

Drug Metabolism and Disposition in Australian Marsupial Koala (*Phascolarctos cinereus*)

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Review Article

ABSTRACT

Aims: Koalas, the unique obligate eucalyptus feeding Australian marsupial, often requires medical treatments after wildlife rehabilitation across Australia. However, little is known about the pharmacology and pharmacokinetics of drugs commonly used in koalas, as well as how they handle and detoxify xenobiotics resulted from both environmental exposure and their unique eucalyptus diet. The aim of this study is to critically evaluate and summarise what is known about the metabolism and pharmacokinetics of drugs in koalas, including those frequently used such as antibiotics fluoroquinolones, fluconazole, chloramphenicol and analgesic meloxicam.

Methodology: Literature regarding drug disposition and pharmacokinetic studies of therapeutic agents commonly used in koalas over the last decade has been critically reviewed. Some older sources from the primary literature search have also been included to determine the background information leading to current rationale behind drug indication, dosage, and route of administration in marsupial koalas and related species.

Results: Most studies reported a much lower bioavailability of orally administered drugs in koalas

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compared to that in humans and other species, and current dosing regimens do not prove to be effective or optimal in order to achieve the best treatment outcomes. It seems likely that oral administration of many drugs in koalas exhibited poor bioavailability due to poor absorption and might be extensive metabolism via hepatic and intestinal enzymes.

Conclusion: Collectively, the findings suggest the need for further pharmacokinetic studies to investigate alternative routes of administration for many commonly used drugs in marsupial koalas, including antibiotics, anaesthetics, and analgesic medicines.

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Keywords: Drug metabolism; marsupial; koala; pharmacokinetics; pharmacodynamics; PKPDs; Phascolarctos cinereus; xenobiotics.

1. INTRODUCTION

The koala (*Phascolarctos cinereus*) is an Australian unique native marsupial. Annually, thousands of koalas are admitted to wildlife rehabilitation facilities across Australia for drug treatment [1]. Despite the large numbers of koalas requiring drug treatment, very little is known about the pharmacokinetics and effectiveness of many drugs used in koala [2]. Wildlife native animals such as koalas are constantly exposed to many exogenous chemicals or “xenobiotics” including drugs. In order to understand the consequences of xenobiotic exposure, it is important to understand how wildlife species handle these chemicals in terms of absorption, distribution, metabolism and excretion, as enzymatic alteration of xenobiotics can alter their function and toxicity [3].

The koala is a specialist folivorous marsupial, which has unique physiology and specialised hepatic metabolism. These unique characteristics have been hypothesised to be important contributors to ineffective allometric scaling [4-9]. The koalas' unique xenobiotic metabolism is thought resulted from their specialised diet consisting solely of select *Eucalyptus* species [3,4,6-8,10,11]. Eucalyptus species often avoid ingestion by many herbivore animals, as they are low in protein, high in fibre and contain high concentrations of phenolics and essential oils, which are comprised of various monoterpenes [3 5,7]. The concentrations of phenolics and essential oils ingested daily by koalas are high enough to be toxic and potentially fatal to many other species including humans [3,6,12]. In order to survive to consume a diet composed entirely of eucalyptus koalas are thought need to detoxify the diet via specialist hepatic metabolism [8]. Pass and Brown study [8] showed that the rate of hepatic metabolism in koalas is more rapid than some other herbivores and postulated this increased rate of metabolism allows koalas to consume

increased quantities of eucalyptus without suffering toxic effects.

The most significant pathway by which koalas appear to detoxify their diets has been hypothesised via increased concentration of various phase I cytochrome P450 monooxygenase (CYP) enzymes, which are able to oxidise dietary terpenes to more easily excreted renal waste products [3-7,9]. Unlike their extensive use of oxidative metabolism, koalas do not appear to readily utilise phase II conjugation, including glucuronidation [7]. As a consequence of the koala's unique metabolism, it is likely that the koalas metabolism of many drugs is significantly different to other species, resulting in the need for pharmacokinetic parameters to be determined for commonly used drugs in koalas. Therefore, in order to effectively medically treat this iconic Australian marsupial, it is critically important to determine the effectiveness of drugs commonly used in their treatment. The current study aimed to summarise what is known about the metabolism and pharmacokinetics of drugs in koalas, in particular, those frequently used such as antibiotics, analgesics and anaesthetics to provide some useful indicators for optimal therapeutics and dosing regimen.

