Cairo University

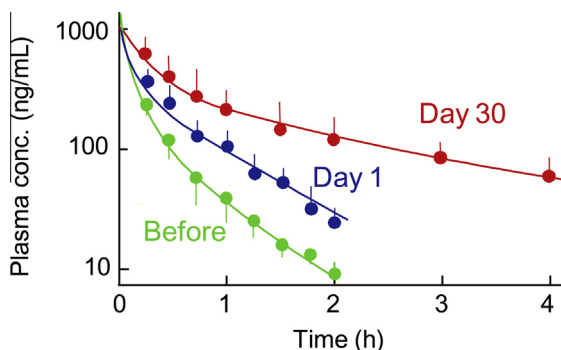**Journal of Advanced Research**

MINI REVIEW

Possible drug–drug interaction in dogs and cats resulted from alteration in drug metabolism: A mini review

Kazuaki Sasaki, Minoru Shimoda *

Faculty of Agriculture, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183-8509, Japan

G R A P H I C A L   A B S T R A C T

Effects of ketoconazole treatment on intravenous pharmacokinetics of midazolam (CYP3A substrate).

A R T I C L E   I N F O

A B S T R A C T

Pharmacokinetic drug–drug interactions (in particular at metabolism) may result in fatal adverse effects in some cases. This basic information, therefore, is needed for drug therapy even in veterinary medicine, as multidrug therapy is not rare in canines and felines. The aim of this review was focused on possible drug–drug interactions in dogs and cats. The interaction includes enzyme induction by phenobarbital, enzyme inhibition by ketoconazole and flu-

* Corresponding author. Tel.: +81 42 367 5770.
E-mail address: ms@cc.tuat.ac.jp (M. Shimoda).
Peer review under responsibility of Cairo University.

ELSEVIER | **Production and hosting by Elsevier**
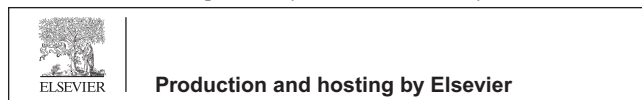
oroquinolones, and down-regulation of enzymes by dexamethasone. A final conclusion based upon the available literatures and author's experience is given at the end of the review.

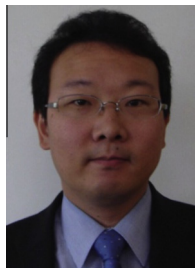© 2015 Production and hosting by Elsevier B.V. on behalf of Cairo University.

Kazuaki Sasaki, got his PhD of Veterinary Medicine from United Graduate School of Veterinary Sciences, Gifu University in 2005. In 2007, he became an Associate Professor of Veterinary Pharmacology, Department of Veterinary Medicine, Faculty of Agriculture, Tokyo University of Agriculture and Technology. The research of Dr. Sasaki is focused on pharmacokinetics, including drug absorption, distribution and elimination (biotransformation and renal excretion) in animals.

Minoru Shimoda, PhD, is a Professor of Veterinary Pharmacology, Department of Veterinary Medicine, Faculty of Agriculture, Tokyo University of Agriculture and Technology. He became an Assistant Professor in 1982, an Associate Professor in 1993 and a Professor in 2005 of the veterinary department. He got PhD from Faculty of Agriculture, University of Tokyo in 1985. The research of Prof. Shimoda is focused on pharmacokinetics, including drug absorption, distribution and elimination (biotransformation and renal excretion) in animals.

Introduction

Pharmacokinetic drug–drug interaction in drug metabolism may result in fatal adverse effects. In human medicine, patients treated with antihistaminic drug (terfenadine) and antifungal (ketoconazole or itraconazole) had Torsades de pointes, life-threatening ventricular tachycardia in 1991. This was resulted from the fact that ketoconazole and itraconazole inhibited CYP3A4 and thereby terfenadine accumulated in the body [1–4]. In 1993, many patients with cancer and herpes zoster, a viral disease, were died from interactions of an antiviral (sorivudine) with anticancer prodrug, 5-fluorouracil. This was due to the inactivation of an enzyme catalyzing the metabolism of 5-fluorouracil by co-administration of sorivudine [5–7]. Since the abovementioned medical accidents, researchers have paid much attention to pharmacokinetic drug–drug interaction originated from the alteration in drug metabolism in human medicine.

Alterations in drug metabolism due to pharmacokinetic drug–drug interaction are well recognized either as enzyme induction or as enzyme inhibition. So far, many drugs have been demonstrated to cause alteration in drug metabolism

in human medicine. Phenobarbital has been used as a CYP inducer in many studies [8–11] and ketoconazole is well characterized as a potent CYP inhibitor [12–15].

In veterinary medicine, pharmacokinetic drug–drug interaction in drug metabolism is an important subject, because multidrug therapy is commonly used for treatment of small animals including dogs and cats. Since there were big differences in drug metabolism, it is unclear whether the interactions that have been demonstrated in humans are substantial to animal species.

Basically, CYP1A1/2, 2C9, 2C19, 2D6, and 3A4 isoforms played important roles in drug metabolism in humans. Similar isoforms have been also found in dogs and cats. Dogs have CYP1A1/2, 2C21, 2D15 and 3A12 isoforms, whereas, CYP1A1/2, 2D6, 3A131 and 3A132 have been identified in cats, although they do not have tolbutamide hydroxylation activity, which is related to CYP2C9 activity in humans. This fact suggests that serious drug–drug interaction in drug metabolism catalyzed by CYPs can happen in dogs and cats. Although the information regarding such kind of interaction is not sufficient in veterinary medicine, it is gradually increasing in dogs and cats.

Scope of the review

This review introduces drug–drug interaction in drug metabolism in dogs and cats as follows: First, enzyme induction of phenobarbital and other drugs in dogs is described. Then, inhibitory effects of azole antifungals, fluoroquinolones, and other drugs on CYP activities in dogs and cats were discussed. Finally, down-regulating effects of dexamethasone on CYP activities in dogs are evaluated. The literature search was conducted using PubMed.

