Review of adverse effects
of some drugs in camels

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RESSOURCES ANIMALES synthèse

Key words

Camel - Drug - Toxicity - Side effect.

Summary

The article reviews the basic pharmacological data on drug metabolism, adverse effects and other toxic reactions of more commonly used antibacterial agents, central nervous system depressants and antiprotozoal agents in the camel. Camel's specificity such as a relatively low glomerular filtration rate, long nephron, low rate of water turnover, changes in erythrocyte shape and low drug metabolizing enzyme activity may modify the pharmacokinetic behavior of drugs in this species.

■ INTRODUCTION

Camels belong to the suborder Tylopoda of the Artiodactyles, which first appeared in the fossil record of the Tertiary period (about 2 million years ago). From a physiological point of view the dromedary exhibits certain characteristics that enable it to survive in arid regions. Camels are adapted in evolutionary terms in such a way that they use ingested water very economically. Water is continuously recirculated in the camel's gut, from the duodenum and colon *via* the blood stream into the forestomach. The alimentary tract functions as a water reservoir and the rate of water turnover is low (66). The water turnover is cut down by reducing metabolism, renal loss and changes in erythrocyte shape (24). Under hydration normal conditions the glomerular filtration rate and renal plasma flow expressed in relation to body weight are two to four times higher in sheep (32) than in dromedary (25). Furthermore, the nephron in the camel is twice as long as in cows or goats (1). These features may affect the rate and mode of drug elimination and account for major differences in drug disposition between camels and other animals (41). Dehydration on the other hand results in longer elimination half life, a larger volume of distribution and slow clearance for chloramphenicol and oxytetracycline (71). The reduced intramuscular and subcutaneous availability is also a significant justifying change in dosage schedules recommended for diseased dehydrated camels. Until recently, knowledge of pharmacological effects of drugs in the camel was considered fragmentary, and little research had been carried out. Usually, drug manufacturers give no specific recommendations for the camel. Therefore, the doses used clinically in this species are in general extrapolated from doses recommended for other large domestic animals. This is not without danger because toxic effects sometimes occur in camels which are given certain drugs at doses apparently harmless to other species (4, 28). This article was carried out to review the adverse effects of the most commonly used drugs in the camel.

■ DRUG METABOLISM

Drug metabolizing enzymes are responsible for the biotransformation of a wide array of xenobiotics to which animals are exposed. The activities of the drug-metabolizing enzymes, cytochromes P-450, aminopyrine-N-dimethylase, aniline-4-hydroxylase and ethoxycoumarin-0-dethylase (a phase I reaction) and UDP-Gucuronyl-transferase and glutathione-S-transferase (a phase II reaction) have been measured *in vitro* in the liver, kidney and duodenal mucosa of camels, and compared to those of sheep, goats and rats (18, 19, 20, 29, 45, 70). The enzymes selected are involved in reactions of phase I and phase II drug metabolism, specifically oxidation and conjugation.

Goats seem to have the highest and camels the lowest enzyme activity when compared to other species. Consequently, goats have the highest and camels the lowest ability to clear antipyrine from the blood circulation (21). Therefore, the increased susceptibility of camels to certain drugs may at least be partly explained by the comparatively low drug metabolizing enzyme activities in this species.

It has been shown that the liver functions of the dehydrated camel differ significantly from those of the normally hydrated camel (8). The clearance of anionic dye bromsulfophthalein and antipyrine is

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significantly smaller and elimination half life is longer in the dehydrated camel, which may suggest a decreased oxidation capacity of the liver (10). However, the effect of dehydration on oxidative enzymes may be selective, inhibiting the isoenzyme involved in the metabolism of antipyrine while those mediating the de-ethylation of lidocaine are unaffected (9).

