Aging as a **Risk Factor** for Medication-Related Problems

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Today we are going to talk about why older people have more problems with medications in ways that younger people do not, as well as discuss specific medication problems that occur in older persons.

Medication use in the elderly is first and foremost about appropriateness. Is the potential benefit of the medication greater than the potential risk? Every medication has some potential risk; however, not every medication has potential benefit, especially in the older person.

Today, we are very fortunate to have an extremely large formulary of medications from which to choose. Many of the drugs available are simply better for older people, either because they are safer, more effective, or are in some way easier with which to comply. We can do a better job choosing the medications that we give to older people if we know about the pharmacology, pharmacokinetics, and pharmacodynamics of the medication, and the clinical aspects of geriatric care.

Age as a Risk Factor

Every medication has some potential risk; however, not every medication has potential benefit, especially in the older person.

Is age itself a risk factor for adverse medication effects? The answer is "yes" and "no." Some studies of the incidence of drug side effects by age alone have shown that once you get over the age of about 50, your

chances of having a drug side effect increase; over the age of 70, the incidence of side effects goes up a great deal. And yet, other published studies indicate that age alone is not the issue.

The discrepancy arises because it is the medical conditions you have; the medications you take; your social situation; and your ability to pay for, comply with, and understand your treatment regimen that are the real problems. The bottom line is: The older you get, the more likely you are to be affected by these factors, which results in a greater chance of developing side effects from drugs.

Polypharmacy

What does polypharmacy mean? It means taking a lot of medications at the same time. However, polypharmacy itself is not really the issue. If you have seven medical conditions, as the average older person does, or 11 medical conditions, which is typical in nursing home residents, chances are you will need a lot of medications.

The question is: Are you taking only those medications you really need? Are you taking the right medications? And are you taking them in the right dose? Do the medications have drug-drug interactions? Are you taking a medication that is good for one problem but contraindicated by another? These are the issues that we need to consider every time we either prescribe, give, or take a medication.

Polypharmacy is itself a problem, since the more drugs you take, the more likely you are to have a drug side effect. If you are taking four or five drugs, your risk of a side effect is almost nine times greater than if you take only one drug. It is important to note that the average person over the age of 65 in the United States takes 4.5 prescription medications at any one time plus another two over-the-counter (nonprescription) medications. Those over-the-counter drugs are often the riskiest drugs of all in the older population.

Who would take six or more drugs? The average nursing home resident takes eight to 10 medications, putting them at nearly four times the level of risk as an older person who takes only one

medication. These numbers, as mind-boggling as they may be, describe the average medication use of older persons in the United States, which is part of why we have such a serious problem.

The following quote is from one of my favorite books, *Love in the Time of Cholera*, by Gabriel Garcia Marquez: “He arose at the crack of dawn when he began to take his secret medicines, bromide to raise the spirits, salicylates for the aches in his bones when it rained, ergosterol drops for vertigo, belladonna for sound sleep. But in his pocket he always carried a little pad of camphor that he inhaled deeply when no one was watching, to calm his fear of so many medicines mixed together.”

This is the very scenario that we have in the United States. We take a lot of medicines. We know we are fearful of them. They sometimes cause side effects that then cause us to take another medicine. We give a diuretic that decreases potassium levels. We give potassium supplements that then cause indigestion. We give medication for the indigestion caused by the potassium supplements. We cause an enormous cascade of problems rather than stepping back and thinking, “Was that first medication needed in the first place? Is there something that we can do to combat the side effects without increasing the number of medications?”

Medication Appropriateness

This takes us back to the issue of appropriateness, which is really the heart of what we’re talking about. Appropriateness has three aspects:

1. Overuse of a medication. Overuse is often cited as the most serious medication-related problem in the elderly, although I do not believe it’s the case. Overuse is defined as the use of a medication when a medication should not have been used at all. Certainly it occurs, and in some areas it occurs frequently: It occurs commonly with the use of antibiotics, with certain gastrointestinal medications, and often with certain sleep medications or medications that affect the central nervous system.

2. Misuse. To me the real problem is misuse, which occurs when a

medication is needed but the wrong drug is chosen, a drug is prescribed at the wrong dose or the wrong frequency, or there is some interaction with another medication.

3. Underuse. The third aspect of appropriateness is underuse of medications, a serious problem in the elderly, especially for certain conditions. Incontinence, heart failure, and depression are grossly undertreated in the elderly. Some of the preventives, like vaccines, are still dramatically underused in the elderly, even though we know that immunization saves lives, reduces morbidity, and saves money.

To understand age as a risk factor for medication-related problems, it is important to appreciate the physiologic changes that may effect medication use-specifically, pharmacokinetic and pharmacodynamic changes.

Pharmacokinetic Changes

Simply put, pharmacokinetics is what the body does to a medication. Pharmacokinetics has three components:

- Absorption-how the medication gets into the body
- Distribution-where the medication goes once it gets into the body
- Clearance-how the medication is ultimately cleared from the body

Absorption

There is little change in absorption with age, regardless of how you take a medication. There are some minor changes in absorption of topical preparations, but oral dosage forms are absorbed much the same way, regardless of age.

Distribution

Most medications are distributed to either body fat or body water. With aging, there is an increase in the percentage of body fat. The typical older person has about 25%-30% more fat than younger persons; the percentage is even higher for older women. With the increase in percentage of body fat, there is a corresponding decrease

in the percentage of the body consisting of water.

In older persons, blood levels of water-soluble medications will be higher than expected because there is less body water to distribute into. Fat-soluble medications stay in the body much longer because there is more fat in which to be stored. This results in increasingly complicated effects of medications in the elderly.