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2. METHODS

2.1 Study Design

Literature data regarding the use of antibiotics, anaesthetics, analgesics, and other commonly used therapeutic agents in the management of diseases in marsupial koalas in the last decade has been systematically reviewed. The primary search terms including *medicine use, drug treatment, pain management, infections, health conditions, diseases, drug pharmacokinetics, marsupial koalas* were used to initially source all peer-reviewed articles published any year, with results being filtered to obtain relevant articles

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published in English over last decade. Some older sources have been utilised to determine the background information leading to current rationale behind drug treatment in koalas.

2.2 Data Source

Sources were found using several search engines (PubMed, CAB Abstracts, Web of Knowledge, Google Scholar). All sources were searched appropriately to ensure that they were of the standard of evident-based medicine, including predominantly primary research papers and also relevant secondary sources on the topic.

3. RESULTS AND DISCUSSION

3.1 A Brief History of Drugs Use in Koalas Prior to Pharmacokinetic Studies

Advances have been made in the field of therapeutic drug use in native marsupials over the past four decades. Dickens [13] has reported about use of short acting barbiturates such as thiopentone sodium and thiamylal sodium as satisfactory anaesthetic agents for use in koalas but did not conduct pharmacological evaluation of these drugs. This study has also found that there had been no unusual findings observed with the administration of antibiotics in koalas. However, another study by Brown and colleagues [14] reported that the use of erythromycin and oxytetracycline to treat chlamydiosis resulted in destruction of gastrointestinal tract microflora. This GI side effect can lead to an emaciating condition that proceeded to death, despite a reduction in the clinical signs of chlamydiosis during antibiotic therapy [15].

3.2 Antibiotic Therapy and Supplementary Feeding

A study by Osawa and Carrick [15] has studied the use of concurrent antibiotic therapy and dietary supplementation as a means of maintaining koala body condition during antibiotic therapy and thereby preventing emaciation and death. In this study, koalas with chlamydiosis were administered oxytetracycline, with half of the koalas also received a soya based supplement. The study continued for 8 weeks, by which time all koalas provided with supplementation had body weights similar to at the studies commencement and had considerably reduced clinical signs of

chlamydiosis. However, the koalas that received only the oxytetracycline all died within 4 weeks of treatment commencement, although they too had significantly reduced clinical signs of chlamydiosis. Prior to death koalas had significant weight loss (up to 33%) and upon post mortem were found to have no specific pathology and hence their death was reported being attributed to emaciation. The study suggested that the cause of emaciation may be due to the destruction of gastrointestinal microflora. This was because these healthy bacteria are important and necessary for the catabolism and absorption of their eucalyptus diet. Thus this elimination of normal gastrointestinal microflora may result in malabsorption. The soya based supplement contained protein, lipids and carbohydrates which are more easily absorbed than the eucalyptus diet and thus this supplement may have allowed the koalas to maintain adequate nutritional intake while allowing the antibiotics to treat their infections [15].

3.3 Anaesthetics

Ketamine, xylazine, acepromazine and nitrous oxide: Robinson [16] reported on the use of intramuscular ketamine, ketamine plus xylazine and ketamine combined with acepromazine and nitrous oxide. The study claimed that anaesthesia with or without xylazine produced light chemical restraint with minimal side effects and good muscle relaxation and the combination of ketamine, xylazine and nitrous oxide produced significant relaxation and a smooth recovery. Dose rate ranges for these drugs were suggested, however no pharmacokinetic data was reported [16].

