CHAPTER 19

Considerations in the Geriatric Poisoned Patient

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Geriatric Patients

In veterinary medicine there is a growing population of geriatric patients, which may be due to advances in the quality of medicine. With this increase in the geriatric patient population, age-related considerations in pharmacology must be considered. Physiologic changes seen in geriatric patients include organ-related dysfunction (e.g., age-related hepatic changes, age-related nephron loss),[1,2] changes in body composition,[1,2] changes in cardiac output (resulting in changes in regional and organ blood flow),[1] decreased compensatory physiologic responses,[2] and other miscellaneous effects on the body (e.g., decreases in metabolic rate, diminished receptor response, underlying diseases).[1,3] Concurrently, oxygen consumption is decreased while there is a decline in physiologic functions (Box 19-1).[3] All these changes may markedly affect the pharmacokinetics (i.e., altered drug concentration at the site of action),[1] pharmacodynamics (i.e., altered drug action),[1] and the four components of drug disposition: absorption, distribution, metabolism, and excretion (Box 19-2). These changes directly affect the body's ability to dispose of drugs and how the body (or tissues) will respond to drugs.[4-6] This chapter will review geriatric pharmacology and how it applies to the geriatric poisoned patient.

The definition of a geriatric patient is one that has reached 75% of the expected lifespan.[2] When a patient reaches geriatric age, approximately 30% of body cells are permanently lost.[3] In human medicine, this is generally defined as 80 years of age.[3] In veterinary medicine, the definition of "geriatric" is not well defined, and is more subjective due to variability in species, breed, and overall size. For example, a 5- to 7-year-old Great Dane may be considered geriatric, whereas for a Chihuahua this may be at 9 to 15 years of age.

Organ-Related Dysfunction

Age-Related Hepatic Changes

As the liver plays a key role in the metabolism of xenobiotics, age-related changes in hepatic function can result in increased potential toxicity of these compounds. Age-related hepatic changes include decreases in hepatic function, decreases in hepatocyte numbers (with a resultant decrease in overall liver mass), decreases in hepatic and splanchnic blood flow, and an overall reduction in the liver's intrinsic activity of drug-metabolizing enzymes.[1,2] Decreases in the ability of the liver to produce sufficient protective compounds (e.g., oxygen radical scavengers), along with alterations in hepatic function, nutrition, and oxygenation, may further contribute to xenobiotic-induced hepatotoxicity in the geriatric patient.[3] All these changes result in a net decrease in both hepatic oxidation and the primary xenobiotic metabolizing enzyme cytochrome P450, resulting in changes in the liver's ability to metabolize compounds that require either capacity-limited or flow-limited hepatic metabolism.[3] For example, nonsteroidal antiinflammatories (NSAIDs) are compounds that

Box 19-1 Age-Induced Physiologic Alterations

Hepatic
Decreased protein synthesis
Decreased numbers of hepatocytes
Phase I xenobiotic metabolism altered
Decreased liver size

Renal
Creatinine clearance decreased, serum creatinine normal
Decreased tubular absorption
Decreased glomerular filtration rate
Decreased renal blood flow

Body Composition
Increased body fat
Decreased total body water
Decreased plasma volume
Decreased plasma albumin
Decreased lean body mass

Gastrointestinal Tract
Increased gastric pH
Decreased active transport
Decreased rate of gastric emptying
Decreased esophageal peristalsis
Decreased gastric secretions

Cardiovascular
Heart
Decreased cardiac output
Cardiac hypertrophy
Decreased stress response

Vascular
Decreased tissue perfusion
Decreased vascular elasticity
Increased systolic blood pressure
Increased vascular wall thickness

Box 19-2 Factors That Affect Xenobiotic Disposition

Pharmacologic Factors
Pharmaceutical interactions
Therapeutic inequivalence
Direct drug-drug interactions
Drug-diet interactions
Pharmacokinetic interactions
Pharmacodynamic interactions

