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Clinical Drug Interactions: A Holistic View

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Abstract: Every time a drug is administered to the animal to treat an ailment, no matter whether it is acute or chronic manifestation, it usually goes together with some other prescription medicine, OTC (Over the counter) formulation, herbs or even food. All the xenobiotics such as drugs, toxins and food components as well as the endogenous compound that are formed in the animal body as a routine phenomenon exert a stimulatory or inhibitory effect on the different physiological and biochemical processes going in the body. These effects may alter the normal metabolism and/or drug transport or its efficacy drastically and thus expose the man and animals to the risk of a potentially dangerous interaction. The present review discusses these potential reactions and their mechanisms that help in navigating the hazardous combinations of drugs with other medicines, food, herbs, vitamins and minerals with confidence.

Key words: Drug, vitamin, mineral, interaction, pharmacokinetics

INTRODUCTION

A drug interaction is said to occur when a drug is administered with any another xenobiotic and the pharmacological response of the drug gets altered either in intensity or duration (Rahal *et al*., 2008; Davis *et al*., 2013). Whenever two or more drugs are taken concurrently, there is a chance of an interaction among the drugs that could manifest as an increase or decrease in their effectiveness or an adverse reaction or a totally new side effect that is not seen with either drug alone that can be severe enough to alter the clinical outcome and warrant hospital admissions, ranging upto 3.8%. In veterinary clinical practice, occurrence of new drug-drug interactions (Rodrigues, 2000; Rahal *et al*., 2007; Singh *et al*., 2009) between a plethora of medications being introduced every day is a common feature, especially in the chronic ailments subjected to poly pharmacy for the treatment of a large number of diseases; thus making it difficult for any physician to remember avoiding potential drug interactions. Such interactions often result in adverse clinical complications.

Drug interactions should always be differentiated from any unusual response occurring during drug therapy (Arnaud *et al*., 2012). Prior to start a treatment for any such plausible adverse drug interaction, it is essential to have the history of previous medication as most of the time patients consult many physician and formulate their own prescription just by amalgamating or substituting the prescribed drugs as usually seen in case of antibiotics, painkillers and other over-the-counter medicines (Valiyil and Christopher-Stine, 2010; Kirking *et al*., 1986). Certain drugs show the risk of generating interactions over and over again through well understood mechanisms

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(Davis *et al*., 2013). When such drugs are started or stopped, the physician needs to be extra alert to the possibility of drug interactions. While it is impossible to list every plausible interaction with the currently available drugs or food (Gysin *et al*., 2011) but the drugs which have high protein binding tendency mostly get involve in such interactions (Rahal *et al*., 2008). Generally, the problem of drug interaction is most commonly encountered with certain groups of drugs that are usually used in combination like Non steroidal anti-inflammatory agents (NSAIDs), and the drugs of low therapeutic index (e.g., Digoxin) are a massive challenge to physicians. Moreover, the commonly used antibiotics and antimicrobials viz., Penicillin, Sulfonamides, along with oral contraceptives and antiepileptic are also responsible for these kind of challenges. The most common examples of such drugs include aspirin, phenylbutazone, carbamazepine, phenytoin, rifampicin and griseofulvin that influence either the protein binding or modulate the process of metabolism and excretion of other drugs. There are many drugs e.g., allopurinol, metronidazole, chloramphenicol, cimetidine, ketoconazole, quinolones and MAO inhibitors; which are responsible for the inhibition of metabolism of other drugs.

