

Drug Use in Elderly & Integrative Medicine

Yaşlıda İlaç Kullanımı ve Bütünleyici Tıp

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ABSTRACT Patients ≥ 65 years old are 9-12% of the population and consume more drugs than younger population. Functional capacity of the major organ systems declines as age increases, resulting in altered pharmacokinetics of some drugs. Diminished/blunted homeostatic responses and altered drug-receptor interactions result in pharmacodynamic changes, which makes the elderly more sensitive to drug action. Geriatric patients use approximately 3-5 drugs daily; addition of non-prescribed, herbal medications (ginseng, ginkgo biloba, glucosamine etc.) under the scope of integrative medicine inevitably increases this number. Use of more than five drugs concurrently increases the incidence of adverse drug reactions and/or drug-drug interactions up to 100%. While prescribing in elderly, careful drug history including the use of vitamins and herbal medications should be taken to prevent any potential drug interactions. This article is focused on the alterations in drug pharmacokinetics and pharmacodynamics in elderly, basic principles of prescribing and integrative medical approaches in advanced age.

Key Words: Aged, Drug use, Pharmacodynamics, Pharmacokinetics, Integrative medicine

ÖZET Yaşlılar nüfusun %9-12'sini oluşturur ve genç nüfusa oranla ilaç kullanımı daha yüksektir. Yaş ilerledikçe büyük organlarda fonksiyonel kapasite azalmaya başlar ve bu durum bazı ilaçların farmakokinetiklerinde değişikliklere neden olur. Farmakokinetik değişikliklerle birlikte homeostatik refleks yanıtın azalması/körleşmesi ve ilaç-reseptör etkileşimindeki değişikliklere bağlı olarak farmakodinamik değişiklikler devreye girer, bu nedenle geriatric hastaların bazı ilaçları etkileim karşı daha duyarlı olduğu dikkati çekmektedir. Yaşlıda günde 3-5 ilaç kullanılmaktadır, ancak bu ilaçlara bütünleyici tıp kapsamında reçetesiz kullanılan ve bitkisel olanlar (ginseng, ginkgo biloba, glukozamin vb) eklendiğinde sayının daha çok artması kaçınılmazdır. Bir hasta beşten fazla ilaç kullanıyorsa advers ilaç reaksiyonu ve/veya ilaç-ilaç etkileşmesi görülme sıklığı %100'e çıkar. Bu nedenle yaşlıda ilaç reçete ederken potansiyel ilaç etkileşmelerini önleyebilmek için detaylı bir ilaç sorgulaması yapılmalı, kullandığı vitaminler ve bitkisel ilaçlar da sorulmalıdır. Bu makalede yaşlıda farmakokinetik ve farmakodinamik değişiklikler, ilaç kullanımındaki temel prensipler ve ileri yaşta bütünleyici tıp uygulamalarının yeri gibi konulara değinilecektir.

Anahtar Kelimeler: Bütünleyici tıp, Farmakodinamik, Farmakokinetik, İlaç kullanımı, Yaşlı

Türkiye Klinikleri J Med Sci 2009;29(Suppl):S76-S79

The fraction of the population over age 65 is growing at a rapid rate and since physiologic aging does not always parallel with chronologic aging, the elderly constitute a particularly heterogenous patient population. Drug usage patterns normally change as a result of the increasing incidence of various diseases with age and the tendency to excessive prescribing for patients in nursing homes.¹ Important changes in responses to some drugs occur with increasing age, while for

other drugs age-related changes are minimal. If prescribed too large in dosage and/or too frequently, drugs given to rectify, ameliorate or palliate the symptoms of the elderly may significantly complicate the underlying changes induced by senescence. Among these changes associated with aging are the altered pharmacokinetics and pharmacodynamics of particular drugs. The health practitioners in charge of older people should be aware of these changes in pharmacologic response and be prepared for how to deal with these changes.

PHARMACOKINETIC CHANGES ASSOCIATED WITH AGING

Functional capacity of most of the major organ systems tends to decline with “normal” aging and this results in changes of major pharmacokinetic characteristics of some drugs, namely absorption, distribution, metabolism and elimination.^{2,3} Many of these changes are independent of the multiple diseases expected in the elderly and for the pharmacologists and the clinician, the most important of these is the decrease in renal function.

