are described elsewhere and physicians who manage patients taking ChEIs (or other drugs, for that matter) metabolized by these enzymes should familiarize themselves with these inhibitors. For example, many elderly patients consume grapefruit juice, which is an inhibitor of CYP 3A4. Such patients should be told that this may increase their donepezil or galantamine levels. More important, this inhibition also may affect their CCB, statin or war-
farin levels. The interaction is not just a cholinesterase-inhibitor issue, but a CYP 3A4 issue that may affect many of a patient’s medications. The same concerns surround the use of macrolides (e.g., erythromycin, clarithromycin), which also are inhibitors of CYP 3A4.

Many patients take selective serotonin reuptake inhibitors (SSRIs) for mood disorders. Paroxetine and fluoxetine, for example, are inhibitors of CYP 2D6. If these SSRIs are taken along with either of the ChEIs mentioned above, the blood levels of the and inhibitors of these enzymes will help not only with the anticholinesterase treatment, but also in terms of any other medications the patient is taking that are metabolized by these enzymes. Rivastigmine does not use the CYP 450 system, so it is not likely to have cytochrome-type interactions. This is a very important characteristic. However, other aspects of this medication must be considered as well. For example, it has a short half-life and requires twice-daily dosing. Also, rivastigmine has a particular pharmacokinetic profile: it has linear pharmacokinetics at doses of up to 3 mg twice daily, but becomes nonlinear at higher doses. This means that doubling the dose from 3 mg twice daily to 6 mg twice daily results in a three-fold increase in AUC. Because of this jump, there may be increased side effects, such as nausea and vomiting.

Conclusions

With the general increase in the use of (and need for) polypharmacy, it is not uncommon to see patients taking eight or 10 medications. The issue of DIs is bound to come up. It is therefore prudent to learn about such interactions so they can be effectively managed. Intelligent choices with respect to medication combinations can be made, and doses can be adjusted to keep patients in safe therapeutic zones. Finally, DIs represent just one aspect of the safe use of medications. Other aspects that must be considered include side effects, compliance, and pharmacokinetic profile. It is with an understanding of all these different aspects of each medication that we can prescribe these therapies safely for our patients.

References:

Because AD is predominantly found in the elderly, the issue of polypharmacy and DIs in this population group is very important. Still, it is important not to discard good medications because of the potential risk of DIs. Instead, knowledge of the interactions should be employed so that appropriate steps can be taken to manage those interactions.

ChEIs may increase. The solution is to choose an antidepressant that has less effect on this enzyme, or to reduce the dose of the ChEI. If a patient is already taking an SSRI that inhibits this enzyme, the addition of the ChEI should begin with a lower dose and titrated upwards to the effective dose.

Inducers of these enzymes would reduce the blood levels of the ChEIs. For example, St. John’s Wort is an inducer of CYP 3A4 and would speed up the metabolism (thereby reducing the levels) of these ChEIs. The patient would therefore need more medication to achieve the same clinical effect.

In general, avoiding inducers and inhibitors of these enzymes will help not only with the anticholinesterase treatment, but also in terms of any other medications the patient is taking that are metabolized by these enzymes.