Enzyme induction

The mechanisms by which enzymes are induced include the following. (1) Medicines (inducers) bound to receptor (known as receptor-type transcriptional factors located in cytoplasm of hepatocytes). (2) Then the receptor was activated to allow its translocation to nucleus. (3) The translocated receptor bound to its response element of DNA. (4) The level of mRNA was correlated to enzyme expression. (5) The increase of mRNA levels results in increases of enzymes [16]. Fig. 1 shows the mechanism by which CYP1A is induced. In cytoplasm, the well defined receptors include aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR), and pregnane X receptor (PXR). The AhR was related to the induction of CYP1A and CAR and PXR were responsible for induction of CYP2B, 2C, and 3A subfamilies.
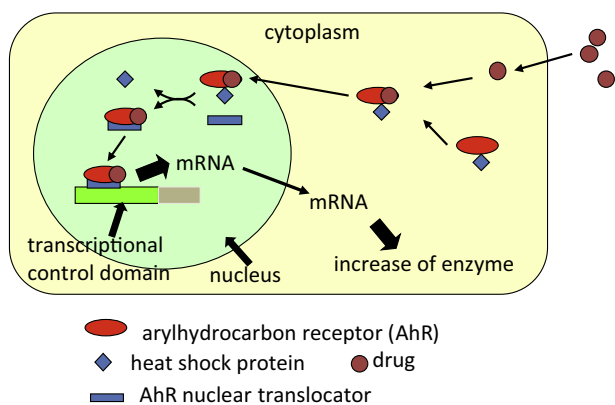
Fig. 1 Mechanism of CYP1A induction Drugs (inducers) binds to AhR-heat shock protein complex in hepatocytes cytoplasm. Then the complex is activated and enters inside the nucleus. The complex releases heat shock protein and binds to a transporter called AhR nuclear translocator. Then the complex binds to its response element of DNA, and the level of mRNA that relates to expression of enzymes increases. Finally, enzymes are induced.

Fig. 2 Antipyrine clearance during phenobarbital treatment in dogs. Dogs were orally administered phenobarbital at 5 mg/kg twice a day for 30 days, during which antipyrine was intravenously injected at 5 mg/kg, and its clearance values were estimated. Each value and vertical bar represent mean and SD, respectively ($n = 5$).

Enzyme induction by phenobarbital

As shown in Table 1 several drugs have been demonstrated to induce various CYPs and UDP-glucuronosyltransferase in humans. Among them, phenobarbital has been found to induce some CYPs in dogs [17–20]. The drug induces enzyme through activating CAR. Graham et al. [17] examined induction of CYP1A, 2B, and 3A after multiple subcutaneous injection of phenobarbital (14 days, 10 – 30 mg/kg/day) in beagle dogs. They found 10- and 2-fold increase in CYP2B and 3A activities in hepatic microsomes, whereas CYP1A activities were not affected. Hojo et al. [18] determined the effects of phenobarbital in its clinical dosage regimen (5 mg/kg/day p.o., bid) on CYP activities in dogs treated for 35 days. The total body clearance (CL) of a CYP3A substrate, antipyrine, was thereafter evaluated after intravenous injection. They found that the CL was increased <3-fold following 9th day of the treatment, and afterward remains steady (Fig. 2). They also examined the hepatic microsomal activities of CYP1A, 2C, 2D and 3A after the same course of treatment (35th day). While the activities of CYP2C and CYP3A were increased 2-and 4-fold (compared to control), the activities of CYP1A and 2D were not affected.

Effects of the oral phenobarbital treatment (5 mg/kg/day p.o., bid for 30 days) on intravenous pharmacokinetics of theophylline (a CYP1A substrate), phenytoin (a CYP2C
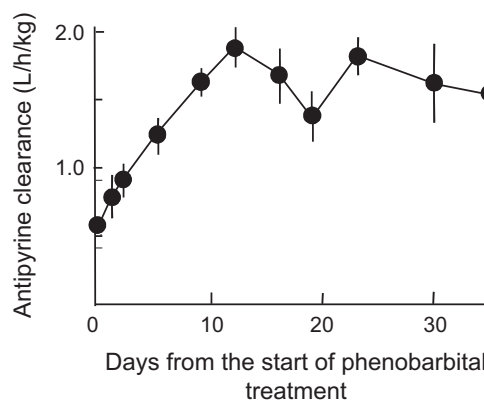
substrate) and quinidine (a CYP3A substrate) have been examined in beagle dogs. The pharmacokinetics of phenytoin and quinidine were affected by the phenobarbital treatment, whereas that of theophylline was not affected as shown in Fig. 3. The intrinsic clearances of phenytoin and quinidine (calculated from multiplying total body clearance by unbound fraction in plasma) were increased by 2- and 3-fold, respectively.

As obvious from the above, the CYP induction by phenobarbital was substantial. Therefore, there were high possibilities of drug–drug interaction with medicines that are mainly metabolized by CY2C or 3A in diseased dogs suffering from epilepsy.

Phenobarbital also induces UDP-glucuronosyltransferase in dogs. Oguri et al. demonstrated 3-fold increase in morphine glucuronidation in hepatic microsomes obtained from dogs treated with phenobarbital [21]. As NSAIDs were mainly eliminated from the body by biotransformation via glucuronidation, we, therefore, examined the effects of the phenobarbital treatment (5 mg/kg/day p.o., bid) on pharmacokinetics of carprofen after intravenous and oral administration in dogs. As a result, the total body clearance of carprofen increased by more than twice, compared to prior treatment. Although oral bioavailability of the drug was not affected, the oral AUC was nearly half compared to prior treatment. These findings indicate that phenobarbital could

Table 1 Drug inducing enzyme activities in humans.

| Enzyme	Inducer
CYP1A2	Omeprazole [81], lansoprazole [81]
CYP2C9	Phenobarbital [82], phenytoin [83], carbamazepine [84], rifampicin [85]
CYP2C19	Phenobarbital [82], phenytoin [83], rifampicin [85]
CYP2E1	Phenobarbital [86], rifampicin [86], isoniazid [86] (ethanol)
CYP3A4	Phenobarbital [82], phenytoin [87], carbamazepine [87], rifampicin [87], dexamethasone [87], taxol [88]
UDP-glucuronosyltransferase	Phenobarbital [89], rifampicin [90]
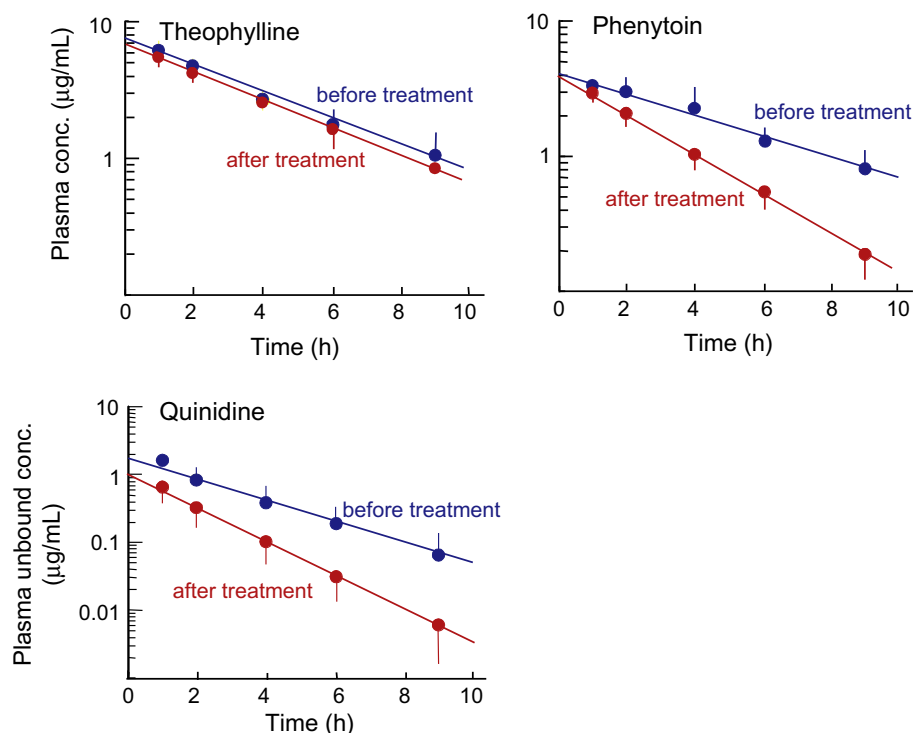
Fig. 3 Effects of phenobarbital treatment on intravenous pharmacokinetics of theophylline (CYP1A substrate), phenytoin (CYP2C substrate) and quinidine (CYP3A substrate) in dogs. Dogs were orally administered phenobarbital at 5 mg/kg twice a day for 30 days or 50 days and then pharmacokinetics of theophylline (5 mg/kg), phenytoin (5 mg/kg) and quinidine (1 mg/kg) were examined following intravenous injection. Each value and vertical bar represent mean and SD, respectively (*n* = 5).