Absorption: Elderly persons exhibit several alterations in gastrointestinal function that might result in impaired or delayed absorption of a drug; namely increases in gastric pH and decreases in the absorptive surface, splanchnic blood flow and gastrointestinal motility.³ Conditions such as altered nutritional habits and greater consumption of nonprescription drugs (antacids, laxatives etc.) may also alter the rate at which some drugs are absorbed. Despite these expected alterations, there is little evidence that drug absorption may alter grossly with increasing age.

Distribution. Lean body mass and both total and percentage body water are reduced, while fat as a percentage of body mass is increased in the elderly.⁴ Diuretics and poor oral intake worsen the decreased body water. Because of these alterations, in general the volume of distribution for water-soluble, hydrophilic drugs (e.g. digoxin, antipyrine, ethanol) decrease and those for lipid-soluble, lipophilic drugs (e.g. benzodiazepins like diazepam and thiopental sodium) increase.⁴ Since the standard dose is based simply on total body weight or surface area, these changes in volumes of distribution may lead to higher or lower plasma concentrations following drug administration in older people. There is usually a decrease in serum albumin which binds many drugs, especially weak acids (e.g. warfarin, phenytoin, acetazolamide, valproic acid, salicylate); thus the ratio of

bound to free drug may be significantly altered. However, free drug also goes to metabolism and clearance and increases in unbound drug concentration may tend to produce toxicity only if/when the function of organs responsible for the metabolism and clearance, namely liver and the kidneys, is impaired.⁵ For this reason, the steady-state effects of a maintenance dosage regimen in the elderly should not be altered by these factors alone; however, the loading dose of some drugs (e.g. digoxin) should be reduced because of the decreased apparent volume of distribution.

Metabolism. The capacity of the liver does not decline consistently with age to affect drug metabolism. Major changes in drug metabolism in the elderly arise from three main topics: i. the decreased liver blood flow, an important variable in the clearance of drugs having a high hepatic extraction ratio and therefore a high first-pass effect (e.g. lidocaine, β -blockers, narcotic analgesics); ii. the decline in the liver's ability to recover from injury, for example that caused by alcohol or viral hepatitis; iii. malnutrition and diseases that affect hepatic function (e.g. congestive heart failure further compromises hepatic blood flow).⁶

Elimination. Since the kidney is the major organ for clearance of drugs from the body, the most consistent effect of age on pharmacokinetics is the age-related decrease in renal functional capacity which is markedly decreased if the elderly patient is also dehydrated. The practical result of this change is marked prolongation of the half-life of some many drugs and the possibility of accumulation to potential toxic levels if dosage is not reduced or the dosage interval is not prolonged. Drugs with predominantly renal elimination and potentially toxic effects in the elderly include aminoglycosides, lithium, amantadine, digoxin and some nonsteroidal anti-inflammatory drug; also drugs with potentially toxic metabolites that are excreted by the kidney, such as meperidine, may potentially be hazardous in the older people.³ While prescribing such drugs, physicians are recommended to make a rough correction of the young adult dosage by using Cockcroft-Gault formula, which is applicable to patients between age 40-80 (Creatinine clearance in mL/min = $[140 - \text{age}] \times \text{weight in kg} / \text{serum creatinine in mg/dL} \times 72$).³ The result should be multiplied by 0.85 for women. If Cockcroft-Gault equation predicts a creatinine clearance of 45 mL/min, this indicates the need for more than 50% reduction in dose or two times increase in dose interval.

PHARMACODYNAMIC CHANGES ASSOCIATED WITH AGING

With increasing age there is an increased intolerance to drugs as a result of altered interaction of the drugs with their receptors at the target organ. Altered response may be due to depletion of neurotransmitters (e.g. acetylcholine, dopamine, serotonin), presence of disease or physiologic changes. Altered end-organ sensitivity may result in an exaggerated pharmacologic response, as seen with the barbiturates and benzodiazepins, or diminished pharmacologic response, as seen with the β -blockers, β -agonists and calcium channel blockers.⁷ Certain homeostatic control mechanisms appear to be blunted in the elderly. In the cardiovascular system, average blood pressure goes up with age, however, the incidence of symptomatic orthostatic hypotension also increases markedly; this is particularly important for some antihypertensive drugs already causing postural hypotension (e.g. α -blockers, direct vasodilators), thus it is beneficial to check for orthostatic hypotension on every visit. Temperature regulation is also impaired and hypothermia is poorly tolerated in the elderly.

Behavioral and lifestyle changes may also affect drug action in the elderly. Some of these (e.g. forgetting to take one's pills) are the result of cognitive changes associated with vascular or other pathologies. Other relate to economic stresses associated with the reduced income and possible increases in the expenses due to illness. One of the most important changes is the loss of a spouse or leaving of kids from the house.

