identify a new toxin and perhaps at some future date a chemical as diagnostic use.

Very few toxicology diagnoses are reportable diseases. Howev cases involving malicious poisonings, a multiple animal outbreak, po risks to the public or misuse of pesticides, it might be judicious to r your findings to an appropriate regulatory agency (e.g., state or fe department of agriculture, or local law enforcement agency). The to ogists should be able to assist and direct you to the appropriate agen individual in these cases.

CONCLUSION

Your approach to using a diagnostic facility should be thoughtful, log and insightful. There is no such test as the "poison screen," and should refine your approach so that it is systematic and reasonable, employs all aspects of the diagnostic laboratory so as to maximize y efforts at an affordable price to achieve a successful resolution to the cas

11

onsiderations Pediatric nd Geriatric oisoned Patients

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A relatively unexplored area in veterinary medicine is that of age-ated responses to toxic xenobiotics. The majority of differences between ult and pediatric patients exposed to toxicants are developmental. nversely, the major differences induced by advancing old age are both siological and pathological, and these are often correlated with organ function. These differences can markedly affect the four components drug disposition: absorption, distribution, metabolism, and excretion. e information contained in this chapter is designed to illustrate these ferences and how they may affect the toxin-exposed pediatric or iatric patient.

EDIATRIC PATIENTS

ps and kittens may be exposed to xenobiotics through several routes—gestion (including the ingestion of mother's milk), topical exposure, halation, and ocular exposure. In dogs and cats, the term pediatric gener-y refers to the first 12 weeks of life.[1] Further division into neonatal (0 to weeks), infant (2 to 3 weeks), and pediatric (6 to 12 weeks) stages is justified cause of the significant developmental changes that occur during the first weeks of life. All aspects of drug disposition—absorption, distribution, etabolism, and excretion—are affected by dramatic developmental anges as the neonate matures.[2,3] Physiological alterations associated ith these stages affect toxin disposition, rendering the pediatric patient

more susceptible to adverse reactions. The clinical significance of t
sequelae varies.

Absorption

Following oral exposure to a xenobiotic, absorption occurs primarily i
the small intestine. In both neonates and adults, the surface area of
small intestine is large. Therefore the extent of drug absorption probab
does not differ clinically between normal pediatric and adult anima
However, the pediatric patient has a decreased gastric emptying time a
irregular intestinal peristalsis and tends to have a slower rate of absorpti
(Table 11-1). These factors may result in the development of lower pe
plasma toxin concentrations. The decreased rate of absorption may ac
ally protect against toxic drug concentrations.[1,2] However, in neona
before colostrum is absorbed, these protective mechanisms may not
present. Before colostrum absorption, the permeability of the intesti
mucosa is increased, which also increases the rate of toxin uptake, inclu
ing the uptake of compounds that normally would not reach the systemi
circulation. Intestinal permeability rapidly decreases after colostru

Table 11–1

Altered Xenobiotic Disposition in Pediatric Patients

Alteration	Impact
Increased intestinal permeability	Increased oral uptake; toxic plasma concentrations
Increased gastric pH	Increased oral uptake of weak bases and acid-labile compounds; prolonged and elevated plasma levels; toxic plasma concentrations
Altered peristalsis (decreased gastric emptying time)	Decreased absorption; lower plasma levels of xenobiotic
Decreased plasma proteins	Toxin may accumulate, leading to more unbound compound and thus a potentially longer half-life
Decreased body fat	Increased plasma levels; decreased accumulation of lipid-soluble xenobiotics
Increased total body water (more extracellular fluid)	Decreased plasma concentrations; longer half-life
Increased uptake of volatile gases	High plasma concentrations; increased response and toxicity
Increased dermal absorption	Higher or prolonged plasma exposure levels; toxicity increased

stion.[1,6] This may well be induced by endogenous release of hydrocor-
ne or adrenocorticotropic hormone (ACTH). Exogenous supplemen-
on of these hormones to the mother within 24 hours prepartum
vents the increase in permeability and uptake of colostrum.