induce UDP-glucuronosyltransferase much enough suggesting drug–drug interaction for remedies whose main elimination route is glucuronidation.

Phenobarbital is also a drug of choice for cats with epilepsy [22–24]. There were, however, few studies on enzyme induction by phenobarbital in cats. Maugras and Reichart [25] found slight increase in CYP levels in microsomes from cats treated with phenobarbital, compared to control ones. Truhaut et al. [26] found no induction of CYP following phenobarbital administration. These findings may suggest that phenobarbital causes minimal cytochrome P450 enzyme induction in cats, and therefore drug–drug interactions mediated by phenobarbital are unlikely to occur in cats.

Cochrane et al. [27] compared phenobarbital pharmacokinetics at steady state of oral administration with that after single oral administration in cats. As phenobarbital is mainly eliminated from the body via oxidation catalyzed by CYP2C, the oral clearance at steady state should be higher than that after single dosing, if induction of CYP2C is substantial. They, however, found no difference in the clearance between steady state and single dosing. This may suggest that drug–drug interactions mediated by phenobarbital are unlikely in cats.

Enzyme induction by other drugs

Among the medicines in Table 1, the inducing effects of omeprazole and rifampicin on CYP enzymes in dogs were previously reported. Nishibe and Hirata [28] examined the inducing effects of omeprazole and rifampicin using primary culture of dog hepatocytes. They found significant induction of CYP1A by omeprazole and CYP3A by rifampicin. Graham et al. [17] demonstrated 3-fold increase in CYP3A activities in dog microsomes after oral administration of rifampicin. These results may suggest that drug–drug interaction mediated by abovementioned remedies can happen in dogs.

Enzyme inhibition

Since drug–drug interaction mediated by enzyme inhibition increases accumulation of medicines, potent inhibitors may result in fatal adverse effects of co-administered drugs. It is, therefore, generally recognized that much attention should be paid to that type of interaction.

Enzyme inhibition by ketoconazole

Ketoconazole is an azole antifungal drug, which is known to inhibit CYP3A potently in humans. Its inhibitory effects on CYP activities have been investigated *in vitro* and *in vivo* in dogs and cats. Kuroha et al. [29] demonstrated that ketoconazole could inhibit competitively midazolam 1′-hydroxylation catalyzed by CYP3A with 24 nM of K_i value, using dog hepatic microsomes. This K_i value was estimated based on unbound concentration of ketoconazole in the assay system. This 24 nM corresponds to 83 nM of its total concentration [29]. The 83 nM is comparable to those obtained from humans (32–180 nM [30–35]). This fact suggests that ketoconazole inducing CYP mediated drug–drug interaction may be serious in dogs as found in humans [1–4].
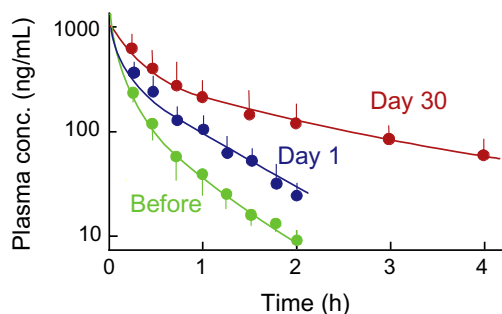
Fig. 4 Effects of ketoconazole treatment on intravenous pharmacokinetics of midazolam (CYP3A substrate). Dogs were orally administered ketoconazole at 20 mg/kg twice a day for 30 days, during which midazolam was intravenously injected at 0.5 mg/kg. Each value and vertical bar represent mean and SD, respectively ($n = 5$).

Fig. 4 shows the effects of ketoconazole on pharmacokinetics of midazolam following intravenous injection. Dogs were treated with ketoconazole (20 mg/kg p.o., bid) for 30 days. As shown in Fig. 4, ketoconazole treatment affected evidently the midazolam pharmacokinetics. The midazolam total body clearance was decreased by less than one-third at the end compared to prior treatments. This finding suggests that the inhibitory effect on CYP3A may be quite potent in dogs. Kukanich et al. have found that 5 day treatment with oral ketoconazole at 12.25 mg/kg would increase the mean residence time of midazolam approximately twice [36].

The inhibitory effects of ketoconazole on CYP3A activities affected also the pharmacokinetics of other drugs that were eliminated by metabolism and catalyzed by CYP3A. Kuroha et al. has demonstrated that the total body clearance of quinidine was decreased from 8.4 to 2.7 ml/min/kg by ketoconazole treatment at clinical dosage [37]. They also demonstrated that the total body clearance of nifedipine was decreased by approximately 50% compared to prior treatment. Additionally, they found twice increase in the oral bioavailability of nifedipine [38]. Kukanich et al. [39] found that C_{max} of methadone after oral administration was increased to more than 30-fold by the co-administered, ketoconazole.

Cyclosporine, an immunosuppressant, was used for treatment of canine atopic dermatitis. The drug was metabolized by CYP3A and possible drug–drug interaction with ketoconazole was evaluated [40–42]. Dahlinger et al. [41] showed that a 3.4 mg/kg dose of cyclosporine with ketoconazole gave similar blood levels of cyclosporine (400–600 ng/mL) compared to 14.5 mg/kg cyclosporine alone. D'mello et al. [42] found that the systemic clearance of cyclosporine was decreased from 7.0 ml/min/kg to 2.5 ml/min/kg by ketoconazole. Because of the inhibitory effect, the co-administrations of ketoconazole with cyclosporine have been recommended, which in turn decreases the therapeutic cost [43–45].