GUIDELINES FOR GERIATRIC PRESCRIBING

The quality of life in elderly patients can be greatly improved and life span can be prolonged by the rational use of drugs, however, there are several practical aspects and a few principles of geriatric pharmacology that the prescribers must take into account.^{2,3,7}

- Evaluate the need for drug therapy. Not all diseases afflicting the elderly require drug treatment. Prescribe only for specific and rational indications (e.g. do not prescribe omeprazole for dyspepsia)

- Take a careful history of habits and drug use. Patients may receive prescriptions from several physicians. The disease to be treated may be drug-induced or drugs being taken may lead to interactions with drugs to be prescribed. Knowledge of existing therapy, both prescribed and nonprescribed, helps prevent potential drug

interactions. "Over-the-counter (OTC)" drug use should be questioned, since some may have potential anticholinergic effects and may result in urinary retention, constipation, dry eyes and mouth, glaucoma, confusion, behavioral changes, memory loss or aggravation of dementia in the elderly. Herbal medications have particular importance, because some may increase the risk of bleeding (e.g. ginkgo biloba, garlic).⁸

- Know the pharmacology of the drug prescribed. Awareness of age-related changes in drug disposition and drug response is helpful.

- "Start low, go slow". The standard dose is often too large for elderly patients. In general, define the goal of drug therapy, begin with relatively small doses and titrate drug dosage with the patient response desired. Opioids and benzodiazepins may need to be down-titrated. Use small doses of a short acting drug, more frequently, until patient is stabilized on it, then switch to a longer acting. For starters, typically use half of the smallest tablet size available. Wait at least three half-lives (adjusted for age) before increasing the dose. For drugs with narrow therapeutic index (e.g. digoxin, theophylline, lithium), prefer therapeutic drug monitoring if possible.

- Simplify the regimen and encourage compliance. For multiple prescription, use drugs that can be taken at the same time of day and try to avoid intermittent schedules, once- or twice-daily dosage is ideal. Label drug containers and labels on prescription bottles should be large enough for the elderly patient with diminished vision. Avoid liquid medications that are to be measured out "by the spoonful" in patients with any type of tremor or motor disability; instead use pediatric dosing syringes. Because of the decreased production of saliva, older patients often have difficulty swallowing large tablets. "Childproof" containers are inappropriate for the patients with arthritis. Explain why the drug is being prescribed to the patient and the caregiver.

- Regularly review the treatment plan and discontinue drugs no longer needed. If the medication does not help within two weeks, stop it. If an elderly person on multiple drugs becomes nausea or confused, it is probably a drug side effect; if the patient becomes dehydrated, reduce medication doses.

INTEGRATIVE MEDICINE IN ADVANCED AGE

Integrative therapies comprise a variety of nonpharmacologic methods that provide pain, anxiety and symptom management. Long referred to as "complementary and

alternative medicine”, these methods include massage and aromatherapy, acupuncture and acupressure, guided imagery, exercises like yoga, Tai Chi and Qigong, music, acutonics (sound healing), reflexology, crystal therapy, energy therapies like Reiki, homeopathy, herbal medicine and phytotherapy and are now more commonly known as “integrative therapies” because they integrate both traditional and nontraditional treatments.⁹ The goal of integrative medicine is to achieve the best quality of life for patients and their families. Older adults frequently use integrative medicine to treat conditions like arthritis, back pain, heart disease, allergies, and diabetes and the use of integrative medicine in hospice and home care of the elderly is rapidly growing.^{10,11} Sleep disturbances are also common in the elderly; although several sleep disorders can be effectively treated with benzodiazepines and other traditional sedative-hypnotic medications, many

older adults are apprehensive about the safety of these pharmacologic agents and may prefer to use complementary and alternative medicine (e.g. melatonin, valerian, St. John’s Wort, passion flower, Tai Chi, acupuncture, acupressure, yoga, and meditation).¹² Patients often use integrative therapies in addition to modern medicine and are reluctant to discuss them with their physicians. Physicians, nurses and gerontological health care providers should be aware of these therapies and their risks and benefits. The use of integrative medicine should be included in visit histories and discussed in an objective, nonjudgmental manner to encourage the patient disclosure. However; as in other areas of health care, studies in the elderly are consistently lacking and there is a major need for large and appropriately designed studies to test the effectiveness and safety of the integrative techniques.

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