Tiletamine HCl and Zolazepam HCl: Bush et al. [17] anaesthetised 47 mature male koalas using an intramuscular injection of 5.0mg to 7.7mg/kg Tiletamine HCl plus Zolazepam HCl. This protocol achieved a rapid and smooth induction and recovery to a surgical plane of anaesthesia with no cardiac or respiratory depression. The authors concluded that the suggested optimum dose rate for anaesthesia of mature male koalas was 7.0mg/kg Tiletamine HCl plus Zolazepam HCl, however no pharmacokinetic measurements of Tiletamine HCl plus Zolazepam HCl were conducted these koalas.

Isoflurane: McGowan et al. [18] investigated the use of the gaseous anaesthetic agent isoflurane in koalas. Anaesthesia was induced in twenty mature male koalas using a rubber canine

anaesthetic mask and oxygen flow rate of 1L/min with an isoflurane concentration of 3.5 to 5%. They found that isoflurane anaesthesia produced a smooth, rapid induction and recovery with minimal cardiac depression. However, similarly to Robinson [16] and Bush [17], study by McGowan and colleagues did not investigate any of the pharmacokinetics of isoflurane in koalas [18].

3.4 Oral Drug Absorption in Koalas

Koalas appear to have limited oral bioavailability and absorption of most drugs, which has restricted treatment routes available for koalas [19,20]. There have been several proposed mechanisms to account for drug low oral bioavailability observed in koalas, however none have been proven. The proposed mechanisms were enhanced rate and efficacy of koala first-pass hepatic metabolism [3-9] and possible enzymatic metabolism within the gastrointestinal wall [21]. Additionally, drug binding to an ingested material, such as cellulose within the gastrointestinal tract has been found to decrease drug absorption, and thus alter their pharmacokinetics [22,23]. The drug binding has been reported for other animals such as horses, which was postulated to occur maybe also in koalas. Finely masticated material often results in drugs being trapped in the proximal gastrointestinal tract and prevents their contact with the gastrointestinal mucosa [24].

Metal cations such as cobalt, zinc and iron are constituents of eucalyptus leaves [25]. Study by Turel [26] has found that metal cations could chelate fluoroquinolones and thus decreased their bioavailability. It has also been suggested that fluoroquinolones including enrofloxacin and marbofloxacin, which are commonly used in the treatment of chlamydiosis in koalas, may become bound to metal cations contained within the koalas' eucalyptus diet, therefore reduced amount of drug available for absorption [20]. Another metal cation, calcium, may also be present in soya or milk based supplements, which is often administered concurrently with antibiotics in koalas [15,20]. Thus collectively, chelation of fluoroquinolones by cations present in eucalyptus leaves or present in concurrent dietary supplementation during antibiotic administration may reduce their oral absorption and overall bioavailability [20,26].

Moreover in humans, active excretion of fluoroquinolones into the large intestine has been reported, and this excretion could result in

reduced both drug absorption and drug efficacy [27]. A study by Griffith and co-workers [20] suggested that similar to humans, intestinal excretion may also occur in koalas for fluoroquinolones and limited bioavailability of fluoroquinolones may be attributable to both large intestinal active excretion and the relatively rapid small intestine transit time of koalas [28] that has been found to limit the rate of absorption of many xenobiotics [29].

3.5 Drug Pharmacokinetic Studies in Koalas

In a retrospective study involving 1061 koala post mortem records, chlamydiosis and cryptococcosis were found to be the most prevalent infectious diseases, affecting 35% and 2.5% of the koala population respectively. After infectious disease causes, trauma was found to be the most frequent post mortem finding, with 28.5% of koalas affected [30]. The aforementioned infectious diseases and trauma represented the largest proportion of diseased animal in the study [30]. Being such significant diseases of koalas, there have been investigations into the pharmacokinetics of drugs commonly being used in the treatment of these conditions.