Pathologic Conditions Modifying Drug Action
Gastrointestinal disease
Hepatic disease
Renal disease
Cardiovascular disease
Pulmonary disease
Neurologic disease
Metabolic disease
Other disease
Drug protein binding

Physiologic Factors
Route of exposure
Species variations
Genetic (breed) factors
Age
Sex
Body weight/surface area
Pregnancy/lactation
Diet/nutrition
Temperament
Environment
Circadian rhythms

require primarily capacity-limited hepatic metabolism, and geriatric patients may exhibit prolonged hepatic clearance.[3] Likewise, drugs like opioids are compounds which undergo flow-limited metabolic hepatic clearance; geriatric patients typically have an increased response that requires 60% to 75% less drug than that needed in younger patients, primarily because of reduced drug elimination.[3,5,7,8]

Hepatic clearance (Cl_H) is determined by the liver's intrinsic ability to extract the drug (hepatic extraction ratio [ER_H]) and the hepatic blood flow (Q_H).[1] High-clearance drugs such as lidocaine, propranolol, morphine, isoproterenol, and verapamil have a high ER_H (approaching 1), meaning that their hepatic clearance is almost equal to hepatic blood flow.[1] Therefore, drugs with a high ER_H are highly influenced by changes in hepatic blood flow.[1] However, when these drugs are given orally, they undergo high "first-pass effect" and

typically do not reach high systemic concentrations because of high clearance of the drug. In the geriatric patient, the first-pass effect is diminished; therefore, in drugs with a high ER_H, systemic toxicity may occur because of increased oral bioavailability of the drug:

$$Cl_H = (Q_H)(ER_H)$$

Conversely, drugs with a low ER_H (<0.2) such as phenobarbital, benzodiazepines, chloramphenicol, and phenylbutazone are not significantly affected by hepatic blood flow.[1] These drugs with a low ER_H are not typically affected by the first-pass effect. Rather, changes in protein binding and hepatic microsomal enzyme systems may affect drug clearance.[1] In the geriatric patient, the level of albumin decreases relative to the increase in globulins (therefore maintaining normal total protein values).[3] If a geriatric patient is exposed to highly protein-bound toxicants, the portion of the xenobiotic that is free (versus protein-bound) may then be increased.[3] For example, most NSAIDs are close to 99% protein bound; even a small decrease of 1% (e.g., 99% to 98% binding) results in a doubling of the concentration of the pharmacologically active drug.[3] Some protection against this elevated plasma concentration may occur with the increased clearance of unbound compound by both the liver and kidneys.[3]

Age-Related Nephron Changes

Also in the geriatric patient, age-related nephron loss occurs along with reductions in renal blood flow. As a result both the glomerular filtration rate and the active secretory rate of the nephron unit are diminished,[3] resulting in a decline in renal xenobiotic clearance. Because most xenobiotics are renally excreted, age-related nephron changes and alterations in renal clearance can lead to increased blood concentrations of the parent or metabolite(s) of the xenobiotic, along with prolonged elimination,[3] placing the geriatric patient at increased risk of toxicosis. For example, the use of certain xenobiotics that are known to be nephrotoxic (e.g., NSAIDs, angiotensin-converting enzyme inhibitors, and aminoglycosides) should be judiciously considered in the geriatric patient.[3] Again, because of the decreased nephron population and increased filtering load per nephron,[3,9] increased plasma concentrations and prolonged exposure per nephron may occur, resulting in nephrotoxicity.

Changes in Body Composition

In the geriatric patient, decreases in total body and interstitial water, decreases in muscle mass, and increases in fat content occur. For example, in human geriatric males, body fat content is typically 50%, whereas in young males, body fat content is typically 18%.[5] Although this has not been well evaluated in veterinary medicine, these changes in body composition can result in altered pharmacokinetics and pharmacodynamics. For example, geriatric patients with decreased muscle mass may have increased plasma concentrations of drugs that distribute normally to skeletal tissue (e.g., digoxin).[2] Likewise, in geriatric patients with decreased total body water, increased plasma concentrations of water-soluble drugs (e.g., aminoglycosides, digoxin) can occur.[2] Because these water-soluble drugs have poor fat distribution, dosing should ideally be performed on lean body weight.