EARLY EVALUATION OF DRUG INTERACTIONS

Today drug-drug interaction and the resulting adverse reactions form a topic of round table discussion among pharmaceutical personnel as well as researchers. Despite this general awareness and concern of the problem of drug interactions and widespread efforts to monitor them, the physician society has so far failed in predicting as well as recognizing them. Because drug interactions could not be generally predicted, one had to wait till they appeared in literature. Recognition of potential interactions should really commence early in the development of new drugs. Now various reliable methods are available to find out the actual or potential drug interactions and such well established method include the study of various processes the drugs undergo after entering and before its exit from the body. Such interactions are studied by pharmaceutical companies during the initial stages of drug development process but pharmacovigilant monitoring in later phases could also reveal interactions although the restrictions of use of concomitant drugs in these phases may not provide optimal information regarding drug interactions. In present system, advanced techniques are applied to assess the drug interaction *in-vitro* to update the clinicians and to avoid untoward interactions particularly for the specific diseases (Davis *et al*., 2013). Based upon the method of the existing methods of evaluating drug interaction many of these interactions can be avoided. However, in-vitro studies do not exactly translate always in the clinical scenario, because of immense in vivo variables that come in to play. Some drugs can be metabolized by more than one enzyme whereas some others like carbamazepine can not only induce a particular isoenzyme (CYP3A4) but also get metabolized by it demanding a gradual dosing, while a few others can inhibit a particular isoenzyme but not be metabolized by it.

Magnitude of the problem: Drug interactions are multifaceted and chiefly inconsistent (Ansari, 2010) as a known interaction may not occur in every individual taking the drug or even a drug in the same class. There is a huge number of the evidences for drug to drug interaction but the tendency of fraternity to disregard the magnitude is further aggravating the condition. There is a common postulation that all drugs in a given class have a homogenous interaction potential but this is actually rare. For example, amongst the macrolide class, while erythromycin and clarithromycin inhibit CYP3A4 leading to interactions with other drugs, azithromycin does not. Likewise while ketoconazole interacts with lovastatin and simvastatin and raises their plasma levels it does not do so with rosuvastatin or pravastatin. Drug interactions also vary individual to individual and even upto 5-7 fold differences have been reported. These variations also change with the change of dose, duration of treatment and route of inoculation (Rahal *et al*., 2006, 2007; Verma *et al*., 2009; Kumar *et al*., 2011, 2012). The matter is often compounded by patients additionally taking herbal drugs that interact with their prescribed medication (Singh *et al*., 2010) about which the doctor may not know; with other modifiers of drug elimination and response and genetics. The potency of drug also depends upon the coadministration of other drugs and depending upon the number of drugs and interaction potential it may go upto 100%. Another early study reported an incidence of 7% when 6-10 drugs were prescribed that rose to 40% when 15-20 drugs were given. Clearly drug interactions present a health threat to patients and a great challenge to the physician as monitoring the patient's therapy is a standard of care expected by the patients and the liability of interactions rests squarely on the physician who fails to recognize potentially harmful interactions to avoid extra costs of healthcare (Thaler *et al*., 2013).

HOW DO DRUG INTERACTIONS OCCUR?

There are various categories of interaction with drugs:

- Drug-Disease interactions
- Drug-Drug interactions
- Drug-Food interactions
- Drug-Herb interactions
- Drug Environmental interactions

Understanding the mechanism by which a given drug interaction occurs is often useful in practice, as the mechanism could influence both the time course and mechanism of evoking the interaction (Rahal *et al*., 2008; Kumar *et al*., 2009, 2011). The past experiences and gender, age, physical conditions drug recommendation vary individual to individual. Depending upon the reports and the clinical trials, the desirable therapeutic regimen of drugs in different possible clinical situations is indicated. Even then, when these drugs are used in field condition, it might result in a totally different scenario of interaction and this is a kind of experience of physician, so the use and indications also depend upon the experience and exposure of clinician/physician (Davis *et al*., 2013).

Because of the complexity of pharmacotherapy needed for the treatment of the basic disease, its underlying causative factors, its complications and accompanying co-morbid factors such as hypertension, diabetes and dyslipidemia, malignancy and respiratory disorders, the number of drugs prescribed increases translating into a major risk factor for potential drug interactions (Thaler *et al*., 2013).