Fluconazole: Cryptococcosis has been found to be the second most common infectious disease of koalas [30]. In koalas, the systemic fungal disease of cryptococcosis is caused by *Cryptococcus gattii* [19]. It may result in disease of the upper and lower respiratory tract, with spread to the central nervous system, spleen, kidneys, skin, lymph nodes and gastrointestinal tract [31]. Cryptococcosis in koalas is often treated orally with the antifungal fluconazole, itraconazole and amphotericin B [24]. In a case report by Kido et al. [32], use of azole antifungals, specifically fluconazole and itraconazole, together with amphotericin B antibiotic was found to be ineffective for the treatment of clinical cryptococcosis infections in koalas. Although no pharmacokinetics studies were carried out, the authors hypothesised that the failure in treatment was possibly due to low intra-gastric acid secretion in koalas, leading to reduced itraconazole absorption. Lim et al. [33] had reported that the absorption of orally administered itraconazole was decreased under conditions of low intra-gastric acidity. However, study by Logan [34] found that koalas actually have increased gastric acid secretion due to the presence of a large cardio-gastric gland present

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within the koala stomach. Thus, the proposed reason for the poor efficacy of itraconazole by Kido and co-workers [32] appeared to be inconsistent with that reported in the literature.

In a study by Black et al. [19] 12 clinically normal koalas were given a single dose of fluconazole. The study found that fluconazole is eliminated at a faster rate in koalas than in other eutherian species. The volume of distribution of fluconazole in the koala fitted the allometric relationship displayed by many other species. However, the average plasma clearance (CL) was approximately seven times lower and elimination half-life ($t_{1/2}$) was approximately six times higher than their respective estimated, allometrically scaled values [19]. Black et al. [19] suggest that the koalas CL and $t_{1/2}$ values may be attributed to its comparatively reduced renal tubular reabsorption, active tubular secretion or biotransformation; mechanisms by which koalas are able to detoxify their eucalyptus diet. The inaccuracy of the estimated allometrically scaled values for koalas highlights the limited effectiveness of this dosing method [35]. Oral absorption was found to be limited compared to mice, dogs, cat, horses and humans [19].

Furthermore, fluconazole protein binding was found to be four times higher than other species previously investigated. Black et al. [19] suggested this increased protein bind may inhibit fluconazole crossing the blood brain barrier and thus limit fluconazole's efficacy as an antifungal treatment of cryptococcosis in central nervous system. In conclusion, results have indicated that fluconazole administered at 10mg/kg per orally every 12 hours is not likely to meet the minimum inhibitory concentration required to eliminate *Cryptococcus gattii* in the koala. Thus the authors have advocated the intravenous administration of fluconazole, however higher dose rate and long term intravenous dosing should be further investigated.

Fluoroquinolones: Chlamydiosis, caused by *Chlamydomphila pneumonia* and *Chlamydomphila pecorum*, is the most prevalent infectious disease of koalas [30]. A study involving 1061 koalas from 1980 to 2003 found that approximately 35% of koalas suffered from chlamydiosis [30]. Chlamydiosis results in significant disease including keratoconjunctivitis, rhinitis, pneumonia, cystitis and reproductive tract disease, which may result in infertility [24]. Koalas with chlamydiosis have often been treated with fluoroquinolones [20]. Antibiotics such as erythromycin and oxytetracycline have

resulted in wasting and death in koalas, despite a decrease in clinical signs throughout administration [14,15]. Griffith et al. [20] conducted a study whereby 43 koalas of varying sex and age, with subclinical or clinical chlamydiosis were treated daily with enrofloxacin or marbofloxacin for 8 weeks. Dose rates were primarily based on those suggested for koalas [36]. All of the koalas in this study maintained their weight throughout the 8-week trial, and all were initially provided with oral nutritional supplementation [20]. This may be attributed to the supplementation [15]. Using liquid chromatography, plasma concentrations of marbofloxacin were too low to be quantified. Drug plasma protein binding was approximately 50% and the minimum inhibitory concentration ratios of C_{max}/MIC and AUC/MIC were considered too low with the doses and routes used. Thus, it was concluded that neither enrofloxacin nor marbofloxacin were likely to inhibit growth of chlamydiae in vivo at the concentrations commonly used [20,36]. Additionally, fluoroquinolones administered orally, have been found to display poor absorption compared to the subcutaneous route, supporting other research suggesting limited oral bioavailability in koalas [20].

