CHAPTER 1

Horse of a different color: Peculiarities of equine pharmacology

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Introduction

Horses are different. Practitioners expect such differences, given the unique anatomy and physiology of the many species encountered within veterinary medicine. Nonetheless, the appropriate use of therapeutic agents can be particularly challenging in the horse. Small animal practitioners have an advantage over other veterinary clinicians when novel therapeutics are investigated for veterinary use, as the pharmacology of investigational drugs is often described in dogs before they are used in people. However, if the dog is the prototypical species of basic pharmacological research, then the horse is just the opposite. The many idiosyncrasies of equine anatomy and physiology can make the behavior of drugs in this species highly unpredictable. Drugs that are well absorbed after oral administration, safe, and efficacious in other species may be poorly absorbed, toxic, or ineffective in horses. This chapter will investigate the sources of some of these pharmacological peculiarities and address strategies for using drugs safely and effectively in horses despite these inherent challenges.

Idiosyncrasies related to route of administration

Enteral absorption

Administration of drugs per os is the most natural route in companion animals. Administering foreign material to the gastrointestinal tract (GIT) is safer than parenteral administration, since the immunological and physical defenses in the GIT are designed to cope with all manner of foreign substances. Particulates, excipients, bacteria, fungi, endotoxins, and other toxins can be devastating if inadvertently administered parenterally, but most of these contaminants will have little impact if inadvertently delivered to the GIT. The cost of a drug formulated for oral administration is often less than its injectable counterpart, because of the stringent requirements needed to prepare safe injectable formulations. In addition, owner and patient compliance is usually better when oral drug administration is employed, especially when the duration of therapy encompasses days, weeks, or even for the remaining life of the patient. For all of these reasons, the oral route of administration is generally preferred in the nonhospitalized equine patient. In counterpoint to all of the advantages of oral drug administration, there are certainly disadvantages that the equine practitioner will recognize. First, getting the drug into the stomach of the horse can be challenging. Some small capsules and powders can be administered as a top-dressing to highly palatable feed. For horses that don't avoid top-dressed drugs and drugs that are palatable, this method of administration probably represents the most effective and convenient method of oral administration. Capsules, tablets, and powders may be hidden in pieces of carrot or apple with space carved or drilled by drug placement. Capsules and powders can also be mixed with applesauce, molasses, or syrup and mixed with feed, bran, or beet pulp. These methods can all be effective but require that the feed bucket be observed after

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administration to confirm that the entire dose was ingested. For unpalatable drugs and horses that avoid top-dressings, a powder can be mixed with applesauce, syrup, or molasses and placed in a syringe. A catheter-tipped syringe can be used for thinner mixtures, or the tip of the syringe can be removed and surfaces sanded smooth for the administration of thicker mixtures. Tablets can be crushed with a mortar and pestle, coffee grinder, or hammer to make a powder for administration. Some tablets and capsules can also be dissolved in a small volume of water. However, not all drugs are soluble and stable in water, so knowledge of the drug's aqueous stability is necessary if the drug does not quickly dissolve and is not immediately administered. Drugs should not be heated to speed solubilization unless aqueous and thermal stability is known, since heating will also speed hydrolysis of an unstable drug. Drugs with beta-lactam rings, including penicillins and cephalosporins, as well as some drugs with ester bonds, such as valacyclovir, have poor aqueous stability (see Chapter 2) [1, 2]. Some tablets and capsules that are insoluble in water will instead dissolve in the acidic pH of lemon juice [3]. The volume of lemon juice should be minimized to limit administration of the acidic solution, and it should be mixed with syrup or feed prior to administration.

Administration of drugs by a nasogastric tube is sometimes employed clinically and is often the route used when the oral absorption of a drug is being investigated. However, nasogastric intubation requires the presence of the veterinarian and is poorly tolerated for chronic dosing regimens. The bioavailability, or the total amount of the drug that reaches systemic circulation, of an orally administered drug is often reported in the initial assessments of a drug's utility in horses. As described in the following text, the knowledge of a drug's oral bioavailability will assist the practitioner with decisions regarding selection of the best available drug for a particular condition, dose modifications, and the likelihood of therapeutic failure with a particular drug. Since bioavailability is often known from studies detailing the drug's pharmacokinetic properties, the presentation of bioavailability after nasogastric administration to a fasted horse represents the best possible bioavailability of that drug in the horse. However, the actual bioavailability in the field, where fasting is difficult and nasogastric administration is seldom used, may be considerably lower than the reported value.