DRUG-DRUG INTERACTIONS

Although tremendous advances have occurred in knowledge of the mechanisms of drug interactions over the last few decades, we still have a long way to go to fully understand them as more than one mechanism may play a part in some drug interactions (Garcia Fernandez *et al*., 2013). Use of any drug is based upon the disease and patients. Many time dose, route and other indication for the same drug vary in different conditions (Kumar and Rahal, 2005; Rahal *et al*., 2009). Whatsoever drugs are to be given simultaneously, it should be based upon previous experience and need of the patient (Mahendra Kumar *et al*., 2011). The clinically most important adverse drug-drug interactions occur with drugs that have easily recognizable toxicity and a low therapeutic index, such that pretty slight change in drug effect can have clinically significant adverse consequences (Garcia Fernandez *et al*., 2013). There are numerous mechanisms by which drugs may intermingle (Hanigan *et al*., 2011) but most of them can be classified as:

- Pharmacokinetic interactions
- Pharmacodynamic interactions
- Additive or synergistic interactions
- Antagonistic or opposition interactions

Adverse drug reactions resulting from simultaneous medication are commonly associated with drugs that are chemically or biochemically antagonistic (Garcia-Barrera *et al*., 2012). All kind of the interaction of the drug interaction depends upon various steps of pharmacokinetics as absorption of the drug from various sites of administration, distribution to different tissues and organs, biotransformation and finally its elimination (Rahal *et al*., 2007) from the host or the interaction of the drug with the receptor, the actual site of bioaction (Rathore *et al*., 2012a, b), ultimately leading to the impact of drug and its implication (Wachter and Verghese, 2012).

PHARMACOKINETIC INTERACTIONS

The science of therapeutics does not merely involve testing of new molecules in medical and veterinary clinical medicine, but it emphasizes upon the treatment of each patient holistically as an individual and it is widely recognized that individuals show wide variability in response to the same treatment (Verma *et al*., 2011). Pharmacokinetic interactions must always be evaluated in the context of their clinical biochemical and pathophysiological relevance. Co administration of two drugs always does not mean any interaction; the interaction depends upon a mixture of factors including relative affinities of each drug for the binding site or the xenobiotic metabolizing enzyme; component of plasma proteins which actually binds the drugs in question like albumin, acidic glycoprotein and nevertheless, the actual free drug concentration available at the tissue site for binding to the receptor and produce a response (Garcia Fernandez *et al*., 2013).

Effect of drug interaction also depends upon the physical and physiological condition of patient (Thaler *et al*., 2013). In general, pharmacokinetic interactions are considered clinically significant when at least a 30% change is seen in Cmax, Tmax and AUC (Rahal *et al*., 2008). Coadministration of drugs which follow different pathway of drug metabolism might be useful with certain consideration, such as the prescribed

dose and its fulfillment, the actually administered dose, its rate and extent of absorption, bioavailability, Tmax, AUC, distribution, metabolism, the rate of elimination (time 1/2), drug concentration attained at the actual site of action, genetic polymorphism in the receptor and the effect of the drug at the receptor.

DRUG ABSORPTION INTERACTIONS

Since the oral route is the one most frequently used to administer drugs, interactions influencing absorption are more likely to occur within the gastrointestinal tract, which more often result in reduced rather than increased absorption. Different interactions of drugs have different implications. Some of them might be useful while others might be deadly. Use of different drug combinations at different dose and route of inoculation always affect these interactions. Various pharmacokinetic actions of drugs as absorption and eliminations are base of these interactions. The common examples of absorption interaction include milk calcium and tetracyclines making calcium unavailable to the body. High doses of drugs may be required to achieve the drug effect in short duration eg., analgesic and have its own clinical significance as most clinically important drug interactions occur due to the following factors:

- Changes in gastrointestinal pH (leading to ion trapping)
- Changes induced by chelation and adsorption (making drug unavailable for absorption)
- Changes in gastrointestinal motility (altering its time course of absorption)
- Transporter based interactions (altering the extent of absorption)
- Intestinal metabolism of drugs (modulating the half-life)

DRUG DISTRIBUTION INTERACTIONS

Many drugs interact by displacement of each other binding to plasma proteins (Rahal *et al*., 2007). Drugs with acidic nature are known to have an affinity to bind to plasma proteins, hence when drugs are administered in combination, competitive binding for the same site or receptor may displace one drug from the protein binding site increasing the amount of the displaced free drug in plasma and various tissues setting up an interaction leading to an enhanced potential for toxicity (Rahal and Malik, 2010, 2011; Trumic *et al*., 2012), such as is seen in the case of concomitant administration of warfarin with phenylbutazone or other highly protein bound drugs that leads to increased levels of warfarin and hence its toxicity, with the clinical implication of frequent and prolonged bleeding. Drug interactions involving alterations in distribution because of volume changes can be exemplified by the combined use of gentamicin and frusemide. As gentamicin is well distributed in extracellular fluid any fall in ECF induced by frusemide reduces the volume of distribution of gentamicin thus increasing its serum levels with the clinical implication of nephro- and ototoxicity.