Several other factors may affect small intestinal drug absorption in
diatric patients. Newborns have a neutral gastric pH, and the rate of
gression to adult levels depends on the species involved.[1,6]
chlorhydria increased gastric pH may cause decreased absorption of
ny compounds that require disintegration and dissolution or that need
be ionized in a less acidic environment (e.g., weak acids). Milk diets
interfere with absorption of toxic compounds by reducing gastric
tility or interacting directly with the toxins. The "unstirred water layer"
jacent to the surface area of the mucosal cells is thicker in the neonate
mpared with the older pediatric patient, and this may limit the rate of
sorption of some compounds. Absorption of fat-soluble compounds
creases as biliary function develops. Both extrahepatic metabolism and
terohepatic circulation may be altered as microbial colonization of the
strointestinal tract occurs.[8] Absorption from the rectal mucosa is rapid
neonates.

Absorption of xenobiotics administered parenterally to pediatric animals
aries from that in adults. As muscle mass develops, with its accompany-
g increase in blood flow and maturation of the vasomotor response, the
te of absorption following intramuscular administration of xenobiotics
altered.[7] Subcutaneous administration of potentially toxic drugs may
hibit variable absorption rates relative to the patient's age. Smaller
mounts of body fat, but greater water volume, may result in quicker
bsorption of toxins compared with that in adults.[9]

It is suspected that environmental temperature influences subcutaneous
bsorption. This is especially true in neonates whose thermoregulatory
echanisms are poorly functional. If the neonate is in a cold environ-
ment, subcutaneous xenobiotic absorption tends to be reduced. The same
hing would be expected for a patient that presents in a hypothermic state.
ntraperitoneal exposure to xenobiotics may exhibit rapid absorption in
he pediatric patient.

Percutaneous absorption of xenobiotics may be greater in pediatric
patients. Percutaneous absorption is directly related to skin hydration,
which is highest in neonates. Topical exposure to potentially toxic lipid-
soluble compounds (e.g., hexachlorophene and organophosphates) places
he pediatric patient at higher risk of significant absorption.

Volatile gases are absorbed rapidly from the pediatric respiratory tract
because of greater minute ventilation.[1] Young animals are more sensitive
to the effects of inhaled gases.

Distribution

The two major differences between adult and pediatric patients relati xenobiotic distribution are those of body fluid compartments and xen otic binding to serum proteins. Body fluid compartments undergo trem dous alterations as the neonate grows. As the neonate matures, signific changes occur in both the percentage of total body water and the rati compartmental volumes. Although both the percentage of total body w and the volume of the extracellular versus the intracellular compartm decrease as the animal ages, the change in the ratio of extracellular intracellular volume is significantly greater.[10] Daily fluid requirements greater in neonatal and pediatric patients because a larger proportio their body weight is represented by body water. The net effect on xeno otic distribution depends on these differences in body compartme Most water-soluble compounds are distributed into extracellular flu Plasma concentrations of these compounds are lower in pediatric patie compared with adults because the volume into which the compound distributed is greater in the young. Unbound lipid-soluble compou have the same type of distribution because they are distributed into to body water. Changes in xenobiotic distribution directly alter the half-l of that xenobiotic. Increases in distribution directly decrease the plas concentration, a fact that may potentially protect the pediatric pati from toxic xenobiotic concentrations.[11]

Distribution of lipid-soluble compounds that accumulate in the (e.g., some organophosphates and chlorinated hydrocarbons) may decreased because of a smaller proportion of body fat in the pediat patient. Xenobiotic plasma concentrations may be higher, but the half-l is shorter. The movement of many fat-soluble compounds may be faci tated by their high tendency to bind to plasma proteins. This bindi decreases their ability to be distributed to target tissues.