Although we expect that cattle and other ruminants will exhibit unique absorption patterns when drugs are administered per os, we may conversely expect that horses will absorb drugs in a similar manner to other monogastric species. Certainly, this expectation is met for some therapeutics, with drugs such as fluconazole being nearly completely absorbed after oral administration to horses and other species [4]. If the bioavailability is less than 100% but still adequate, an increase in dose can be used to obtain therapeutic results comparable to that of intravenous (IV) administration [5]. However, other drugs, such as acyclovir and azathioprine, are subject to abysmal oral bioavailability in horses [6, 7]. There are numerous pharmacological examples of drugs, such as furosemide, tramadol, metformin, ciprofloxacin, and amoxicillin, that are adequately absorbed after oral administration to other monogastric species but are poorly absorbed in horses, with average bioavailability of less than 10% [8–13]. Such drugs are rarely if ever administered orally to adult horses due to the recognition that their bioavailability is too low to allow a predictable therapeutic effect at doses that are practical to administer.

Parallels may be drawn between ruminants and horses, with ruminants often exhibiting very poor oral absorption of therapeutics due to the propensity of ruminal microbes to cleave xenobiotics to an inactive form and the dilution of drugs by the tremendous volume of the ruminal fluid [14]. Although horses have a monogastric digestive system, the poor bioavailability of some drugs in horses can also be attributed to their herbivorous diet. Whereas horses do not maintain the full complement of cellulolytic gastric bacteria as ruminants, both ruminants and horses do ingest a large volume of herbaceous feed, and horses do maintain some fermentative bacteria as part of the normal stomach flora [15]. Although the effect of the equine gastric flora on drug stability is poorly understood, it has been shown that some drugs, such as ampicillin, will specifically bind to equine ingesta, limiting their bioavailability [16]. Although feeding status also impacts some drug absorption profiles in other species, the presence of feed can be even more important to the absorption of orally administered drugs in horses. For example, the *rate* of flunixin absorption is greatly affected by fasting in horses, with the time of maximal plasma drug concentration occurring much later in fed horses (7 h) than in fasted ones (<1 h) [17]. Interestingly, whereas the *rate* of flunixin absorption was dependent on feeding, the *extent* of absorption was not, so efficacy is probably unaffected. However, a decrease in the maximal plasma drug concentration that occurs with slower

absorption can reduce the efficacy of drugs that must reach some threshold concentration to obtain the desired effect, since a slower rate of absorption will produce a lower peak plasma concentration. Alternatively, the presence of feed may affect both the rate and extent of absorption of some drugs, such as moxidectin [18]. It should also be noted that the presence of feed does not affect the absorption of some orally administered drugs. For example, the absorption of orally administered meclofenamic acid is not affected by feeding status [19].

For those drugs that are poorly absorbed after feeding, strategic fasting can increase the peak concentration, the extent of absorption, or both properties. However, fasting can be difficult to implement with a prolonged multiple-dose regimen. Complicating the design of a strategic fasting schedule, the amount of fasting time required to enhance drug absorption in horses is poorly defined, with some studies reporting enhanced absorption with fasting for as little as a few hours before and after oral drug administration and others after fasting overnight [17, 20]. The rate of gastric emptying depends on both diet composition and amount ingested, with large amounts of high-starch feeds taking longer to leave the equine stomach as compared to smaller meals with a lower proportion of starch [21]. Since it takes longer than a few hours of fasting to completely empty the equine stomach, it appears that a reduction of gastric volume, rather than complete gastric emptying, can enhance drug absorption. Such a goal makes pharmacokinetic sense, since dilution of drug by stomach contents will reduce the drug concentration in gastric juice and thereby reduce the concentration gradient between gastric juice and blood, which is the driving force of diffusion into systemic circulation.

Further support for the notion that the herbaceous diet of adult horses is to blame for sporadic poor bioavailability of drugs is found in the adequate oral absorption of some drugs, such as amoxicillin, when administered to foals, despite their poor absorption in adult horses [8, 9, 22]. As a consequence, some drugs that are not clinically useful in adult horses due to poor oral absorption are well absorbed in foals and so can be used in young, prefermentative animals (see Chapter 7).

Even drugs that are adequately absorbed after oral administration to horses may be subject to considerable variability in plasma concentrations due to erratic and unpredictable absorption patterns. Inconsistent therapeutic responses can follow such unpredictable absorption patterns, and the clinical importance of variable bioavailability is often underappreciated. For example, the absorption of metronidazole exhibits oral bioavailability (74 ± 18%, mean ± SD) that is fairly typical of a drug with adequate oral absorption in horses. A casual inspection of these values might suggest that there will be little variation in the plasma metronidazole concentrations between different horses, leading to a reliable therapeutic effect. However, a closer inspection of this data shows that the 95% confidence interval for metronidazole bioavailability for the extrapolated population would then be from 52 to 96%. As a consequence of this nearly twofold difference in bioavailability, plasma drug concentrations would also vary by at least twofold between horses at the lower and higher ends of typical bioavailability. The impact of erratic bioavailability on plasma concentrations will be further compounded by variability in other aspects of drug disposition, such as the extent of drug distribution and the rate of drug metabolism. Although pharmacokinetic differences between horses can be important sources of therapeutic failure for a drug administered by any route, interindividual differences are particularly pronounced when drugs are administered orally, as the initial variability in absorption combines with all other sources of variation.

