Journal of Advanced Research (2015) 6, 383–392

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

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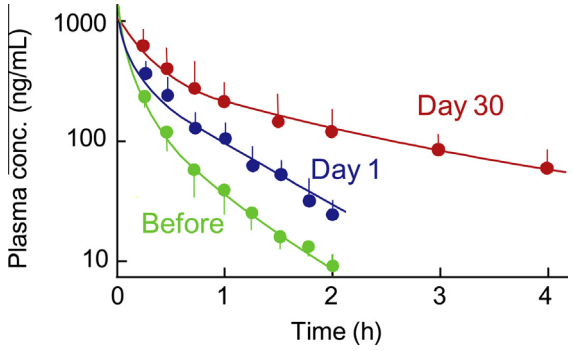
GRAPHICAL ABSTRACT



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

ARTICLE INFO

Article history:
Received 7 August 2014
Received in revised form 10 February 2015
Accepted 15 February 2015
Available online 24 February 2015

ABSTRACT

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-

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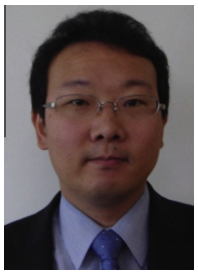
Peer review under responsibility of Cairo University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jare.2015.02.003

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.

Keywords:
Drug–drug interaction
Drug metabolism
Pharmacokinetics
Dogs
Cats



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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.