Despite the factors described above for distribution interactions, recent research recommend that although in-vitro many commonly used drugs are capable of being displaced by others, in the body, these effects/interactions seem to be so well buffered that the outcome may not normally be clinically important. Moreover, as some interactions which were originally assumed to be due to protein binding, have later on been shown to have other mechanisms involved, it has been suggested that the importance of this plasma proteins alone being responsible for the interaction has been overstated.

DRUG METABOLISM INTERACTIONS

The animal or human body is constantly exposed to foreign substances (drugs) not found naturally in the body. These compounds alter the body function to achieve a therapeutic end and are modified or metabolized by a plethora of enzymes. The processes by which the enzymes alter an active drug inside the body to an inactive one or two active or toxic metabolites are commonly referred to as drug metabolism or biotransformation (Thaler *et al*., 2013). To exert their systemic effect, most drugs need to reach a site of activity and for this they need to be lipid soluble so as to be able to penetrate the lipid plasma membrane barrier. The lipophilic drugs after they fulfil their pharmacological role, further need to be converted into a water soluble form to be excreted efficiently by the renal route. Liver has the chief responsibility of metabolism and enables these processes in two phases-phase 1 and 2.

In phase I, oxidation/reduction reactions convert the drugs into a more hydrophilic form, while phase 2 reactions provide another set of mechanisms involving conjugation/hydrolysis with substances like glucuronic acid, aminoacids and other endogenous metabolites for modifying drugs into inactive compounds to enable their excretion. The cyotchrome p 450 family present in the hepatic microsomes are mainly responsible for carrying out these modifications in drug molecule and together account for 90-95% of xenobiotic biotransformations

taking place in the body; the complete cytochrome P450 family is a collection of diverse subfamily of enzymes with substrate specificity and nonspecificity and shows high genetic variability. Therefore exact proportion of role for different subfamilies in the biotransformation of a single drug entity is highly unpredictable.

A drug's action on a molecular already results in a biological complex that could be influenced further by disease. In addition to all these factors, genetic polymorphisms that influence change in this biological complex can greatly influence drug response. These differences in the variability to metabolize different drugs could account for a few persons manifesting toxicity with interacting drugs while others do not exhibit any symptoms. The clinical implication of this polymorphism is exemplified by omeprazole, where poor metabolisers having higher drug levels with standard dosages had markedly high healing rates 100% compared to otherwise normal metabolizers; highlighting the need for identification of such polymorphisms early in a drug's development. Although, significant metabolism takes place in the liver, other organs like the kidney and gut are also involved. On the basis of the extent to the drug gets metabolized in liver, the drugs are categorized as high extraction drugs, moderate extraction drugs and low extraction drugs. The high extraction drugs have shorter half-life, shorter therapeutic index and productive life in comparison to the low extraction drugs. However, lower the therapeutic index of a drug, greater is the risk to turn out into a grave clinical outcome owing to metabolism and excretion pattern changes (Garcia Fernandez *et al*., 2013).