CYP3A inhibition by ketoconazole has also been reported in cats. Shah et al. [46] showed in his *in vitro* experiment using feline hepatic microsomes that ketoconazole can inhibit midazolam 1′-hydroxylation in a non-competitive manner. They estimated the inhibition constant of ketoconazole to be 2 μM. Although this value might be quite low to cause drug–drug interaction, it is more than 20-fold higher compared to the estimated value in dogs [29]. Because of this fact,

ketoconazole related drug–drug interaction may occur at smaller extent compared with those in dogs and humans. Shah et al. [46] have demonstrated that the decrease in quinidine clearance by ketoconazole treatment was less than a half in cats. However, they showed a time-dependent decrease in midazolam 1′ hydroxylation by pre-incubation of feline microsomes with ketoconazole. This suggests that ketoconazole has a mode of mechanism based inhibition in cats, although the mode has not been reported in dogs and humans. McAnulty and Lensmeyer [47] showed in his study the inhibitory effects of ketoconazole on cyclosporine pharmacokinetics, which can be implied from two times maximum cyclosporine blood concentration in cats treated orally with ketoconazole.

Ketoconazole can inhibit CYP activities other than CYP3A. In this context, Kuroha et al. [48] showed the inhibition of CYP1A, 2C, and 2D activities using 7-ethoxyresorufin O-deethylation, tolbutamide methyl hydroxylation, and bufuralol 1′-hydroxylation, respectively. The drug inhibited CY1A and 2C activities with 10.6 and 17.0 μM of K_i values, respectively. These values may be small enough to cause drug–drug interaction, although they are quite higher than that for CYP3A activities.

Enzyme inhibition by fluoroquinolones

It was reported that fluoroquinolones could inhibit CYP1A activities [49–53]. Among them, ciprofloxacin, enoxacin, and norfloxacin can cause drug–drug interaction with xanthine derivatives and potentiate its toxicity in human medicine [54–58].

Enrofloxacin, ciprofloxacin, ofloxacin, orbifloxacin, and norfloxacin inhibit CYP1A activities in dogs. Regmi et al. [53] demonstrated that the aforementioned fluoroquinolones could inhibit 7-ethoxyresorufin O-deethylation in a non-competitive manner in hepatic microsomes obtained from dogs. The K_i values were ranged from 0.7 for ciprofloxacin to 10 mM for ofloxacin; the values suggest that the inhibitory effects are quite small. On the other hand, ciprofloxacin, ofloxacin, and orbifloxacin showed mechanism based inhibition. Although it was not reported that ciprofloxacin and ofloxacin could have mechanism based inhibition in humans, and ofloxacin inhibits CYP1A activities by this manner in hepatic microsomes obtained from humans [59].

Drug–drug interaction of fluoroquinolones with theophylline has been reported in dogs. Intorre et al. examined intravenous injection of enrofloxacin on steady stale levels of theophylline following oral administration in dogs [60]. They found increases in the steady state blood theophylline concentrations; due to enrofloxacin treatment. This could be implied from the mechanism based inhibition of enrofloxacin metabolite, ciprofloxacin. Enrofloxacin itself does not have this type of inhibitory mode and reversible inhibition is quite small [53]. Although ofloxacin shows the mode of mechanism based inhibition, it does not affect theophylline pharmacokinetics in dogs [61]. Furthermore, levofloxacin does not affect theophylline pharmacokinetics in humans [62], although some fluoroquinolones would affect.

In cats there were no reports describing the inhibitory effects of fluoroquinolones on CYP1A activities. In our laboratory, we have examined this effect in cats and noticed that enrofloxacin, ofloxacin, norfloxacin, and orbifloxacin could

Table 2 Drugs inhibiting enzyme activities in dogs.

Enzyme	Inhibitor
CYP1A2	Ciprofloxacin [53] orbifloxacin [53], enrofloxacin [60], ketoconazole [48,66], miconazole [66], fluvoxamine [67], ondansetron [66]
CYP2C21	Vincristine [66], fluoxetine [67], clomipramine [67]
CYP2D15	Loperamide [66,67], vincristine [66], fluoxetine [66,67], ketoconazole [48,66], miconazole [66]
CYP3A12	Ketoconazole [29,36,39,66], miconazole [66], loperamide [66], cyclosporine A [66]

inhibit 7-ethoxyresorufin O-deethylation in a competitive manner, whereas, ciprofloxacin inhibited the enzyme by a noncompetitive manner. The obtained K_i values ranged from 0.12 mM (for norfloxacin) to 1.2 mM (for ofloxacin). Although these values are smaller than those obtained in dogs, the reversible inhibitions may not result in a drug–drug interaction with other medicines, which are substrates for CYP1A enzyme. We also found a mechanism based inhibition for ciprofloxacin and ofloxacin in cats. Similar to dogs [60], enrofloxacin may cause a drug–drug interaction with theophylline in cats.

Fluoroquinolones can also inhibit CYP3A activities in humans [52,63], rats [52], and chickens [64]. Enrofloxacin, ciprofloxacin, ofloxacin, norfloxacin, and orbifloxacin, however, did not affect Michaelis–Menten kinetics of 1'-hydroxylation of midazolam using dog hepatic microsomes. Additionally, enrofloxacin and ofloxacin did not affect the pharmacokinetics of a CYP3A substrate, quinidine, following intravenous injection in dogs [65]. Although we examined the effects in cats, the results were almost the same as reported in dogs [65]. Therefore, fluoroquinolones may not be responsible for a CYP3A mediated drug–drug interaction in dogs and cats.

Enzyme inhibition by other drugs

Many drugs other than ketoconazole and fluoroquinolones may inhibit CYP activities in dogs and cats, same as in humans. Aidasani et al. [66] evaluated the CYP reversible inhibition of many drugs used in veterinary medicine using canine hepatic microsomes. As a result, they found that ondansetron and miconazole were potent inhibitors for CYP1A; vincristine is a potent inhibitor for CYP2C; and loperamide, vincristine, clomipramine, and fluoxetine were potent inhibitors for CYP2D. On the other hand, they reported that loperamide,

miconazole, and cyclosporine A were potent CYP3A inhibitors. The inhibitory effect of erythromycin and cimetidine was not so strong, although they are potent inhibitors in humans. Mills et al. [67] have found that fluvoxamine could inhibit canine CYP1A activities with K_i value = 3 µM. Additionally, they declare that fluoxetine and clomipramine were potent inhibitors for CYP2C and 2D. Table 2 shows those medicines that could inhibit canine CYP activities.

In cats Shah et al. [46] examined the inhibitory effects of the aforementioned drugs. They demonstrated that both drugs inhibited non-competitively 1'-hydroxylation of midazolam with K_i value of approximately 3 mM. This value suggests that the inhibitory effects of erythromycin and cimetidine on CYP3A activities were quite small and hence may not cause drug–drug interaction with CYP3A substrates in cats.