Chloramphenicol: Chloramphenicol, a broad-spectrum antibiotic, has also been used to systemically treat chlamydiosis [2,37-38]. Govendir et al. [37] investigated the pharmacokinetic of chloramphenicol base used in nine mature koalas with clinical chlamydiosis. The koalas were treated daily, over a maximum of 45 days with the widely accepted dose rate of 60mg/kg chloramphenicol subcutaneously as suggested in the literature [24]. Koalas were nutritionally supplemented during this study in accordance with accepted protocol to prevent antibiotic associated emaciation. The study found that at this dose rate koalas with mild chlamydiosis and chlamydial shedding were controlled during and shortly after treatment cessation, despite the plasma concentration of chloramphenicol generally remaining at sub-therapeutic levels. However, more severe clinical chlamydiosis cases were not controlled. It has been reported in the literature that permanent urogenital clinical signs such as inflammation and fibrosis, as a result of chlamydial infection, have been observed in treated koalas [39]. Govendir and colleagues [37] thus proposed permanent urogenital inflammation and fibrosis as a possible reason for chlamydial persistence despite chloramphenicol administration in their study. Other reasons suggested by the authors

for infection persistence included the possibility of auto-immunity due to antigen-antibody complexes persisting within tissues after the clearance of the chlamydiae organisms or the continuation of intracellular latent chlamydiosis infection, which has been reported in untreated koalas [39]. Moreover, koalas exhibited increased drug elimination times compared to other species. The slower elimination has been hypothesised being caused by study differences in drugs formulation, the route of administration and the disease status of the animals. Due to the koalas' reported rapid hepatic metabolism [8], Govendir and co-workers suggested the significance of the prolonged elimination of subcutaneously administered chloramphenicol, and its potential as a relatively more effective treatment.

Similar to other drugs, Black et al. [2] reported that chloramphenicol dose rates attained for koalas using allometric extrapolation are insufficient, emphasizing the importance of conducting pharmacokinetics studies for chloramphenicol in koalas. A study by Govendir et al. [37] reported the potential of chloramphenicol administered subcutaneously to clinically infected koalas as a treatment of chlamydiosis lead to an investigation by Black et al. into the pharmacokinetics of intravenously administered chloramphenicol in several formulations to healthy koalas. In the later study, nineteen clinically healthy koalas received either a single dose of 25mg/kg intravenous chloramphenicol sodium succinate, 60mg/kg subcutaneous chloramphenicol sodium succinate or 60mg/kg subcutaneous chloramphenicol base. The pharmacokinetics of chloramphenicol administered as chloramphenicol sodium succinate were found to be allometrically similar to other species, however this formulation reached much higher plasma concentrations and was eliminated at an increased rate compared to chloramphenicol base [2]. Thus, there was likely a toxicity risk with chloramphenicol sodium succinate administration and it may be necessary to increase the frequency of administration and to lower the dose in koalas. Similar to that observed in the study conducted by Govendir et al., Black and co-workers study found that subcutaneously administered chloramphenicol base was eliminated at a relatively slow rate, due to a slower rate of absorption, and thus suggested this formulation may be the most efficacious for use in koalas. The authors also pointed out that the commonly suggested accepted dose rate of 60mg/kg from the literature for subcutaneous chloramphenicol [24] appeared to be inadequate for koalas.