Similarly, intrarectal administration, as is routinely employed for metronidazole administration to horses, may result in even more irregular absorption. For example, the average intrarectal bioavailability for metronidazole in horses is 30 ± 9%, giving a 95% confidence interval of 19–41% or a greater than twofold difference in absorption. For any drug where mean bioavailability is relatively low, perhaps 50% or less, there will be a substantial chance of clinically relevant variability in drug absorption between horses. This variability arises because a relatively small change in drug absorption will have a disproportionately large effect on fluctuation in plasma drug concentrations. As illustrated earlier for intrarectally administered metronidazole, as well as for more poorly absorbed orally administered drugs like digoxin, the range in the bioavailability of such drugs will generally vary by at least twofold [23]. Plasma drug concentrations that are lower or higher than expected can lead to therapy that does not produce the desired effect or, conversely, to drug toxicity. Such pharmacokinetic considerations should therefore be considered in horses that fail to respond to therapy as expected. The solution to such a failure may be to change the dose to the upper or lower end of the range of suggested doses or to switch to an alternate drug that is more reliably absorbed in horses. Drugs with bioavailability less than

10% are rarely useful when orally administered to horses due to low and erratic plasma drug concentrations. The oral administration of ciprofloxacin to horses is such an example, with a reported bioavailability of 7±5%. [13] The associated 95% confidence interval for oral ciprofloxacin bioavailability in horses, therefore, varies almost sevenfold. Such extreme variability typically accompanies the very poor bioavailability of such drugs, as small absolute changes in absorption account for a large change in the overall proportion of drug absorbed. This high variability generally precludes the safe and effective use of drugs with very low bioavailability, since the variability in drug absorption will continue at the higher dose rate. Consequently, even if a higher dose is administered in an attempt to reach targeted plasma concentrations, the resulting highly variable drug plasma concentrations will lead to a similarly unpredictable therapeutic response. Thus, very low bioavailability of drugs is usually an insurmountable obstacle to their clinical utility, necessitating a more reliable route of administration for the drug to be useful.

Formulations that enhance oral bioavailability

Poor bioavailability of some classes of drugs is a problem not only of horses but of other species as well. Therefore, specific drug formulations have been developed to combat poor oral absorption, and horses have benefited from many of these "designer drugs." For example, erythromycin base is rapidly hydrolyzed by the acidic pH of gastric juice, so it is administered in other species as an enteric-coated tablet, where the enteric coating prevents drug dissolution until the tablet reaches the more basic pH of the small intestine [24]. Grinding of the enteric-coated tablet for administration to horses disrupts the enteric coating, so the erythromycin is hydrolyzed in the stomach and subject to poor bioavailability. However, administration of an erythromycin estolate formulation produces much higher plasma erythromycin concentrations as the ester form is much more stable in acidic conditions [25]. As a prodrug, the ester bond must be broken by drug-metabolizing enzymes that are primarily present in enterocytes, the blood, and the liver, as only the liberated ester base will be active. Several other drugs, such as valacyclovir and cefpodoxime proxetil, are also ester prodrugs with enhanced bioavailability of the active drug in horses or foals [26, 27]. However, ester prodrugs are not always advantageous in horses, as is the case with prednisone, an ester prodrug of prednisolone. Both prednisone and prednisolone are well absorbed after oral administration to people, but prednisone was the first synthetic glucocorticoid developed for use in patients and so was the first synthetic, orally administered glucocorticoid to be widely used [28]. Despite administration of oral prednisone to equine patients for many years, only within the past decade was it reported that horses do not absorb orally administered prednisone well and do not readily convert prednisone to its active form, prednisolone, by the hepatic enzymes that are quite effective in dogs and people [29]. As prednisone is inactive, its administration cannot therefore be expected to produce a therapeutic effect in the horse. This finding shows again how important species-specific differences in drug absorption and metabolism can be. In addition, the dramatic differences between the metabolism of the ester bonds of prednisone and more useful prodrugs, like erythromycin estolate, demonstrate that the activation of prodrugs cannot be assumed in horses, but must be determined individually for each prodrug.

Parenteral routes of administration

Horses with altered perfusion, shock, or colic cannot be expected to absorb orally administered drugs normally, so IV administration should be selected in the physiologically compromised patient. IV administration is also preferred when a rapid onset of action is needed, such as for the administration of anesthetic agents or for assurance that the entire dose reaches the systemic circulation. Some drugs, such as potassium penicillin, must be administered slowly when given IV in order to avoid side effects associated with rapid administration (see Chapter 2). Other drugs, such as phenylbutazone, are irritants and will cause phlebitis and sloughing if any portion of the dose is administered extravascularly (see Chapter 5). Drugs that are known irritants, or those with very high or low pH in solution, should be administered very carefully to avoid extravasation and the possible sequelae of clostridial myositis [30]. Most irritants can only be administered topically or IV via a large vessel; the intramuscular (IM) and subcutaneous (SC) routes should be avoided to prevent tissue damage [31].