Medical herbs may also inhibit CYP activities in dogs. Liu et al. [68] and Abd El-Aty et al. [69] have found that the volatile extracts from *Nigella sativa* seeds and decursin and decursinol angelate can inhibit CYP1A activities in hepatic microsomes obtained from dogs.

Drug induced down-regulation of enzymes

It is well known that CYPs are down-regulated by diseases, including renal failure [70,71], infection [72,73] and inflammation [74,75]. However; down-regulation induced by drugs was not known well and only few reports were recorded. Zhang et al. [76] examined the Michaelis–Menten kinetics of reactions catalyzed by CYPs using hepatic microsomes obtained from dogs treated with oral dexamethasone at clinically relevant doses (0.25 and 0.75 mg/kg) for 5 days. They found dose-dependent decreases in the reaction of bufuralol hydroxylation (catalyzed by CYP2D) and midazolam 4-hydroxylation (catalyzed by CYP3A), and the decreases were due to a decrease in maximal velocity but not K_m values as shown in Fig 5.
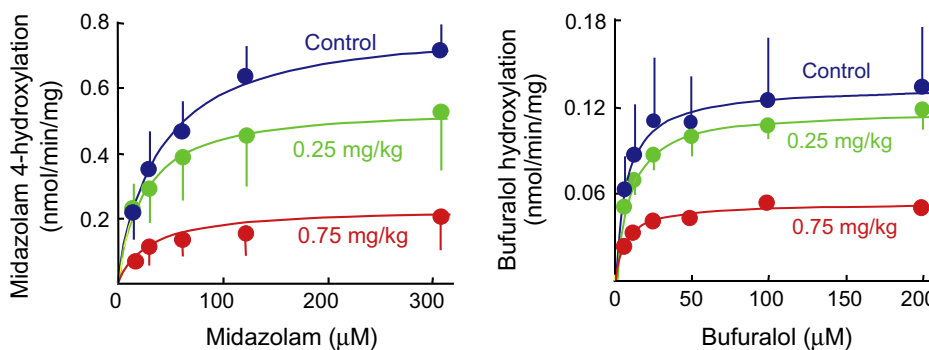

Fig. 5 Effects of dexamethasone treatment on Michaelis–Menten kinetics of midazolam 4-hydroxylation and bufuralol hydroxylation in hepatic microsomes from dogs treated with dexamethasone. Dogs were orally administered dexamethasone at 0.25 or 0.75 mg/kg/day for 5 days. Each value and vertical bar represent mean and SD, respectively ($n = 5$).

Fig. 6 Effects of dexamethasone treatment on intravenous pharmacokinetics of quinidine (CYP3A substrate) in dogs. Dogs were orally administered dexamethasone at 0.25 or 0.75 mg/kg/day for 5 days. Each value and vertical bar represent mean and SD, respectively ($n = 5$).
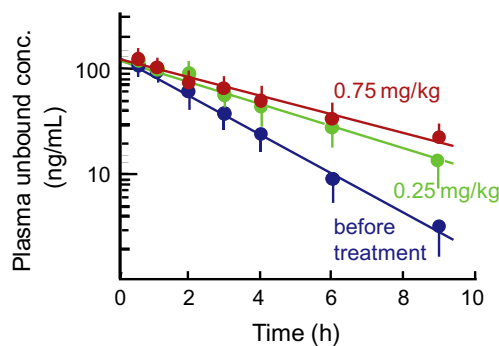
They also examined the inhibitory effects of dexamethasone on midazolam 4-hydroxylation and showed a small competitive inhibition with K_i value of 200 μM. From these data, Zhang et al. concluded that the decreases in CYP2D and 3A activities in dogs are due to down-regulation caused by dexamethasone, although steroids are well known as CYP3A inducer [77–79]. In the same study, the effects of dexamethasone treatment on Michaelis–Menten kinetics of midazolam 4-hydroxylation were also examined in rats. Maximal velocities of the reaction were increased by the treatment schedule set at a high dose (48 mg/kg for 5 days), suggesting CYP3A induction. However, the maximal velocities of the reaction were decreased by treatment at a low dose regimen (0.75 mg/kg for 5 days), suggesting down-regulation of CYP3A. These data may suggest that dexamethasone down-regulates CYP3A at a clinically relevant dose in various animal species.

The down regulating effects of dexamethasone may result in drug–drug interaction with substrates metabolized by CYP2D or CYP3A. Zhang et al. [80] examined the effects of dexamethasone treatment (0.25 and 0.75 mg/kg/day for 5 days) on intravenous pharmacokinetics of quinidine in dogs. Since dexamethasone decreased plasma levels of alpha 1-acid glycoprotein (the main binding protein for quinidine) they analyzed the unbound concentration–time curves. As obvious from Fig. 6, the elimination of quinidine became slower in a dose-dependent manner. Intrinsic clearance was approximately a half, compared to prior treatment. This indicates that the down-regulating effect of dexamethasone can cause drug–drug interaction with quinidine in dogs.

Conclusions

So far, many drugs have been demonstrated to cause alteration in drug metabolism in human medicine. In veterinary medicine, however, only some drugs have been investigated as described in this review. More advanced medical care is recommended to be used in dogs and cats. This may accelerate multidrug therapy in these animal species, using many kinds of drugs like in humans. This may result in increased possibilities of drug–drug interaction that induces fatal toxicity of the drug. The author expects much more investigations on this area in future.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

References

[1] Tran HT. Torsades de pointes induced by nonantiarrhythmic drugs. Conn Med 1994;58(5):291–5.

[2] Woosley RL. Cardiac actions of antihistamines. Annu Rev Pharmacol Toxicol 1996;36:233–52.

[3] Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000;38(1):41–57.

[4] Pohjola-Sintonen S, Viitasalo M, Toivonen L, Neuvonen P. Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. Eur J Clin Pharmacol 1993;45(2):191–3.

[5] Okuda H, Nishiyama T, Ogura K, Nagayama S, Ikeda K, Yamaguchi S. Lethal drug interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. Drug Metab Dispos 1997;25(5):270–3.

[6] Miyauchi S, Imaoka T, Okada T, Motoyama M, Kawaguchi T, Akiyama H, et al. Leukopenia-inducing effect of a combination of a new 5-fluorouracil (5-FU)-derived drug, BOF-A2 (emitefur), with other 5-FU-derived drugs or BV-araU (sorivudine) in rats. Jpn J Pharmacol 1996;70(2):139–48.

[7] Diasio RB. Sorivudine and 5-fluorouracil; a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. Br J Clin Pharmacol 1998;46(1):1–4.

[8] Gährs M, Roos R, Andersson PL, Schrenk D. Role of the nuclear xenobiotic receptors CAR and PXR in induction of cytochromes P450 by non-dioxin like polychlorinated biphenyls in cultured rat hepatocytes. Toxicol Appl Pharmacol 2013;272(1):77–85.