Moreover, the slow elimination rate of chloramphenicol base in koalas was found to be allometrically similar to other species, and the authors had hypothesised that this may be due to the utilisation of the glucuronidation pathway of metabolism. In other species chloramphenicol is metabolised using the glucuronidation pathway [40] and therefore due to the allometrically similar excretion rates of chloramphenicol base in the koalas, it is proposed that koalas may have a comparable capacity for glucuronidation [2]. As highlighted previously, phase I oxidative metabolism appears to be the most utilised hepatic metabolism pathway in koalas, with minimal reliance on phase II conjugation [7]. Thus, Black and co-workers [2] suggested exploiting the koalas' lack of phase II conjugation, including the limited use of glucuronidation, by selecting drugs metabolised via this pathway, which may be more efficacious in koalas. Also the predicted unbound steady-state plasma concentration of chloramphenicol base at the commonly accepted single daily dose rates used in Black et al. study did not reach the optimal therapeutic value, which means the appropriate plasma concentration required for therapeutic efficacy may not have been attained. The authors therefore suggested that it would be beneficial to investigate pharmacokinetics associated with twice daily dosing of lower dose rates, however with extreme caution as subcutaneous doses of 80mg/kg daily have been reportedly associated with fatal destruction of gastrointestinal microflora. The authors also reported an irregular absorption profile across the koala population tested, attributed this mostly to the unpredictable absorption of the insoluble chloramphenicol base formulation used, and thus have also recommended investigation further with alternative formulations.

Meloxicam: One of the primary reasons for the medical treatment of koalas is due to trauma, caused mainly by motor accidents and dog attacks [41]. Meloxicam is commonly used as an anti-inflammatory and analgesic in koalas, thus the meloxicam pharmacokinetics has been well investigated in this species [42,43]. Kimble et al. [43] conducted a study of the pharmacokinetics of meloxicam administered to fifteen clinically normal koalas. Results showed that the clearance rate of meloxicam after intravenous administration was much more rapid than has been recorded in any other eutherian species. The authors suggested that this rapid clearance rate might be due to the koalas' increased rate of hepatic metabolism. Chesne et al. [44] have

reported that meloxicam is metabolised by CYP enzymes in humans. Based on this information, Kimble and colleagues in their study postulated that meloxicam might be metabolised in the same manner and at an increased rate in koalas due to the increased concentrations of CYP enzymes in this species. The authors also found that the oral absorption of meloxicam was extremely low, similar to the limited bioavailability found with other orally administered drugs in koalas [2,20]. They suggested that the limited bioavailability of meloxicam in koalas may be due to material within the gastrointestinal tract binding to xenobiotics, and the relatively rapid transit time of material through the gastrointestinal tract. Kimble and co-workers concluded that the current recommended dose rate of meloxicam for koalas is inadequate via every route of administration and that this highlights the limitations of dose extrapolations from one species to another, especially in an animal as physiologically unique as the koala.

Other drug treatments: Severe pain in koalas, commonly caused by trauma or urogenital disease [30], has been treated with methadone, buprenorphine HCl and pethidine [24]. However, there have been no pharmacokinetic parameters established for these drugs in koalas. In humans and other species, methadone primarily undergoes oxidative biotransformation by phase I cytochrome P450 monooxygenase (CYP) enzymes and pethidine undergoes phase I hydrolysis and N-demethylation [45,46]. However, koalas have been found to have rapid phase I metabolism and consequently many pharmaceuticals metabolised via this method do not appear to be efficacious with current dose regimes [2,19,20,37,43]. Unlike methadone, buprenorphine HCl undergoes extensive phase II glucuronidation in other species and thus may be metabolised in a similar way in koalas, potentially making it a more effective analgesic than methadone in this species. Also, it is possible that the current methadone and pethidine dose rates and frequency of dosing used in koalas do not provide adequate analgesia and consequently investigation into the pharmacokinetics of methadone and pethidine in koalas are recommended [47].