IM administration is generally preferred over IV administration if an owner must administer therapeutics, as personnel with insufficient training are at an increased risk of inadvertent intracarotid administration when attempting to use the jugular vein. Intracarotid

administration is associated with severe effects on the central nervous system (CNS), such as seizure, and so IV administration should be used judiciously. IM drug administration can be preferred to the oral route for some drugs with low oral bioavailability, such as penicillin G. Some drugs are subject to higher bioavailability when administered IM rather than orally, but without prior pharmacokinetic study, the clinician cannot predict whether the IM route will provide faster or better absorption than the oral route. One of the most important advantages of the IM route of administration as compared to IV or oral routes is that depot drug formulations can be administered IM for a prolonged effect. The extended effect of depot formulations can be ascribed to "flip-flop" kinetics, where drug absorption from the site of administration is the rate-limiting step of disposition and is much slower than the rate of drug elimination. Consequently, the slow absorption rate instead appears to be the rate of drug disappearance from the plasma, and the drug's effect can persist much longer than if the same dose was administered IV. However, the drug effect will only occur for as long as the drug concentration is able to remain at effective plasma concentrations, since depot formulations produce lower peak drug concentrations than do equivalent doses of the nondepot formulations. Penicillin benzathine formulations are an example of a depot formulation for which the resulting low plasma concentrations may reduce drug efficacy (see Chapter 2). Depot formulations also include corticosteroids, such as methylprednisolone acetate, which are most often used in joints for a prolonged anti-inflammatory effect, and several important antibacterial agents, such as procaine penicillin G and ceftiofur crystalline free acid (see Chapters 2 and 13). The neck, semitendinosus/semimembranosus muscle (buttocks), and, occasionally, the pectoral muscles are the sites most often used for IM administration. Injections may be rotated between sites when drugs, such as procaine penicillin G, are given more frequently. For drugs given infrequently, such as ceftiofur crystalline free acid, clinicians should select the site for which pharmacokinetic or efficacy data is available, since the site of administration can affect drug absorption [32]. Side effects specific to the IM route of administration are infrequent but can occur and, on rare occasion, are life threatening. Localized reactions can range from stiffness and swelling to bacterial abscessation and clostridial myositis. Because the rump or gluteal muscles are poorly drained in the event of abscess formations, this site is seldom used unless rotation between multiple IM sites is needed [33]. Administration of drugs into the buttocks has the advantage of injecting into a large, well-vascularized muscle mass, which can decrease the chance of tissue reactions and infection [30]. Clostridial myositis has followed the administration of a variety of drugs and vaccines IM but is most closely linked with the IM administration of flunixin meglumine, so it is most judicious to avoid IM administration of flunixin and other nonsteroidal anti-inflammatory drugs (NSAIDs) and use oral or IV routes instead [30]. Inadvertent administration of procaine penicillin G into the vasculature supplying muscle can result in CNS signs ranging from excitement to seizure, probably due to the rapid delivery of high concentrations of procaine to the CNS (see Chapter 2). For this reason, the IM injection site should be checked for inadvertent intravascular placement prior to injection.

Drug interactions

Over several decades, equine practice has become increasingly sophisticated in its use of therapeutic agents. There has been an exponential increase in studies investigating the therapeutic potential of novel agents, and new drugs have been specifically developed for use in horses. With the availability of new therapeutic options and treatment modalities, equine patients are increasingly likely to be exposed to multiple drug regimens or the inadvertent combination of several drugs to treat concurrent diseases. Drug combinations can be advantageous, detrimental, or neutral, with no net effect on efficacy or toxicity. Although some combinations are specifically chosen for their advantageous properties, most combinations that the clinician encounters are not adequately characterized to allow better than empirical predictions of their effects. With little information available regarding drug interactions in horses and the increasing use of "polypharmacy" in veterinary medicine, clinicians must be alert to potential interactions when administering multiple drugs to a patient. With clinical experience of common drug combinations, as well as knowledge of a drug's mechanism of action and pharmacokinetic properties, the clinician can assess the odds of a drug interaction and identify the most likely side effects.

Pharmacodynamic drug interactions

Drug–drug interactions can be either pharmacodynamic or pharmacokinetic in nature. Pharmacodynamic interactions occur when one drug increases or decreases the effect of another. Synergistic and potentiated combinations can be therapeutically beneficial and are most commonly selected for the use of antimicrobial, anesthetic, and analgesic agents. For example, the combination of penicillin with gentamicin produces a synergistic antibacterial effect (see Chapter 2). In addition, the anesthetic effects of isoflurane are potentiated by the addition of ketamine and lidocaine (see Chapter 3). Similarly, the use of multimodal analgesia can reduce the doses of each individual drug, thus decreasing the potential for adverse effects while still providing effective pain relief (see Chapter 4). On the other hand, drug combinations can instead be detrimental. Chloramphenicol coadministered with enrofloxacin can produce an antagonistic effect that impedes bacterial killing (see Chapter 2). The simultaneous administration of multiple drugs with similar mechanisms of action can enhance toxicity, as in the combination of firocoxib and phenylbutazone (see Chapters 5 and 13).