To predict drug interactions well it is mandatory that a proper understanding of drugs influencing CYP 450 enzyme induction and inhibition be made. Interactions involving drug metabolism can alter the amount of drug available for action by inhibition or induction of metabolism. Inhibition is usually more predictable than induction which is influenced by genetic differences between patients. Inhibitors battle with other drugs for a particular enzyme thus affecting the optimal rate of metabolism of the substrate drug that then accumulates in the body resulting in toxicity (Lynch and Price, 2007). CYP isozymes escalate the rate of metabolism in the presence of inducers and that lead to rapid clearance of substrate from the system. Because of the dependency on enzyme synthesis and time 1/2 of the inducing drug, these type of interactions occur slowly. Attainment of steady state concentrations always reported to increase CYP enzymes. However, if the half-life (time 1/2) of the affected drug is long, it may take a week to reach steady state levels. This inhibition leads to decreased metabolism of drugs acted upon by the enzyme, prolonging its time 1/2 and reducing clearance, thus growing plasma levels that lead to interactions (Alavijeh *et al*., 2005). Some drugs are converted to toxic endproducts by enzymes (Farukbhai, 2010) and enzyme inducers can increase the formation of these toxic metabolites. Paracetamol is primarily converted to nontoxic metabolites but a small amount is converted to toxic metabolites; however if administered with an enzyme inducer it could lead to hepato-toxicity.

DRUG ELIMINATION REACTIONS

The major routes for elimination of drugs remain the kidney and gastrointestinal tract. There are no noteworthy drug-drug interactions through bile elimination, except for drug-disease ones. There are many modes of interaction for the drugs excreting out through renal route and theses interactions are mainly because of urinary pH alteration and passive reabsorption at renal tubule. Other common causes include glomerular filtration alteration and drug to drug interaction (Freudenthaler *et al*., 1998). Active secretion into the renal tubules is an important excretion pathway for a few drugs (Ip *et al*., 1988), which get affected by the co-administration of certain other drugs, thereby affecting their therapeutic response. The capacity of a drug to inhibit the renal excretion of another is dependent on an interaction at active transport at reabsorption sites. The beneficial probenecid-penicillin/amoxicillin interaction exemplifies one of the many reported interactions at the anion transport site; the two drugs competing for excretion by modifying active transport in the renal tubules resulting in probenecid being excreted and the antibiotics being retained and reabsorbed, with the clinical implication of increasing their plasma levels to a desirable level to increase its therapeutic effect and prolonging the plasma time 1/2. The interaction between quinidine and digoxin is reported to have severe consequences due to the reduction of renal excretion of digoxin even upto 50% and that includes reduction of about 50% in digoxin excretion in bile as well as by its P-gp mediated inhibition of transcellular transport and also inhibition in the gut.

The rate of excretion of a drug or its metabolites can be influenced by other drugs that increase or decrease glomerular filtration due to changes in renal blood flow. A mild increase in renal clearance may lead to a clinically significant decrease in the plasma levels of drugs with low therapeutic index. An alteration in the urinary pH can also significantly modulate the excretion pattern of the drug. The repercussion of this mechanism is reflected in the management of salicylate or amphetamine poisoning by alkalinizing with antacids or acidifying the urine,

respectively. The drugs which have acidifying nature e.g., ascorbic acid, might lead to increased levels of phenobarbitone.

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions are reasonably common in practice and occur when a precipitant drug alters the clinical effects of the object drug at its site of action. One drug may alter the normal physiological milieu whereby it can increase or decrease the effects of another drug. This may be illustrated by the interaction produced by diuretic induced hypokalemia with the simultaneous use of digoxin resulting in digoxin toxicity. Synergistic and additive reaction are the outcome of interaction of similar active principle or due to the simultaneous administration of drugs of similar action. The drugs used in combination may or may not act on the same class receptor to produce these effects and the effect is one of duplication where the clinical effect is intensified. There are numerous examples of such a response like that is seen when a cold remedy and a pain reliever (both containing paracetamol) are taken together. Likewise the simultaneous use of two nephrotoxic drugs can aggravate renal damage, where the dose of either drug may have been insufficient to produce toxicity. Many allopathic drugs have serious hazardous effects as amphotericin when applied with pentamidine it may lead to severe nephrotoxicity. Whereas, interaction of gancyclovir and zidovudine might be the cause of bone marrow depression. The simultaneous prescription of potassium supplements to patients already on spironolactone or triamtrene and those on ACE inhibitors leads frequently to severe hyperkalemia.