Several protocols for the treatment of koalas' chlamydiosis had been suggested, including eye ointment preparations containing various combinations of oxytetracycline, oleandomycin phosphate, neomycin sulphate, ofloxacin, polymyxin B sulphate, chloramphenicol, glucocorticoids including hydrocortisone acetate and dexamethasone, for the treatment of

keratoconjunctivitis [24]. However, no study to date has examined the pharmacokinetics or pharmacodynamics of these drugs via this route of administration in koalas. The pharmacokinetics of the ointment constituents has also not been examined with the exception of chloramphenicol [2,37]. In other species the gene 11 β -HSD 1 is expressed in the liver as 11 β -hydroxysteroid dehydrogenases which act to metabolise cortisol and cortisone. However, the koala has been found to lack the 11 β -HSD 1 gene and hence it is unlikely that koalas would exhibit pharmacokinetics similar to other species when treated with glucocorticoids [48]. Furthermore, due to previous findings of antibiotic induced gastrointestinal microflora destruction and subsequent death by emaciation, and the apparent insufficient dose regimes of chloramphenicol and fluoroquinolones at treating chlamydiosis, it may be beneficial to examine the pharmacokinetics and pharmacodynamics of the above mentioned drugs, especially with regards their absorption, clearance rate, effects on gastrointestinal microflora and plasma concentration in relation to efficacious dose rates [2,15,20,37].

3.6 Future Perspectives

Collectively, there is a current need for further research to be carried out in order to determine normal pharmacokinetic parameters absorption, distribution, metabolism, and excretion (ADME) of drugs used commonly in healthy koalas, as these findings would help to assess more accurately pharmacokinetic data attained in diseased animals [20]. Several studies have also demonstrated that dose rates attained for koalas using allometric scaling, a process in which a pharmacokinetic parameter (ADME) is measured from three to five species and the weight of the animals is then plotted against the acquired data to estimate pharmacokinetics in other species, are insufficient to achieve therapeutic levels in the koala [2,19,20,34,37,43]. For allometric scaling to produce relatively accurate dose rates, the species included in the data analysis should be as closely related as possible and be physiologically similar to the species being scaled [7]. For koalas, allometric scaling has been found not to be effective at predicting pharmacokinetics and dose rates, attributed to koalas' unique physiology and specialised hepatic metabolism resulted from their unique eucalyptus diet, thus it is necessary to determine the pharmacokinetic parameters of drugs that are commonly used in koalas [19]. As the minimum inhibitory concentration necessary to inhibit koala

chlamydial strains are currently unknown, it is suggested that in vitro susceptibility testing should be investigated in order to guide determination of effective dose rates of antimicrobials in koalas and the use of placebo groups of koalas in future pharmacokinetic studies would be important despite the controversy of not treating an iconic diseased Australian marsupial. This was because these authors believe that the inclusion of a placebo group of diseased animals would provide beneficial comparative pharmacological data, which could potentially benefit koalas overall population [2,37].

Also for drugs that have already had their pharmacokinetic parameters measured in koalas, namely fluoroquinolones, fluconazole, chloramphenicol and meloxicam, further investigation into dose rates and route of administration is necessary to maximise drug efficacy in this species, specifically further long-term investigation into intravenous dose rates of fluconazole, subcutaneous dose rates of fluoroquinolones, dose rate and frequency of meloxicam, and alternative formulations for chloramphenicol including florfenicol [2]. Furthermore, as it is common in the treatment of koalas to concurrently administer fluconazole with antifungal drug amphotericin B, which had been found to be nephrotoxic causing decreased renal perfusion and slower elimination of fluconazole as well as altered fluconazole's pharmacokinetics, further research should be conducted to examine the pharmacokinetics of fluconazole when administered simultaneously with amphotericin B [49].

4. CONCLUSION

In summary, proposed hypotheses for the reduced oral bioavailability drugs in koalas include, but not limited to increased hepatic metabolism, enzymatic metabolism within the gastrointestinal wall by normal flora, binding of ingested material to drugs, trapping of drugs within ingested material leading to decreased drug contact with mucosa, chelation of drugs with metal cations found in eucalyptus leaves and soya or milk based supplements, active excretion of drugs into the large intestine, and the relatively rapid transit time of matter through the gastrointestinal tract. Due to the lack of proper pharmacokinetic and necessary studies to confirm the suggested hypotheses for limited oral bioavailability, future research is therefore critically important to investigate the mechanisms underlying the suggested hypotheses to better

understand the limitations of orally administered drugs in koalas.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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