Pharmacokinetic drug interactions

Pharmacological compounds are xenobiotics, originating outside the body. As such, one can conceptualize drug metabolism as the body's attempt to render such substances inactive and more readily excreted. Whereas some drugs, such as gentamicin and penicillin, are primarily excreted intact into the urine, many other drugs are too highly protein bound or too lipophilic to be efficiently excreted into the urine. Biotransformation either activates or inactivates such drugs but will generally make them more polar, so that the resulting metabolite will be more readily excreted. Metabolism can also conjugate a bulky, highly charged moiety to the backbone of the drug, allowing biliary and/or renal excretion of the resulting metabolite. Although there are multiple sites, including the liver, blood, enterocytes, and lung, in the body where metabolizing enzymes are located, the liver metabolizes the majority of therapeutic substances. Both cytosolic and membrane-bound enzymes, such as cytochrome P450 enzymes, perform similar functions in the metabolism of xenobiotics. Surveys of drugs approved for use in people reveal that the majority of approved therapeutics are metabolized by P450 enzymes [34]. Due to wide interspecies variability, cytochrome P450 density and activity require direct study for each substrate in each species, with horses expressing high metabolizing activity for some drugs but low activity for others [35]. Since metabolites might be active or inactive, P450 metabolism is often responsible for drug–drug interactions due to induction or inhibition of their activity, with increased metabolism to active metabolites being an important source of drug toxicity. Phenobarbital induction of P450 enzymes is a well-recognized interaction that speeds the metabolism of phenobarbital itself but also increases the metabolism of other therapeutic drugs (see Chapter 12). Since the method of enzyme induction involves upregulation of expression and requires synthesis of new enzyme, induction is a relatively slow process, requiring days to weeks for the full effect to be realized. Conversely, inhibitors of P450 enzymes, such as ketoconazole, can immediately inhibit the metabolism of numerous other drugs (see Chapter 2). Other interactions involve more subtle competition for metabolism when two drugs are metabolized by the same P450 isoform. Cytochrome P450 isoforms are the expression of related metabolizing enzymes that differ with respect to their xenobiotic specificity and tissue location. P450 isoforms are divided into families, such as CYP1A, CYP3A, CYP2D, and CYP3C, by genotypic homology. The CYP3A family, specifically the CYP3A4 isoform, metabolizes the majority of therapeutics in people. Unfortunately, the CYP isoforms, their metabolizing specificity, and products are species specific, although CYP families are conserved between mammals. As a consequence, drug–drug interactions noted in one species, such as in humans, do not definitively indicate the likelihood of interactions in other species, such as in horses [36]. Such interactions are well recognized in people, where the individual hepatic P450 isoforms have been cloned, expressed in recombinant systems, and are routinely used to test all new therapeutics for interactions against a panel of substrates [37]. Even though the dog may be considered the model species of pharmacology and recombinant canine P450 isoforms are commercially available, recognition of drug–drug interactions is poorly understood even in this species [38]. Nonetheless, clinically relevant interactions, such as the inhibition of ketamine metabolism by concurrent medetomidine administration, have been noted in dogs [39]. However, if pharmacokinetic drug–drug interactions are poorly understood in dogs, then their recognition in horses is nearly in its infancy. Some equine P450 isoforms have been sequenced and expressed in

recombinant systems, but are not yet commercially available for routine testing [40, 41]. Therapeutics that are used in horses and have been found to present clinically relevant pharmacokinetic interactions in other species include the P450 inducers phenobarbital and rifampin and the inhibitors ketoconazole, itraconazole, cimetidine, and erythromycin (Table 1.1). Some of these drugs have been used in combination (e.g., rifampin with erythromycin in foals with *Rhodococcus equi* pneumonia) in horses with apparent efficacy and safety. However, dramatic interactions have also been reported, such as a 90% decrease in the oral bioavailability of clarithromycin when rifampin was coadministered to foals for several weeks [42]. Interestingly, this decrease in clarithromycin bioavailability by rifampin coadministration appears to be due to both the well-recognized P450-inducing effects by rifampin and a decrease in unknown intestinal transporters [43]. Conversely, ivermectin increased the bioavailability of cetirizine when ivermectin was administered 12 h prior to cetirizine but not when administered 1.5 h before [44]. On the other hand, a known inhibitor of P450 enzymes in people, cimetidine, failed to decrease the metabolism of coadministered phenylbutazone in horses [45]. Furosemide has been well recognized for its propensity to decrease the urine concentrations of drugs of regulatory interest, but the diuretic actions of furosemide are also blunted by the coadministration of NSAIDs [46]. Where novel or poorly studied combinations are used, clinicians should be alert to potential interactions when administering multiple drugs to a patient. Particular vigilance is warranted in drugs that are known inhibitors or inducers of P450 enzymes in other species, even though species-specific differences may preclude such interactions (Table 1.1).