■ ANTIBACTERIAL DRUGS

Sulfonamides

In camels, sulfadimidine (SDM) is eliminated slowly from the body; the final elimination half life ranges from 8.7 to 16.5 h (67). The total body clearance of SDM is lower than that reported in adult ruminants like goats, but also in birds and man. The main SDM metabolite detected in the plasma of camels is the N_4-acetyl derivative. Neither the hydroxy nor glucuronide derivatives have been detected. Thus, SDM acetylation predominates over the hydroxylation pathway of metabolism in camels. The plasma concentration time file exhibits zero-order kinetics. The cause of SDM zero-order kinetics may be the unique water conservation system in the camel. The ability of camels to reabsorb water extensively is due to the long loops of Henle (1). It is well known in other species that renal SDM clearance is urine flow-dependent (67). Analogously, extensive renal SDM reabsorption may occur due to the low urine flow in the camel (in normal circumstances: 0.76-2.2 l/day; 66) and, consequently, accumulation that may sometimes lead to toxicity. SDM being mainly excreted as an acetylated form in the camel (67) is likely to precipitate crystal-luria. However, the alkaline properties of camel urine may reduce the incidence of occurrence in this species. Since dehydration may aggravate such condition the free access to unlimited water supplies during SDM treatment is essential (14). In the camel SDM is used clinically in the treatment of coccidiosis. The prepa-ration available is a sulfadimidine 33.3% solution. The recom-mended dose is 0.2 g/kg body weight initially followed by 0.1 g/kg body weight daily for four days. For prevention of SDM accumu-lation, it is suggested that a dosage interval of 48 h is advisable (67).

Antibiotics

Knowledge of mechanisms for elimination of antibiotics is essential, especially when excessive plasma or tissue concentra-tions of the drug cause serious toxicity. Most antibiotics and their metabolites are eliminated primarily by the kidneys (50). The increased concentration of antibiotic occurring after the first trip may result from the absorption from the kidney or bladder as it has been shown that antibiotics are extensively reabsorbed from the urinary tract in ruminant species (38). Furthermore, the nephron in the camel is twice as long as that of the cow or goat (1). It has been demonstrated that benzylpenicillin elimination occurs more slowly in the dromedary than in sheep (39), suggesting that the use of the same dosage regimen for both ruminant species may lead to significant differences in plasma concentration, therapeutic efficacy and maybe toxicity. Such variations indicate that the dose regimen of ampicillin and other drugs should be based on kinetic studies of these drugs. A lower dosage and frequency should perhaps be adopted for the camel. One must be particularly careful when using aminoglycosides, since these drugs are completely eliminated by renal mechanisms and their toxicity appears to correlate with their concentrations in plasma and tissue (50). For example, tobramycin, an aminoglycoside, is eliminated by glomerular

filtration unchanged in urine. The half life in camels is 188 min (2), which is higher than that reported for humans (98 min; 16), dogs (70 min; 59) and cats (70 min; 31). This would suggest that the glomerular filtration rate is lower in hydrated camels than in man, dogs, cats and cows (65). A striking data feature concerning the lack of dehydration effect on gentamicin kinetics in camels has been reported (68), suggesting an adaptive clearance mechanism operating in dehydrated camels. In addition, poor drug absorption from the intramuscular injection site in dehydrated camels could be due to reduced peripheral blood circulation.

For antibiotics metabolized by the liver such as quinolones (10) erythromycin, chloramphenicol and clindamycin (14) dosages must be reduced in camels with hepatic injury, as it has been reported that parasites (fasciolosis), toxic plants or toxic substances (dieldrin, latex) reduce activities of drug-metabolizing enzymes (22, 23). Other adverse effects of antibiotics in the camel can also occur. Prolonged oral treatment with broad spectrum antibiotics like tetracycline can significantly alter the gut flora and allow the proliferation of potentially pathogenic fungi such as *Candida albicans* (14). The extensive use of antibiotics can lead to the development of resistant micro-organism populations (37). A long-acting antibiotic formulation oxytetracycline-like appears desirable in terms of therapeutic compliance and camel husbandry, which is dominated by nomadic pastoralism. Unfortunately, such formulations are criticized because the so-called long-acting effects may be related to prolonged drug resistance at the injection site attributable to local irritation and induced tissue damage (41).