[9] Morita R, Yafune A, Shiraki A, Itahashi M, Akane H, Nakane F, et al. Enhanced liver tumor promotion activity in rats subjected to combined administration of phenobarbital and orphenadrine. J Toxicol Sci 2013;38(3):415–24.

[10] Wu Q, Zhang YH, Zhao X, Shi WL, Pu XP. Proteome studies on liver tissue in a phenobarbital-induced rat model. Eur J Pharmacol 2011;670(2–3):333–40.

[11] Zhang JG, Ho T, Callendrello AL, Crespi CL, Stresser DM. A multi-endpoint evaluation of cytochrome P450 1A2, 2B6 and 3A4 induction response in human hepatocyte cultures after treatment with β-naphthoflavone, phenobarbital and rifampicin. Drug Metab Lett 2010;4(4):185–94.

[12] Atsmon J, Dingemanse J, Shaikevich D, Volokhov I, Sidharta PN. Investigation of the effects of ketoconazole on the pharmacokinetics of macitentan, a novel dual endothelin receptor antagonist, in healthy subjects. Clin Pharmacokinet 2013;52(8):685–92.

[13] Perdaems N, Blasco H, Vinson C, Chenel M, Whalley S, Cazade F, et al. Predictions of metabolic drug-drug interactions using physiologically based modelling: two cytochrome P450 3A4 substrates coadministered with ketoconazole or verapamil. Clin Pharmacokinet 2010;49(4):239–58.

[14] Elsherbiny ME, El-Kadi AO, Brocks DR. The metabolism of amiodarone by various CYP isoenzymes of human and rat, and the inhibitory influence of ketoconazole. J Pharm Sci 2008;11(1):147–59.

[15] Ogawa R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. Clin Pharmacokinet 2010;49(8):509–33.

[16] Handschin C, Meyer UA. Induction of drug metabolism: the role of nuclear receptors. Pharmacol Rev 2003;55(4):649–73.

[17] Graham RA, Downey A, Mudra D, Krueger L, Carroll K, Chengelis C, et al. Parkinson A. In vivo and in vitro induction of cytochrome P450 enzymes in beagle dogs. Drug Metab Dispos 2002;30(11):1206–13.

[18] Hojo T, Ohno R, Shimoda M, Kokue E. Enzyme and plasma protein induction by multiple oral administrations of phenobarbital at a therapeutic dosage regimen in dogs. J Vet Pharmacol Ther 2002;25(2):121–7.

[19] Graham RA, Tyler LO, Krol WL, Silver IS, Webster LO, Clark P, et al. Temporal kinetics and concentration-response relationships for induction of CYP1A, CYP2B, and CYP3A in primary cultures of beagle dog hepatocytes. J Biochem Mol Toxicol 2006;20(2):69–78.

[20] Kawalek JC, Howard KD, Farrell DE, Derr J, Cope CV, Jackson JD, et al. Effect of oral administration of low doses of pentobarbital on the induction of cytochrome P450 isoforms and cytochrome P450-mediated reactions in immature Beagles. Am J Vet Res 2003;64(9):1167–75.

[21] Oguri K, Kurogi A, Yamabe K, Tanaka M, Yoshisue K, Ishii Y, et al. Purification of a phenobarbital-inducible UDP-glucuronosyltransferase isoform from dog liver which catalyzes morphine and testosterone glucuronidation. Arch Biochem Biophys 1996;325(2):159–66.

[22] Finnerty KE, Barnes Heller HL, Mercier MN, Giovanella CJ, Lau VW, Rylander H. Evaluation of therapeutic phenobarbital concentrations and application of a classification system for seizures in cats: 30 cases (2004–2013). J Am Vet Med Assoc 2014;244(2):195–9.

[23] Pakozdy A, Sarchahi AA, Leschnik M, Tichy AG, Halasz P, Thalhammer JG. Treatment and long-term follow-up of cats with suspected primary epilepsy. J Feline Med Surg 2013;15(4):267–73.

[24] Cochrane SM, Parent JM, Black WD, Allen DG, Lumsden JH. Pharmacokinetics of phenobarbital in the cat following multiple oral administration. Can J Vet Res 1990;54(3):309–12.

[25] Maugras M, Reichart E. The hepatic cytochrome level in the cat (Felis catus): normal value and variations in relation to some biological parameters. Comp Biochem Physiol B 1979;64(1):125–7.

[26] Truhaut R, Ferrando R, Graillot C, Gak JC, Fourlon C, Moraillon R. Induction of cytochrome P 450 by phenobarbital in cats. CR Acad Sci Hebd Seances Acad Sci D 1978 Jan 30;286(4):371–3.

[27] Cochrane SM, Parent JM, Black WD, Allen DG, Lumsden JH. Pharmacokinetics of phenobarbital in the cat following multiple oral administration. Can J Vet Res 1990;54(3):309–12.

[28] Nishibe Y, Hirata M. Effect of phenobarbital and other model inducers on cytochrome P450 isoenzymes in primary culture of dog hepatocytes. Xenobiotica 1993;23(6):681–92.

[29] Kuroha M, Azumano A, Kuze Y, Shimoda M, Kokue E. Effect of multiple dosing of ketoconazole on pharmacokinetics of midazolam, a cytochrome P-450 3A substrate in beagle dogs. Drug Metab Dispos 2002;30(1):63–8.

[30] Gascon MP, Dayer P. In vitro forecasting of drugs which may interfere with the biotransformation of midazolam. Eur J Clin Pharmacol 1991;41(6):573–8.

[31] Wrighton SA, Ring BJ. Inhibition of human CYP3A catalyzed 1′-hydroxy midazolam formation by ketoconazole, nifedipine, erythromycin, cimetidine, and nizatidine. Pharm Res 1994;11(6):921–4.

[32] Prueksaritanont T, Gorham LM, Ma B, Liu L, Yu X, Zhao JJ, et al. In vitro metabolism of simvastatin in humans [SBT] identification of metabolizing enzymes and effect of the drug on hepatic P450s. Drug Metab Dispos 1997;25(10):1191–9.

[33] Perloff MD, von Moltke LL, Court MH, Kotegawa T, Shader RI, Greenblatt DJ. Midazolam and triazolam biotransformation in mouse and human liver microsomes: relative contribution of CYP3A and CYP2C isoforms. J Pharmacol Exp Ther 2000;292(2):618–28.

[34] Galetin A, Ito K, Hallifax D, Houston JB. CYP3A4 substrate selection and substitution in the prediction of potential drug-drug interactions. J Pharmacol Exp Ther 2005;314(1):180–90.

[35] Ogasawara A, Kume T, Kazama E. Effect of oral ketoconazole on intestinal first-pass effect of midazolam and fexofenadine in cynomolgus monkeys. Drug Metab Dispos 2007;35(3):410–8.

[36] KuKanich B, Hubin M. The pharmacokinetics of ketoconazole and its effects on the pharmacokinetics of midazolam and fentanyl in dogs. J Vet Pharmacol Ther 2010;33(1):42–9.