Species-specific difference in hepatic metabolizing enzymes not only results in unique drug–drug interaction but can also result in metabolites that are unique to a particular species. As these unique metabolites can either be active or inactive, differences in drug activity between species can occasionally be explained by differences in drug metabolites. In equine pharmacology, however, the identity of drug metabolites can be particularly important when identifying whether prohibited drugs have been administered to horses where forensic testing of plasma or urine is employed (see Chapter 9). Specific analysis of postrace or show samples may include testing for both the restricted parent drug and its metabolite, as the existence of the metabolite corroborates a positive finding since it suggests metabolism of the parent drug by the body, as opposed to contamination of the sample with the parent drug alone. The metabolic pathways of many illicit and prohibited drugs are well understood in people, due to the forensic testing routinely employed by high-stakes athletic competitions. In order for such metabolite testing to be accurate in equine competitions, the metabolic patterns of the restricted drug within horses must be similarly elucidated, since the existence of a particular major metabolite in human beings does not mean that the same metabolic pathways will predominate in horses. Some drugs for which oxidative or phase I metabolism produces unique major metabolites in horses include fentanyl, ractopamine, and nimesulide [57–59]. Synthetic or phase II metabolites may also differ between horses and other species, with glucuronyltransferase being the major high-capacity conjugative enzyme system, often producing glucuronidated metabolites that are similar to those found in people and dogs [60]. In the forensic setting, equine urine is routinely incubated with glucuronidase in order to liberate the conjugated metabolite from the parent drug or oxidative metabolite for identification. Although the glucuronidated metabolite can also be directly measured, cleavage of the glucuronide moiety simplifies analysis and so is routinely employed [61].

Veterinary compounding pharmacies

Introduction

The ethics, safety, and liability of prescribing drugs prepared by compounding pharmacies are issues that face all facets of veterinary practice. However, in 2009, the shocking deaths of 21 polo ponies that received an IV administered, compounded vitamin supplement illustrated the worst of the compounding industry woes, where a seemingly small measurement error can have disastrous consequences for all involved [62]. Veterinarians are faced daily with the therapeutic challenge of treating species and conditions for which no approved drug exists. Other challenges include the differing needs of patients that have species-specific requirements, as well as individual needs for palatability and formulation. Some of these needs can be met by extralabel drug use under the regulations of the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 [63]. However, extralabel drug use is insufficient if

Table 1.1 Pharmacokinetic and pharmacodynamic drug interactions in horses

Drug	Effect	Drugs affected	Possible effect	Evidence
P450 enzyme inducers/increased elimination rate				
Phenobarbital	Increases its own metabolism by autoinduction	Phenobarbital	Decreased efficacy	*In vivo* [47]
Phenylbutazone	Decreased elimination half-life and distribution of coadministered drug	Gentamicin	Decreased efficacy	*In vivo* [48]
Rifampin	Increases clearance of coadministered drug	Phenylbutazone, clarithromycin	Decreased efficacy	*In vivo* [42, 49]
Rifampin	Decreased bioavailability of coadministered drug	Clarithromycin	Decreased efficacy	*In vivo* [42, 43]
P450 enzyme or efflux pump inhibitors				
Chloramphenicol	Decreases clearance of coadministered drug	Thiamylal, phenylbutazone	Increased activity and toxicity	*In vivo* [49]
Ivermectin	Increased bioavailability of select drugs	Cetirizine	Increased activity and toxicity	*In vivo* [44]
Ketoconazole	Decreases clearance of coadministered drug	Ketamine	Increased activity and toxicity	*In vitro* [50]
Methadone	Decreased metabolism of coadministered drug	Ketamine	Increased activity and toxicity	*In vitro* [51]
Quinidine	Decreases clearance of coadministered drug	Digoxin	Increased activity and toxicity	*In vivo* [52]
Xylazine	Decreased metabolism of coadministered drug	Ketamine	Increased activity and toxicity	*In vitro* [51]
Pharmacodynamic/miscellaneous				
Furosemide	Dilution of urine by diuresis	Clenbuterol, phenylbutazone, flunixin, fentanyl, and others	Decreased urine drug concentrations	*In vivo* [46, 53, 54]
Ketamine	Increases effectiveness of other anesthetics	Halothane	Increased activity and toxicity	*In vivo* [55]
NSAIDs	Decrease diuretic effects	Furosemide	Decreased activity	*In vivo* [46, 56]

a drug is no longer available as either a human or veterinary formulation, if the palatability of a formulation is poor, or if a formulation needs to be a different strength than the approved product. Under these circumstances, compounded drugs are often used. Drug compounding can be described as a change in the dosage form of a drug from that of the approved product. Although provisions for compounding are included under AMDUCA, much of the regular practice of compounding stands outside of clear regulatory guidelines. In the wake of considerable regulatory confusion and disturbing accounts of therapeutic failure with compounded products, veterinarians, pharmacists, and regulators are revisiting the role of compounding pharmacies in veterinary practice.