Changes in Cardiac Output

In geriatric humans, cardiac output decreases by 30% to 40% over time (typically at a rate of approximately 1% a year). In veterinary medicine, a decrease in cardiac output also occurs in our geriatric pets, resulting in decreases in regional and organ blood flow[1] and a resultant increase in circulatory transit time.[3] Alternations in these cardiovascular dynamics likely affect the disposition (e.g., absorption, distribution, metabolism, and excretion) of drugs.[3] Xenobiotic plasma or tissue concentrations can be affected in either direction—decreased absorption and distribution or increased metabolism and excretion.[5,10] As a result of decreased cardiac output, blood is preferentially shunted to key organs (e.g., heart, brain), which can result in increased risk of toxicity to these organs

receiving more blood flow.[1,3] Likewise, decreased cardiac output can result in a prerenal azotemia, which can affect renally cleared drugs (e.g., furosemide, enalapril, digoxin).

Decreased Compensatory Physiologic Responses

In geriatric humans, response to catecholamines is diminished. As a result, compensatory responses to hypotension or cardiac arrhythmias may be blunted, resulting in poor response to drug-induced hypotension or hypovolemia. As geriatric patients often have underlying cardiac (e.g., chronic valvular heart disease) or metabolic (e.g., hyperthyroidism) disease, further ability to compensate may be affected. Geriatric patients also have age-related alterations in GABA receptors and decreased dopamine concentrations; this may make geriatric patients more sensitive to excessive sedation and adverse events (e.g., tremoring from metoclopramide) to drugs, respectively.[2]

Miscellaneous Changes (e.g., Decreases In Metabolic Rate, Diminished Receptor Response, Underlying Diseases)

Geriatric patients have reduced gastrointestinal motility (including pharyngeal and esophageal),[3] decreased salivation and deglutition,[3] decreased absorptive capacity, and diminished gastric acid secretion (resulting in secondary increased gastric pH). In addition, age-related atrophy of intestinal villi may occur, increasing the potential for risk of bacterial overgrowth.[3] As a result, geriatric patients exposed to xenobiotics may be at greater risk of adverse gastrointestinal effects by certain compounds (e.g., chemotherapeutic agents, NSAIDs).[3]

Age-related changes are also seen in the pulmonary system. Decreases in residual lung volume, vital capacity, and overall respiratory function occur in the geriatric patient, resulting in low arterial partial pressure of oxygen (PaO_2).[3] Higher than normal alveolar-arterial gradients are seen in geriatric patients. Finally, geriatric patients have diminished central nervous system responses to hypoxemia or hypercapnea, making them less likely to compensate for xenobiotics that potentially affect ventilation (e.g., opioids, baclofen).

Geriatric patients have diminished immune system function as compared with young patients, which may increase the risk of toxicosis from immunosuppressive agents (e.g., 5-fluorouracil, chemotherapeutic agents, steroids).[11] Lastly, geriatric patients are more likely to have underlying metabolic disease (e.g., hepatic, renal, neoplasia), which may affect xenobiotic disposition.

Conclusion

Geriatric patients may have alterations in pharmaokinetics and pharmacodynamics because of age-related changes. Geriatric patients exposed to toxicants should be carefully assessed for underlying organ-related dysfunction (e.g., age-related hepatic changes, age-related nephron loss),[1,2] changes in cardiac output (resulting in changes in regional and organ blood flow),[1] changes in body composition,[1,2] decreased compensatory physiologic responses,[2] and other miscellaneous effects on the body which may affect the patient's response.[1,3] Because geriatric patients are often receiving multiple drugs for underlying medical conditions, there is potential for increased risk of drug-drug or drug-toxin interactions.[3] Aggressive therapy (including decontamination) and evaluation of underlying metabolic disease is imperative in geriatric poisoned patients for the best outcome.

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