Clinically important interactions of drugs acting at different sites are seen with the combined use of certain antibiotics in managing infections or combinations of cytotoxic drugs in management of malignancies. Drugs with conflicting or antagonistic pharmacodynamic effects reduce response to either drug. NSAID's especially the COX-2 inhibitors that would normally increase blood pressure tend to inhibit the hypotensive action of diuretics, ACEI's and beta blockers. The overdosing of drugs being treated with their physiological or pharmacological antagonist also demonstrate the beneficial effects of antagonism. The physiological antagonism can best be evidenced in the control of involuntary activities of the body. Atropine is an excellent example of pharmacological antagonist of muscarinic effects. The effects of benzodiazepines get inhibited with the concurrent administration of theophylline.

DRUG-DISEASE INTERACTIONS

Drug-disease interactions can occur when a medication has the potential to worsen a disease. The effect a drug has in certain patients may be unexpected not related to the drug per se but because of the patient's disease pattern (Thaler *et al*., 2013). It is important for the physician to know the patients entire disease profile to plan a suitable therapeutic regimen to avoid drug interactions carefully balancing the need to ensure that the patient is given appropriate medicines to cover his ailments and simultaneously at the same time, selecting such drugs from various therapeutic categories that do not or have a lesser potential for inducing drug interactions.

DRUG-FOOD/NUTRIENTS INTERACTIONS

The myth that natural products are completely harmless, creates a need for responsible, public/physician education specially as they are widely used by our rural/semi-urban population (Mahima *et al*., 2012a); hence the need to be fully aware of these interactions and as a large number do not inform the physicians about their intake, the potential and true incidence of these interactions is largely unknown (Kumar and Rahal, 2005). In majority of cases multiple reasons are responsible for these kind of interaction and most common among them are the presence of contamination, lack of standardization of the application of faulty or improper methods of standardization. The mechanisms of food-induced interactions are essentially the same as that of drug interaction; however these occur chiefly due to alterations in absorption that may impair their nutritional benefit and to some extent due to altered metabolism. Many nutrients affect the metabolism of other nutrients and drugs. There interaction may be synergistic or antagonistic for example Calcium, phosphorous and vitamin D; Zinc and vitamin A; Selenium and vitamin E; calcium, manganese and vitamin K; iron and vitamin B6; cobalt and vitamin B12; sulphur and other vitamins (Chaudhary *et al*., 2010; Mahima *et al*., 2012b).

CONCLUSION

The nature of drug interactions is complex and not an exact science due to interplay of multiple mechanisms that requires the prescriber's care in choosing or changing medication when necessary; adjusting the dose, time and sequence of administration as maybe required or continue the treatment regimen recognizing the significance of the interaction weighing the therapeutic risks versus benefits

to the patient. Moreover, the use of newly designed drugs and its interaction with other drugs are always challengeable to physician and this interaction depends upon the age, sex, nutritional and physiological status of patient. It is impossible to remember or document all clinically significant drug interactions but this article attempts to cover the broad mechanisms and principles of the manner in which these interactions occurs exemplifying significant ones that are governed by these principles that clinicians may find useful in their practice. Of particular importance in assessing such adverse reactions that result after addition of any new drug to a formerly stable regimen that could possibly account for the adverse effect or alteration in the patient's physiological functions in handling the administered drugs. Diseases apart, physiological changes in renal and hepatic function with advancing age, malnutrition and reduced homeostatic mechanisms makes the elderly more responsive to the additive effect of two or more drugs rendering them more prone to serious drug interactions. Whenever drugs are to be indicated there should be a balance between the positive and negative interaction and balance is a key for the successful treatment.

REFERENCES

Alavijeh, M.S., M. Chishty, M. Zeeshan Qaiser and A.M. Palmer, 2005. Drug metabolism and pharmacokinetics, the blood-brain barrier and central nervous system drug discovery. NeuroRx, 2: 554-571.

Ansari, J.A., 2010. Drug interaction and pharmacist. J. Young Pharm., 2: 326-331.

Arnaud, L., A. Mathian, J. Boddaert and Z. Amoura, 2012. Late-onset systemic lupus erythematosus: Epidemiology, diagnosis and treatment. Drugs Aging, 29: 181-189.