What are the rules?

There are several laws and regulations to consider in the legality of drug compounding. First, the federal government was given regulatory authority over drugs by the Pure Food and Drugs along with the Food, Drug, and Cosmetic Acts of 1906 and 1938. However, regulations that specifically covered drug compounding took longer. Human compounding was addressed by the Food and Drug Administration (FDA) Modernization Act in 1997, but veterinary use was ignored. Like extralabel

drug use, veterinary use of compounding was included in the AMDUCA of 1994. This act laid the provisions for both extralabel drug use and for drug compounding, resulting in some confusion among veterinary practitioners about which regulations cover which specific practice. Given these combinations of provisions, FDA guidelines for drug compounding include [64].

1 A valid veterinarian–client–patient relationship (VCPR) must exist.
2 The health of an animal must be threatened or suffering or death may result from failure to treat.
3 There must be no FDA-approved commercially available animal or human drug that, when used as labeled or in an extralabel fashion in its available dosage form and concentration, will appropriately treat the patient.
4 The product must be made from an FDA-approved commercially available animal or human drug.
5 The product must be compounded by a licensed veterinarian or a licensed pharmacist on the order of a veterinarian within the practice of veterinary medicine.
6 The compounded product must be safe and effective.
7 The amount of product compounded must be commensurate with the need of the animal identified in the VCPR-based prescription.
8 For animals produced for human consumption, the veterinarian must establish an extended withdrawal interval for the compounded product and ensure food safety. Compounding is not permitted if it results in violative food residue or any residue that may present a risk to public health.
9 No drug may be compounded for food animals from drugs listed on the prohibited list.
10 Veterinarians must comply with all aspects of the federal extralabel drug use regulations including record-keeping and labeling requirements.
11 All relevant state laws relating to compounding must be followed.

Suggestions issued by the AVMA for compounding provisions include (https://www.avma.org/KB/Resources/Reference/Pages/Compounding.aspx):

1 The decision to use a compounded drug should be veterinarian (not pharmacist) driven, based on a VCPR. Whenever possible, the veterinarian should make that decision utilizing evidence-based medicine.
2 Compounding must be implemented in compliance with the AMDUCA and the FDA Compliance Policy Guide (CPG) 608.400 titled Compounding of Drugs for Use in Animals. Use of compounded drugs in food animals is accompanied by food safety concerns that preclude their use unless information exists to assure avoidance of illegal tissue residues.
3 The use of a compounded drug should be limited to:
   (a) Those drugs for which both safety and efficacy have been demonstrated in the compounded form in the target species
   (b) Disease conditions for which response to therapy or drug concentration can be monitored
   (c) Those individual patients for which no other method or route of drug delivery is practical
4 Use of a compounded drug should be accompanied by the same precautions followed when using an approved drug, including counseling of the client regarding potential adverse reactions and attention to the potential for unintended human or animal exposure to the drug.

A quick review of these requirements reveals several areas where common compounding practices may deviate from federal regulations. First, the need for a valid VCPR dictates that compounding cannot occur independent of the needs of a specific patient. As a consequence, the practice of stocking compounded drugs before the need for these drugs arises would be in violation of the first and seventh requirements. This presents a problem for veterinary practices that routinely need compounded products on an emergency basis, without the luxury of time required to fill a prescription and obtain the final compounded product. The 2004 FDA CPG, last issued in 2003, attempts to clarify some of the confusion arising from existing compounding regulations with regard to obtaining compounded product without a VCPR and to resale of a compounded product. The CPG states that FDA regulatory enforcement may be undertaken under the condition of "compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving prescriptions issued within the confines of a valid VCPR." The CPG further opposes third-party (e.g., veterinarian) sale of drugs compounded by a pharmacy. State pharmacy regulations also apply and may differ somewhat, with some allowing a practitioner to stock and sell a small supply of compounded medications sufficient for an anticipated patient need until the compounded prescription can be filled. Taken together, these statements suggest that practitioners may keep a very limited supply of routinely needed medications on hand to administer or dispense while a compounded prescription is concurrently filled. However, the practice of purchasing large amounts of

compounded medications in the absence of a specific patient in need of that compounded product and especially of reselling such products is clearly discouraged by the FDA CPG and by most state pharmacy regulations.