Predicting the distribution of highly protein bound compounds is com plicated in the pediatric patient. Most compounds are bound to seru albumin, and basic xenobiotics have a high affinity for α_1-glycoprotei Both of these proteins are available in lower concentrations in pediatr patients.[12] Additionally, differences in albumin structure and competitio with endogenous substrates (e.g., bilirubin) for binding sites may decrea protein binding.[5,13] If bound xenobiotics are displaced, the risk of toxici increases as the concentration of free pharmacologically active com pounds rises. When a compound has a narrow therapeutic index an is highly protein bound, these age-related changes are significan Xenobiotic half-life may rise because of increased amounts of compou

are unbound, allowing free distribution to the tissues and decreasing plasma xenobiotic level.[13] Despite the increased volume of distribu- the half-life of a compound may be "normalized" by the increased rance of free xenobiotic.

Pediatric patients also have differences in regional organ blood flow may alter xenobiotic disposition. Significant differences in renal blood can result in alterations in xenobiotic excretion.[14,15] Proportionally ater blood flow to the heart and brain in pediatric patients[1] increases risk of adverse effects that may result from lower exposures to cardiac central nervous system toxins. Neonatal patients have an increased meability of the blood-brain barrier. This protects the brain from defi- ncies in nutritional fuels in stressful states because oxidizable substrates, ch as lactate, can pass from the blood into the central nervous system.[16] owever, this mechanism also increases the potential for central nervous stem exposure to toxins. Brain cells that are normally protected in adults e at higher risk of exposure to toxins in the neonate.

etabolism

epatic and renal excretion is limited in neonatal and pediatric animals, is decreasing xenobiotic elimination. Absorption of xenobiotics by ung animals may be manifested by decreased clearance.[3,5] Near-term d neonatal puppies have incomplete hepatic metabolism.[17-19] Both ase I (e.g., oxidative) and phase II (e.g., glucuronidation) reactions are duced. Maturation of various metabolic pathways occurs at different tes. Neonatal puppies may not manifest phase I activity until the ninth y of life; this activity steadily increases after day 25 until it reaches ult levels at day 135.[18] Because hepatic xenobiotic metabolism is creased, plasma clearance of xenobiotics is decreased; plasma half-life increased; and toxic plasma compound concentrations may result. Until iliary function matures, the absorption of fat-soluble compounds may be paired.

The oral bioavailability of compounds with a significant first-pass etabolism is probably greater in pediatric patients. Xenobiotics whose oxicity is generated from toxic metabolites may be less toxic because there decreased formation of active components. For example, children less han 9 to 12 years of age have a lower incidence of hepatotoxicity follow- ng overdose of acetaminophen than do adults.[20] Pediatric hepatic metab- lizing enzymes (e.g., cytochrome P450) do appear to be inducible by henobarbital and other drugs.

Excretion

Pups have reduced renal excretion, which decreases the cl
renally excreted parent compounds and the products of hepat
metabolism. As pups age, glomerular filtration and renal tubul
steadily increase.[15,21] The total number of glomeruli remains
Adult levels of glomerular filtration and tubular function are a
2½ months of age. If normal levels of body fluids and electr
maintained, pediatric renal tubular resorption is equivalent
adults.[22,23] In this pediatric renal environment, water-soluble x
have decreased clearance and extended half-lives. An example o
nomenon is the recommendation that pediatric patients requ
doses (because of the increased volume of distribution and long
intervals (because of increased distribution and decreased clea
gentamicin. One can anticipate alterations in excretion in sick
drated pediatric patients.