[37] Kuroha M, Shirai Y, Shimoda M. Multiple oral dosing of ketoconazole influences pharmacokinetics of quinidine after intravenous and oral administration in beagle dogs. J Vet Pharmacol Ther 2004;27(5):355–9.

[38] Kuroha M, Kayaba H, Kishimoto S, Khalil WF, Shimoda M, Kokue E. Effect of oral ketoconazole on first-pass effect of nifedipine after oral administration in dogs. J Pharm Sci 2002;91(3):868–73.

[39] Kukanich B, Kukanich KS, Rodriguez JR. The effects of concurrent administration of cytochrome P-450 inhibitors on the pharmacokinetics of oral methadone in healthy dogs. Vet Anaesth Analg 2011;38(3):224–30.

[40] Gray LL, Hillier A, Cole LK, Rajala-Schultz PJ. The effect of ketoconazole on whole blood and skin ciclosporin concentrations in dogs. Vet Dermatol 2013;24(1):118–25.

[41] Dahlinger J, Gregory C, Bea J. Effect of ketoconazole on cyclosporine dose in healthy dogs. Vet Surg 1998;27(1):64–8.

[42] D'mello A, Venkataramanan R, Satake M, Todo S, Takaya S, Ptachcinski RJ, et al. Pharmacokinetics of the cyclosporine-ketoconazole interaction in dogs. Res Commun Chem Pathol Pharmacol 1989;64(3):441–54.

[43] O'Neill T, Edwards GA, Holloway S. Efficacy of combined cyclosporine A and ketoconazole treatment of anal furunculosis. J Small Anim Pract 2004;45(5):238–43.

[44] Patricelli AJ, Hardie RJ, McAnulty JE. Cyclosporine and ketoconazole for the treatment of perianal fistulas in dogs. J Am Vet Med Assoc 2002;220(7):1009–16.

[45] Mouatt JG. Cyclosporine and ketoconazole interaction for treatment of perianal fistulas in the dog. Aust Vet J 2002;80(4):207–11.

[46] Shah SS, Sasaki K, Hayashi Y, Motoyama S, Helmi AR, Khalil WF, et al. Inhibitory effects of ketoconazole, cimetidine and erythromycin on hepatic CYP3A activities in cats. J Vet Med Sci 2009;71(9):1151–9.

[47] McAnulty JF, Lensmeyer GL. The effects of ketoconazole on the pharmacokinetics of cyclosporine A in cats. Vet Surg 1999;28(6):448–55.

[48] Kuroha M, Kuze Y, Shimoda M, Kokue E. In vitro characterization of the inhibitory effects of ketoconazole on metabolic activities of cytochrome P-450 in canine hepatic microsomes. Am J Vet Res 2002;63(6):900–5.

[49] Pea F, Furlanut M. Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions. Clin Pharmacokinet 2001;40(11):833–68.

[50] Kinzig-Schippers M, Fuhr U, Zaigler M, Dammeyer J, Rüsing G, Labedzki A, et al. Interaction of pefloxacin and enoxacin with the human cytochrome P450 enzyme CYP1A2. Clin Pharmacol Ther 1999;65(3):262–74.

[51] Fuhr U, Anders EM, Mahr G, Sörgel F, Staib AH. Inhibitory potency of quinolone antibacterial agents against cytochrome P450IA2 activity in vivo and in vitro. Antimicrob Agents Chemother 1992;36(5):942–8.

[52] McLellan RA, Drobitch RK, Monshouwer M, Renton KW. Fluoroquinolone antibiotics inhibit cytochrome P450-mediated

microsomal drug metabolism in rat and human. Drug Metab Dispos 1996;24(10):1134–8.

[53] Regmi NL, Abd El-Aty AM, Kuroha M, Nakamura M, Shimoda M. Inhibitory effect of several fluoroquinolones on hepatic microsomal cytochrome P-450 1A activities in dogs. J Vet Pharmacol Ther 2005;28(6):553–7.

[54] Antoniou T, Gomes T, Mamdani MM, Juurlink DN. Ciprofloxacin-induced theophylline toxicity: a population-based study. Eur J Clin Pharmacol 2011;67(5):521–6.

[55] Andrews PA. Interactions with ciprofloxacin and erythromycin leading to aminophylline toxicity. Nephrol Dial Transplant 1998;13(4):1006–8.

[56] Loi CM, Parker BM, Cusack BJ, Vestal RE. Aging and drug interactions. III. Individual and combined effects of cimetidine and cimetidine and ciprofloxacin on theophylline metabolism in healthy male and female nonsmokers. J Pharmacol Exp Ther 1997;280(2):627–37.

[57] Marchbanks CR. Drug-drug interactions with fluoroquinolones. Pharmacotherapy 1993;13(2):23S–8S.

[58] Batty KT, Davis TM, Ilett KF, Dusci LJ, Langton SR. The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. Br J Clin Pharmacol 1995;39(3):305–11.

[59] Pan X, Wang P, Hu N, Liu L, Liu X, Xie L, Wang G. A physiologically based pharmacokinetic model characterizing mechanism-based inhibition of CYP1A2 for predicting theophylline/antofloxacin interaction in both rats and humans. Drug Metab Pharmacokinet 2011;26(4):387–98.

[60] Intorre L, Mengozzi G, Maccheroni M, Bertini S, Soldani G. Enrofloxacin-theophylline interaction: influence of enrofloxacin on theophylline steady-state pharmacokinetics in the beagle dog. J Vet Pharmacol Ther 1995;18(5):352–6.

[61] Regmi NL, Abd El-Aty AM, Tomita A, Shimoda M. Effect of ofloxacin on theophylline pharmacokinetics at clinical dosage in dogs. J Vet Pharmacol Ther 2006;29(5):403–8.

[62] Gisclon LG, Curtin CR, Fowler CL, Williams RR, Hafkin B, Natarajan J. Absence of a pharmacokinetic interaction between intravenous theophylline and orally administered levofloxacin. J Clin Pharmacol 1997;37(8):744–50.

[63] Brouwers EE, Söhne M, Kuipers S, van Gorp EC, Schellens JH, Koks CH, et al. Ciprofloxacin strongly inhibits clozapine metabolism: two case reports. Clin Drug Invest 2009;29(1):59–63.

[64] Hu HF, Gao ZX, Cheng YY. Inhibition of CYP3A mRNA and protein expression, and enzymatic activity, by enrofloxacin in chickens. J Vet Pharmacol Ther 2010;33(6):546–50.

[65] Regmi NL, Abd El-Aty AM, Kubota R, Shah SS, Shimoda M. Lack of inhibitory effects of several fluoroquinolones on cytochrome P-450 3A activities at clinical dosage in dogs. J Vet Pharmacol Ther 2007;30(1):37–42.