Clearance

The most dramatic change with age is seen in clearance. Medications are either cleared (eliminated) through the kidneys, or they are metabolized in the liver.

There is about a 50% decline in the renal (kidney) clearance of medications when persons reach age 75 to 80. That is a dramatic decrease. However, the traditional measure of creatinine clearance-serum creatinine-is unchanged with aging. The amount of muscle mass and muscle turnover, which contributes to creatinine level, decreases linearly with age, so we get a poor understanding of kidney function from serum creatinine level. There are equations we can use to approximate creatinine clearance given the age and weight of a person.

Hepatic (liver) changes are also dramatic with age. Hepatic blood flow decreases by about half, which has a substantial effect on certain medications. More importantly, the major enzymatic system by which the liver metabolizes medications-the P_{450} system-is rapidly saturated in old age, so medications are not metabolized nearly as well. Fortunately, the other mechanism of hepatic metabolism- glucuronyl transferase-is not dramatically affected by aging, which allows pharmaceutical manufacturers the opportunity to produce safer medications for older people.

For example, if you give a young person a dose of the antianxiety drug diazepam, the liver rapidly metabolizes the medication, and its level in the body falls off. However, the liver produces a metabolite of diazepam that is also a sedating agent, which is then excreted quickly by the kidneys. Just as rapidly as the diazepam level falls, the

desmethyl metabolite increases until it is eliminated by the kidneys.

When you give diazepam to a 68-year-old man, the P_{450} enzyme system is rapidly saturated. After an initial decrease in diazepam level, there is a very, very slow, continuous fall off. As the metabolite is produced by the liver, the kidneys are slow to excrete it, which results in a prolonged half-life of the drug in older people-96 hours. Medications continue to accumulate for six half-lives; therefore diazepam, if taken daily, will continue to accumulate for almost three weeks.

This is the scenario that we see. The medication is started in the hospital, where the average length of stay is about five to six days. If the patient is admitted to the nursing home still on the medication, two weeks later we find them dazed, confused, and unable to get out of bed. If they go home, two to three weeks later they are delirious and readmitted to the hospital. Careful monitoring for the first few days of therapy is not sufficient to avoid medication-related problems in this case; it requires an understanding of the pharmacokinetics of the medication.

Pharmacodynamic Changes

The second area of clinical change with aging is pharmacodynamics, or what the drug does to the body. Age-related changes in pharmacodynamics compound the pharmacokinetic issues described above.

As we get older, we are more sensitive to most drugs rather than less sensitive. This is especially true for medications that affect the central nervous system. For example, a single 30-mg dose of the sedative flurazepam will cause measurable side effects in nearly half of persons over age 60; in younger people, only 5%-10% experience side effects. Even at the lower dose, 10% of older people have side effects.

There are many changes that occur in the brain with aging that effect sensitivity to medications. Changes in the blood-brain barrier allow more drugs to enter the central nervous system at higher levels. The

older brain is far more sensitive to all drugs that cross the blood-brain barrier. Dr. Jerry Avorn said it best: “In the elderly, every drug can be psychoactive.” The list of medications causing confusion or central nervous system changes in the elderly is very long.

In younger people, when you stop a medication, you generally see complete reversal of the side effects within a day or two; in the elderly, these symptoms can take weeks to resolve, for all the reasons I’ve described: pharmacokinetic and pharmacodynamic changes, as well as the older brain’s reduced ability to recover.

In discussing age as a risk factor for medication-related problems, I have described a typical 70-kilogram older person. But older people are not all alike; the older we get, the more different we become. There will be people at both ends of the spectrum: the person with fabulous renal function, great hepatic function, and enormously athletic, to whom much of this does not apply; and the 50-year-old who is out of shape, has poor renal function, and poor hepatic function, to whom this does apply. Those elders in nursing homes tend to be among the frailest.

Conclusion

Can we then really identify the medications that are most problematic in the elderly? The answer is “yes.” We now know enough about pharmacology, pharmacokinetics, and pharmacodynamics, and have data from outcomes research, to identify the most egregious prescribing problems in the elderly. This is at the heart of what we have tried to do in identifying medications potentially inappropriate for use in the older population. When we know the adverse effects of medications and the potential benefits of medications, we can establish criteria to guide us in our prescribing.

I have published two consensus papers that define, as a starting point, the most problematic medications in the elderly. I am very pleased the Health Care Financing Administration (HCFA) has incorporated these guidelines in the federal regulations governing nursing home care. The guidelines are already in widespread use by consultant pharmacists and are being used in outpatient settings as

well. In a later presentation you will hear how these guidelines are being used in drug utilization review (DUR) programs as a way to create first-level alerts for practitioners.

The guidelines are not the be-all and end-all of prescribing review—that takes clinical expertise—but they do provide a starting point and, I think, an important one to guide interventions to improve prescribing. The guidelines can be used as the basis for educating physicians, pharmacists, nurses, and other health care professionals; they can be provided to patients and caregivers; and they can be incorporated into computerized medication dispensing systems.

Now that we have a sense of the complexity and extent of medication-related problems in older persons, we should use our knowledge of pharmacology, pharmacokinetics, and pharmacodynamics; medication appropriateness guidelines; and any other information available to fashion interventions to improve prescribing.

Preventing medication-related problems in older persons requires an understanding of the differences between younger people and older people, what these differences mean for the way we prescribe medications and monitor medication use, what these differences mean for the way we develop drugs, and what these differences mean for the way we monitor new medications after they are out in the marketplace. All of these are critical if we are going to improve the care of older people.

Sources

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