Chaudhary, M., A.K. Garg, G.K. Mittal and V. Mudgal, 2010. Effect of organic selenium supplementation on growth, se uptake and nutrient utilization in guinea pigs. Biol Trace Elem. Res., 133: 217-226.

Davis, M.W., S. Wason and J.L. Digiacinto, 2013. Colchicine-antimicrobial drug interactions: What pharmacists need to know in treating gout. Consult. Pharm., 28: 176-183.

Farukbhai, N.M., 2010. A study of Druf-drug interaction between lercanidipine and glipizide inrats. Msater's Thesis, VL College of Pharmacy, Raichur, India

Freudenthaler, S., I. Meineke, K.H. Schreeb, E. Boakye, U. Gundert-Remy and C.H. Gleiter, 1998. Influence of urine pH and urinary flow on the renal excretion of memantine. Br. J. Clin. Pharmacol., 46: 541-546.

Garcia Fernandez, V., M. Garrido Arevalo, E. Labrada Gonzalez and F.J. Hidalgo Correas, 2013. Fatal drug-drug interaction between 5-fluorouracil and brivudine. Farmacia Hospitalaria, 37: 72-73.

Garcia-Barrera, T., J.L. Gomez-Ariza, M. Gonzalez-Fernandez, F. Moreno, M.A. Garcia-Sevillano and V. Gomez-Jacinto, 2012. Biological responses related to agonistic, antagonistic and synergistic interactions of chemical species. Anal. Bioanal. Chem., 403: 2237-2253.

Gysin, S., M. Salt, A. Young and F. McCormick, 2011. Therapeutic strategies for ing ras proteins. Genes Cancer, 2: 359-372.

Hanigan, M.H., B .L. Dela Cruz, S.S. Shord, P.J. Medina, J. Fazili and D.M. Thompson, 2011. Optimizing chemotherapy: Concomitant medication lists. Clin. Pharmacol. Ther., 89: 114-119.

Ip, T.K., P. Aebischer and P.M. Galletti, 1988. Cellular control of membrane permeability. Implications for a bioartificial renal tubule. ASAIO Trans., 34: 351-355.

Kirking, D.M., J.W. Thomas, F.J. Ascione and E.L. Boyd, 1986. Detecting and preventing adverse drug interactions: The potential contribution of computers in pharmacies. Soc. Sci. Med., 22: 1-8.

Kumar, A. and A. Rahal, 2005. Relevance of oral xenobiotic in ruminants. Proceedings of the 2nd Round Table Conference on Rumenology, April 6-7, 2006, Bhubneshwar, India, pp: 57-58.

Kumar, A., A. Rahal, R. Ragvendra, A. Prakash, R. Mandil and S.K. Garg, 2012. Pharmacokinetics of levofloxacin following intravenous and intramuscular administration in cattle calves. Asian J. Anim. Vet. Adv., 7: 1006-1013.

Kumar, P., A.H. Ahmad, A. Rahal and K.P. Singh, 2009. Bioavailability and pharmacokinetics of ketoprofen in buffalo calves. J. Vet. Pharmacol. Toxicol., 8: 52-55.

Kumar, P., A.H. Ahmad, A. Rahal and K.P. Singh, 2011. Bioavailability bioequivalence and pharmacokinetics of florfenicol in buffalo calves. Online J. Pharmacol. Pharm., 7: 1-9.

Lynch, T. and A. Price, 2007. The effect of cytochrome P450 metabolism on drug response, interactions and adverse effects. Am. Fam. Physician, 76: 391-396.

Mahendra Kumar, B.J., M. Kumaraswamy and L. Mahadevamma, 2011. Incidence and pattern of potential drug interactions of antimicrobial agents in the department of medicine in a tertiary care teaching hospital: A prospective study. Asian J. Pharm. Clin. Res., 4: 31-36.

Mahima, A.K. Verma, A. Kumar, A. Rahal, V. Kumar and D. Roy, 2012a. Inorganic versus organic selenium supplementation: A review. Pak. J. Biol. Sci., 15 : 418-425.