The third requirement of drug compounding—that no FDA-approved veterinary or human drug currently exists that can meet the needs of the patient—is clearly counter to common practice. A perusal of current catalogs of compounding pharmacies shows many products and formulations that are substituted for approved drugs. The practice of substituting compounded drugs for approved drugs may be necessary in a few special circumstances, such as when the concentration of the approved drug is inappropriate for an individual patient or when palatability of the approved product is an issue for a particular patient. However, substitution of compounded products for approved products is often performed in an effort to reduce costs of drug therapy. A price reducing intention is clearly counter to FDA guidance and can expose patients to unnecessary risk, as some of these substitute products are prepared from drug stocks of unknown purity and potency. This raises the most contentious issue currently surrounding the practice of veterinary compounding: the use of bulk drugs to prepare the compounded product. Bulk drug is a compound in its raw, often powdered, form that is ordered directly from a chemical or pharmaceutical manufacturer. Some drugs, such as cisapride and some antidotes, are not currently manufactured as approved drugs and so can only be prepared from bulk ingredients [65]. Other compounded drugs may be prepared from bulk supplies in order to meet a specific concentration need. However, the majority of drugs compounded from bulk chemicals have the appearance of being cost-saving measures.

In order to put the use of bulk chemicals into perspective, let's compare the manufacture of approved drugs with that of bulk drugs used in compounding. Pharmaceutical companies will use bulk drugs as one step of the manufacturing process. However, pharmaceutical companies are also subject to strict oversight and regulations, such as Good Manufacturing Practice, that are designed to establish and maintain the purity, potency, stability, and sterility (if applicable) of the final manufactured product. Compounding pharmacies are bound to no such manufacturing regulations, with the result that the patient, client, and veterinarian are left to trust completely that a compounding pharmacy can reliably ascertain whether the drug source, preparation steps, product stability, and sterility all meet high standards. Several independent studies of compounded pharmaceutical products have demonstrated that compounded drugs often fail to meet such standards [66–69]. While bulk drug may be certified by the US Pharmacopeia (USP) to be of high purity, the use of many USP drugs will result in final compounded product that is at least as expensive as the FDA-approved product. Therefore, many bulk drugs are instead obtained from uncertain and questionable sources where certificates of analysis are not performed by independent testing. Given the not-too-distant melamine scare in pet foods, independent testing for purity and potency has become a matter of great concern when using drugs of unknown origin. Further, the use of bulk drugs introduces an extra preparation step that a pharmacy technician must undertake, which can increase the chance of formulation errors. The 2009 deaths of 21 polo ponies that received a compounded vitamin supplement was apparently due to just such a formulation error, which can all too easily happen without sufficient oversight and redundancy in the formulating process. Similarly, the well-publicized outbreak of fungal meningitis in people treated with a supposedly sterile compounded formulation of methylprednisolone acetate illustrated the disastrous consequences of microbial contamination of injectable drugs [70].

Can self-regulation be enough?

There is clearly a need for compounding of selected veterinary products, and compounding pharmacies fill an important role in veterinary practice. Compounding pharmacies have themselves recognized the challenges that face their industry and have formed several organizations that seek to maintain and improve the practice of compounding. The International Academy of Compounding Pharmacists (IACP) was founded in 1991 and has become the main trade group and advocate of compounding pharmacies [71]. Although IACP is probably most visible as an advocacy and lobbying group, they are also one of the founders of a more recent organization, the Pharmacy Compounding Accreditation Board (PCAB), established in 2004. In an attempt to facilitate voluntary regulation of compounding pharmacies, PCAB has established ethical, record-keeping, and practice standards that all pharmacies are required to meet before being accredited. Participation in PCAB is voluntary, however, so its ability to standardize compounding practices is still being explored. In the meantime, legislative action resulting from the fungal meningitis outbreak mentioned earlier is unlikely to substantially affect veterinary compounding practices at this time [72].

What the veterinarian can do

In addition to looking for PCAB accreditation, the following are some commonsense guidelines that can help veterinarians to select high-quality compounding pharmacies:

1 Are they ethical?
- **(a)** Do they sell compounded versions of marketed, approved drugs?
- **(b)** Do they sell without a veterinary–client–patient relationship?
- **(c)** Do they offer financial incentives to physicians to buy their product?

2 Is there a licensed pharmacist on-site?
- **(a)** Is the pharmacist trained in veterinary pharmacology and physiology?
- **(b)** Do they have additional compounding training? Membership in
  - **(i)** International Academy of Compounding Pharmacists
  - **(ii)** Professional Compounding Centers of America
  - **(iii)** PCAB Accreditation

3 Where are the bulk chemicals coming from?
- **(a)** Is the supplier FDA licensed and/or registered?
- **(b)** Do the bulk drugs come with a certificate of analysis?
- **(c)** How is quality control testing performed on the bulk chemical?

4 What quality testing is being done on end product?
- **(a)** Are there records of adverse reactions?
- **(b)** Were any trials done on the products?
- **(c)** Were these trials done by a disinterested, masked third party?
- **(d)** Any information on bioavailability? Shelf life? Strength?

5 How are sterile drugs formulated?
- **(a)** Is there a laminar flow hood?
- **(b)** Is sterility of the product checked?

6 Is there appropriate product labeling?
- **(a)** Preparation date
- **(b)** Expiration date: Is there one and has it been verified by testing?
- **(c)** Storage advice
- **(d)** Proper directions for use labels

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