GERIATRIC PATIENTS

With advancing age comes increased organ dysfunction and
metabolic and physiological changes that may alter the responses o
patients to xenobiotic exposure Box 11-1. The two major pharma
areas most affected are drug disposition and tissue response to dr

The age at which body functions convert from a period of g
period of decay (16 to 18 years in humans) has not been well
dogs and cats. No age has been established as the boundary
"geriatric" in dogs and cats, whereas humans are generally co
have reached that boundary at 80 years. This "geriatric" boun
likely differs in various canine breeds. Approximately 30% of a
the body are lost permanently as the patient ages, and oxygen
tion is equally decreased. Significant changes in body compo
regional blood flow occur as aging progresses, and there is a stea
in physiological functions. Human basal metabolic rates decr
by 0.4%.[25] Changes in individual body systems that might be im
animals with potentially toxic exposures are listed below.

Cardiovascular system

In humans cardiac output decreases 30% to 40% in the geriatr
tion. This occurs at a rate of approximately 1% a year. Cardia

Physiological Alterations

rotein synthesis
umbers of hepatocytes
obiotic metabolism altered
iver size

learance decreased, serum creatinine normal
ubular absorption
lomerular filtration rate
enal blood flow

tion

body fat
otal body water
lasma volume
lasma albumin
ean body mass

al Tract

gastric pH
ctive transport
ate of gastric emptying
esophageal peristalsis
gastric secretions

cardiac output
ypertrophy
tress response

issue perfusion
ascular elasticity
ystolic blood pressure
ascular wall thickness

aged animals as well, with a resultant increase in circulatory
Additionally, regional and organ blood flow rates decrease
ly.[25] These alterations in cardiovascular dynamics are likely to
position (i.e., absorption, distribution, metabolism, and excre-
ns. Xenobiotic plasma or tissue concentrations can be affected
rection—decreased absorption and distribution or increased
and excretion.[2] Decreases in cardiac function are matched
atory mechanisms that may alter the risk and type of response
cs.[27] Blood flow may be preferably redistributed to the brain

and heart, thereby increasing their exposure and potential for incr toxicity.

Nervous system

Decreases in brain weight and peripheral nerve fibers accompany ag Additionally, connective tissue infiltrates the peripheral nervous tissu Blood flow to the brain decreases along with lowered oxygen consu tion. Selected neurotransmitters decrease in geriatric animals.

Respiratory system

Respiratory function decreases as the geriatric patient ages. Decrease residual lung volume (by 50%) and vital capacity occur, resulting in arterial PO_2. Central nervous system responses to decreases in oxyge increases in carbon dioxide make the geriatric patient less able to comp sate for the effects of compounds that decrease respiration (e.g., opioid Therefore any exposure to xenobiotics that is capable of inhibiting re ration may have greater potential for toxicity in the geriatric patient.

Gastrointestinal system

Older animals experience decreases in pharyngeal and esophageal moti along with reductions in salivation and deglutition. Gastric pH increased secondary to loss of secretion of hydrochloric acid by atroph gastric mucosa. Gastrointestinal motility is generally reduced. Atrophy the intestinal macrovilli and microvilli also occurs, which increases the of bacterial overgrowth. The consequences of these changes decrease the plasma xenobiotic concentrations of ingested toxins beca absorption of these compounds may be reduced. The geriatric pati may be at greater risk of adverse gastrointestinal effects by compoun such as nonsteroidal antiinflammatory drugs (NSAIDs) and chemothe peutic agents. It should be noted that these classes of drugs are prescrib more frequently in older patients than in the general animal populatio

Because of the major role played by the liver in the metabolism xenobiotics, geriatric changes in hepatic function significantly affect t potential toxicity of these compounds. Hepatic function and hepatocy numbers themselves are decreased, as are both hepatic and splanch blood flows. The net effect is a decrease in both hepatic oxidation and t

ry xenobiotic metabolizing enzyme cytochrome P450. Therefore etabolism of both capacity-limited and flow-limited compounds is ed. First-pass (flow-limited) metabolic hepatic clearance of compounds as opioids is decreased in geriatric patients. In older human patients henomenon is manifest as an increased response that requires 60% % less drug than that needed in younger patients, primarily because educed drug elimination.[25,28,29] Compounds that require primarily city-limited hepatic metabolism, such as NSAIDs, exhibit prolonged atic clearance. Alterations in hepatic function, nutrition, and oxygena- may predispose the geriatric liver to xenobiotic-induced hepato- city. This may reflect the inability of the liver to generate sufficient ective compounds (e.g., oxygen radical scavengers).