Mahima, A.K., A. Rahal, R. Deb, S.K. Latheef and H.A. Samad *et al*., 2012b. Immunomodulatory and therauptic potential of herbal, traditional/indigenous and ethanoveterinary medicine. Pak. J. Biol. Sci., 15: 754-774.

Rahal, A., A. Kumar, A.H. Ahmad, J.K. Malik and V. Ahuja, 2006. Pharmacokinetics of enrofloxacin in sheep following intravenous and subcutaneous administration. J. Vet. Pharmacol. Therap., 29: 321-324.

Rahal, A., A. Kumar, A.H. Ahmad and J.K. Malik, 2007. Pharmacokinetics of cipro?oxacin in sheep following intravenous and subcutaneous administration. Small Ruminant Res., 73: 242-245.

Rahal, A., A. Kumar, A.H. Ahmad and J.K. Malik, 2008. Pharmacokinetics of diclofenac and its interaction with enrofloxacin in sheep. Res. Vet. Sci., 84: 452-456.

Rahal, A., V. Singh, D. Mehra, S. Rajesh and A.H. Ahmad, 2009. Prophylactic efficacy of *Podophyllum hexandrum* in alleviation of immobilization stress induced oxidative damage in rats. J. Nat. Prod., 2: 110-115.

Rahal, A. and J.K. Malik, 2010. Pharmacokinetics, Urinary Excretion and Plasma Protein Binding of 2,3-Butanedione Monoxime in Goats. Small Ruminant Res., 93: 19-23.

Rahal, A. and J.K. Malik, 2011. Pharmacokinetics, Urinary Excretion and Plasma Protein Binding of Pralidoxime in Goats. Small Ruminant Res., 95: 179-183.

Rathore, R., A. Rahal and R. Mandil, 2012a. *Cimicifuga racemosa* potentiates antimuscarinic, anti adrenergic and antihistaminic mediated tocolysis of buffalo myometrium. Asian J. Anim. Vet. Adv., 6: 300-308.

Rathore, R., A. Rahal, R. Mandil, A. Prakash and S.K. Garg, 2012b. Comparative anti-inflammatory activity of *Cimicifuga racemosa* and *Mimosa pudica*. Aust. Vet. Practitioner, 42: 274-278.

Rodrigues, R.J., 2000. Information systems: The key to evidence-based health practice. Bull. World Health Organ., 78: 1344-1351.

Singh, V., A. Rahal, K.P. Singh and A.H. Ahmad, 2009. Effect of ethanolic extract of *Withania somnifera* roots on antioxidant defence in mercury induced toxicity in HepG2 cell line. Online J. Pharmacol. Pharm., 5: 65-72.

Singh, V., A. Rahal, K.P. Singh and A.H. Ahmad, 2010. Evaluation of prophylactic potential of *Withania somnifera* roots extract on mercury-induced oxidative damage in various rat tissues.Evaluation of prophylactic potential of *Withania somnifera* roots extract on mercury-induced oxidative damage in various rat tissues. J. Vet. Pharmacol. Toxicol., 9: 64-67.

Thaler, S., C. Neumeier and G. Flury, 2013. Drug-induced malignant arrhythmias: IT prevents lethal drug mixtures. Internist

Trumic, E., N. Pranjic, L. Begic, F. Becic and M. Asceric, 2012. Idiosyncratic adverse reactions of most frequent drug combinations longterm use among hospitalized patients with polypharmacy. Med. Arh., 66: 243-248.

Valiyil, R. and L. Christopher-Stine, 2010. Drug-related myopathies of which the clinician should be aware. Curr. Rheumatol. Rep., 12: 213-220.

Verma, S., A.H. Ahmad, A. Rahal and K.P. Singh, 2009. Pharmacokinetics of Florfenicol Following Single Dose Intravenous and Intramuscular Administration in Goats. J. App. Anim Res., 36: 93-96.

Verma, S., A.H. Ahmad, K.P. Singh and A. Rahal, 2011. Acute toxicity study of albendazole formulations in rats. Indian J. Vet. Pharmacol. Toxicol., 10: 58-60.

Wachter, R.M. and A. Verghese, 2012. The attending physician on the wards finding a new homeostasis. JAMA, 308: 977-978.