[66] Aidasani D, Zaya MJ, Malpas PB, Locuson CW. In vitro drug-drug interaction screens for canine veterinary medicines: evaluation of cytochrome P450 reversible inhibition. Drug Metab Dispos 2008;36(8):1512–8.

[67] Mills BM, Zaya MJ, Walters RR, Feenstra KL, White JA, Gagne J, Locuson CW. Current cytochrome P450 phenotyping methods applied to metabolic drug-drug interaction prediction in dogs. Drug Metab Dispos 2010;38(3):396–404.

[68] Liu X, Park JH, Abd El-Aty AM, Assayed ME, Shimoda M, Shim JH. Isolation of volatiles from Nigella sativa seeds using microwave-assisted extraction: effect of whole extracts on canine and murine CYP1A. Biomed Chromatogr 2013;27(7):938–45.

[69] Abd El-Aty AM, Shah SS, Kim BM, Choi JH, Cho HJ, Hee-Yi C, et al. In vitro inhibitory potential of decursin and decursinol angelate on the catalytic activity of cytochrome P-450 1A1/2, 2D15, and 3A12 isoforms in canine hepatic microsomes. Arch Pharm Res 2008;31(11):1425–35.

[70] Dani M, Boisvert C, Michaud J, Naud J, Lefrançois S, Leblond FA, et al. Down-regulation of liver drug-metabolizing enzymes in a murine model of chronic renal failure. Drug Metab Dispos 2010;38(3):357–60.

[71] Leblond FA, Petrucci M, Dubé P, Bernier G, Bonnardeaux A, Pichette V. Downregulation of intestinal cytochrome p450 in chronic renal failure. J Am Soc Nephrol 2002;13(6):1579–85.

[72] Carvalho RS, Friedrich K, De-Oliveira AC, Suarez-Kurtz G, Paumgartten FJ. Malaria downmodulates mRNA expression and catalytic activities of CYP1A2, 2E1 and 3A11 in mouse liver. Eur J Pharmacol 2009;616(1–3):265–9.

[73] Shimamoto Y, Sasaki M, Ikadai H, Ishizuka M, Yokoyama N, Igarashi I, et al. Downregulation of hepatic cytochrome P450 3A in mice infected with Babesia microti. J Vet Med Sci 2012;74(2):241–5.

[74] Kusunoki Y, Ikarashi N, Hayakawa Y, Ishii M, Kon R, Ochiai W, et al. Hepatic early inflammation induces downregulation of hepatic cytochrome P450 expression and metabolic activity in the dextran sulfate sodium-induced murine colitis. Eur J Pharm Sci 2014;11(54):17–27.

[75] Saitoh T, Kokue E, Shimoda M. The suppressive effects of lipopolysaccharide-induced acute phase response on hepatic cytochrome P450-dependent drug metabolism in rabbits. J Vet Pharmacol Ther 1999;22(2):87–95.

[76] Zhang K, Kuroha M, Shibata Y, Kokue E, Shimoda M. Effect of oral administration of clinically relevant doses of dexamethasone on regulation of cytochrome P450 subfamilies in hepatic microsomes from dogs and rats. Am J Vet Res 2006;67(2):329–34.

[77] Corcos L. Phenobarbital and dexamethasone induce expression of cytochrome P-450 genes from subfamilies IIB, IIC, and IIIA in mouse liver. Drug Metab Dispos 1992;20(6):797–801.

[78] Martin P, Riley R, Back DJ, Owen A. Comparison of the induction profile for drug disposition proteins by typical nuclear receptor activators in human hepatic and intestinal cells. Br J Pharmacol 2008;153(4):805–19.

[79] Lu C, Li AP. Species comparison in P450 induction: effects of dexamethasone, omeprazole, and rifampin on P450 isoforms 1A and 3A in primary cultured hepatocytes from man, Sprague-Dawley rat, minipig, and beagle dog. Chem Biol Interact 2001;134(3):271–81.

[80] Zhang K, Kohno S, Kuroha M, Kokue E, Shimoda M. Clinical oral doses of dexamethasone decreases intrinsic clearance of quinidine, a cytochrome P450 3A substrate in dogs. J Vet Med Sci 2006;68(9):903–7.

[81] Curi-Pedrosa R, Daujat M, Pichard L, Ourlin JC, Clair P, Gervot L, Lesca P, Domergue J, Joyeux H, Fourtanier G. Omeprazole and lansoprazole are mixed inducers of CYP1A and CYP3A in human hepatocytes in primary culture. J Pharmacol Exp Ther 1994;269(1):384–92.

[82] Ohno M, Motojima K, Okano T, Taniguchi A. Induction of drug-metabolizing enzymes by phenobarbital in layered co-culture of a human liver cell line and endothelial cells. 2C, 3A. Biol Pharm Bull 2009;32(5):813–7.

[83] Chaudhry AS, Urban TJ, Lamba JK, Birnbaum AK, Remmel RP, Subramanian M, et al. CYP2C9*1B promoter polymorphisms, in linkage with CYP2C19*2, affect phenytoin autoinduction of clearance and maintenance dose. J Pharmacol Exp Ther 2010;332(2):599–611.

[84] Oscarson M, Zanger UM, Rifki OF, Klein K, Eichelbaum M, Meyer UA. Transcriptional profiling of genes induced in the livers of patients treated with carbamazepine. Clin Pharmacol Ther 2006;80(5):440–56.

[85] Chen Y, Goldstein JA. The transcriptional regulation of the human CYP2C genes. Curr Drug Metab 2009;10(6):567–78.

[86] Madan A, Graham RA, Carroll KM, Mudra DR, Burton LA, Krueger LA, et al. Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. Drug Metab Dispos 2003;31(4):421–31.

[87] Luo G, Cunningham M, Kim S, Burn T, Lin J, Sinz M, et al. CYP3A4 induction by drugs: correlation between a pregnane X receptor reporter gene assay and CYP3A4 expression in human hepatocytes. Drug Metab Dispos 2002;30(7):795–804.

[88] Nallani SC, Goodwin B, Buckley AR, Buckley DJ, Desai PB. Differences in the induction of cytochrome P450 3A4 by taxane anticancer drugs, docetaxel and paclitaxel, assessed employing primary human hepatocytes. Cancer Chemother Pharmacol 2004;54(3):219–29.

[89] Ramírez J, Komoroski BJ, Mirkov S, Graber AY, Fackenthal DL, Schuetz EG, et al. Study of the genetic determinants of UGT1A1 inducibility by phenobarbital in cultured human hepatocytes. Pharmacogenet Genomics 2006;16(2):79–86.

[90] Reinach B, de Sousa G, Dostert P, Ings R, Gugenheim J, Rahmani R. Comparative effects of rifabutin and rifampicin on cytochromes P450 and UDP-glucuronosyl-transferases expression in fresh and cryopreserved human hepatocytes. Chem Biol Interact 1991;121(1):37–48.