inary system

al blood flow decreases in the geriatric patient. This reduces the merular filtration rate and the active secretory rate of the nephron . The net effect is a progressive decline with age of renal xenobiotic rance. Renal excretion is the major route of elimination of many obiotics. These alterations in renal clearance lead to prolonged elimi- ion of compounds and promote increased plasma concentrations of parent or possible metabolites of a xenobiotic, placing the geriatric ient at increased risk of toxicity. Toxicity is enhanced in the aged ney, which has a decreased nephron population and an increased filter- load per nephron.[30] Xenobiotics that are known to be associated with al toxicity are of particular concern in the older patient with increased ma concentrations and prolonged exposure per nephron. Examples lude such compounds as aminoglycosides, NSAID analgesics, and iotensin-converting enzyme inhibitors. It is not inconsequential that iatric patients are often routinely taking these compounds in response other age-induced medical conditions.

ody weight and composition

the aged animal, body fat increases and lean body mass decreases. eriatric male humans often have a body fat content of 50%, whereas ung males average approximately 18% body fat.[25] Other manifestations companying increases in body fat are decreases in cell mass and total dy water. The percentage of total body water that is composed of extra- llular fluid increases, even though the total amount of extracellular fluid

stays the same. This change significantly alters the ratio of extracellu
intracellular fluid volume. The disposition of a toxin is a function
solubility. Plasma concentrations of water-soluble compounds inc
because of decreases in total body water. In the geriatric patient, how
plasma concentrations of fat-soluble compounds tend to be lower bec
of increased distribution into the larger available fat stores.

Albumin

Total serum protein generally remains the same as the individual a
However, the percentage of albumin decreases relative to the increas
gamma globulins. This decrease in serum albumin can have profo
manifestations when the geriatric body is exposed to highly protein-bo
toxins. That portion of the xenobiotic that exists as free compoun
increased. For example, most NSAIDs are close to 99% protein bound
decrease of 1% (i.e., 99% to 98% binding) doubles the concentratio
pharmacologically active drug. Some protection against this eleva
plasma concentration may occur with the increased clearance of unbou
compound by both the liver and kidneys.

Receptor sensitivity

Geriatric patients do respond differently to some drugs, suggesting t
tissue receptor sensitivity to these compounds may be altered. Altho
not documented, it has been hypothesized that differences in recep
number or responsiveness may underlie this phenomenon.[25,26] Anot
hypothesis is that physiological alterations in neurotransmission or int
cellular constituents may also occur. This idea is derived from evide
that geriatric patients have less perception or expression in response
pain stimuli. The need for analgesic therapy in geriatric patients is oft
not detectable.[31] Additionally, these patients may have a decreas
response to analgesic drugs.

Disease

Most geriatric patients have an underlying pathological condition tha
although not induced by the toxin, may profoundly alter xenobiotic disp
sition (Box 11-2) and possibly tissue receptivity to the toxin.[29] Studies ha
demonstrated decreased immune system function in the aged[32] that ma

11-2
ors That Affect Xenobiotic Disposition

macological Factors
harmaceutical interactions
herapeutic inequivalence
irect drug-drug interactions
rug-diet interactions
harmacokinetic interactions
harmacodynamic interactions

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

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

crease the risk of exposure to immune suppressive compounds. In addi-
on, the geriatric patient may well be receiving multiple drugs for under-
ng medical conditions, thus enhancing the risk of drug-drug or
rug-toxin interactions. Underlying diseases in specific target organs may
redispose those tissues to increased toxin-induced injury.

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