■ GENERAL DEPRESSANTS

Sedatives and tranquilizers

Xylazine hydrochloride

Xylazine has been used in camels (15) at a dose rate of 0.1-0.15 mg/kg body weight. Another dose rate of 0.87 mg/kg and atropine sulfate (0.2 mg/kg body weight) is also recommended (47). The drug has sedative, adrenergic, cholinergic and centrally mediated analgesic and muscle relaxant properties (14). It has temporary hypertensive properties and produce bradycardia and respiratory depression due to central and peripheral suppression of the sympathetic trunk (44). Xylazine may increase a previously existing metabolic alkalosis and can cause respiratory acidosis due to respiratory depression (57). Xylazine may cause transient hypothermia and temporary reduction in erythrocytic count, hematocrit and hemoglobin content, leukocytopenia, lympho-cytopenia, eosinopenia and neutrophilia (6). However, it is not known whether drug induced thermal instability has adverse effects in the camel as this species exhibits wide diurnal fluctuations in temperature in response to changing environment, the camel becoming progressively dehydrated during periods of water deprivation (63). Rumination may be suppressed particularly during the first hour. In ruminants, xylazine is said to cause strong uterine contraction leading to premature expulsion of the fetus during the third stage of pregnancy, but this is unknown in camels. There is slight hyperglycemia 30 min after administration, and a first degree atrioventricular block, sinus arrhythmia and wander pacemaker in the sinoatrial node. Primary T-wave changes and S-T segment elevation are also observed (4). Blood gas analysis shows evidence of respiratory acidosis and arterial hypoxemia (42). Severe fatal effects may occur in uremic

camels (57). Such effects may be reversed by a combination of I.V. yohimbine (0.125 mg/kg) and 4-aminopyridine (0.3 mg/kg), a combination successfully employed in xylazine over dosage in the llama (46).

Chlorpromazine hydrochloride

This drug can be used at the dose of 1-3 mg/kg body weight either intramuscularly (I.M.) or I.V. The I.V. injection may cause a primary stage of excitement followed by deep sedation (49). A combination of chlorpromazine (2 mg/kg) and pentazocine (2 mg/kg) provides sufficient and satisfactory sedation in camels (56).

Propionylpromazine

This drug may be given at a dose of 0.5 mg/kg body weight I.M. It produces sufficient sedation. The drug causes muscle relaxation, vasodilation, hypotension and marked tachycardia (34). Penile prolapse has not been reported in the camel, due to anatomical differences. Propionylpromazine, like other phenothiazine derivatives, are contraindicated in shock and should be used with care in animals with circulatory instability as severe hypotension may result particularly when the circulating blood volume is reduced (62).

General anesthesia

Chloral hydrate

Chloral hydrate is a good hypnotic but poor anesthetic having a very weak analgesic action, and has to be given slowly (in approximately 5 min) in large doses before it produces general anesthesia. The compound is highly irritant to tissues, and care must be taken to ensure intravascular administration because perivascular injection will result in tissue necrosis. The major disadvantage of chloral hydrate anesthesia in the camel is its cardiac effect and the possibility of producing cardiac fibrillation and A-V block produced by vagal action causing death during the recovery period (53, 54, 55). There has been marked tachycardia with sustained hypotension and respiratory acidosis with arterial hypoxemia.

Chloral hydrate is mostly used at a 10% solution but it may be used at 12% with a dose rate of 0.58 ml/kg. Combination of chloral hydrate and magnesium sulfate (12% each; 0.43 ml/kg) and thiopentone sodium (1.33%, 0.41 ml/kg) I.V. may be used effectively (55) and be expected to increase the therapeutic index of chloral hydrate in this species.

Barbiturates

Significant changes recorded after thiopentone administration are leucopenia after recovery, respiratory acidosis and arterial hypoxemia 24 h post administration. There is also an increase in blood glucose concentration (43). Major changes after administration of pentobarbitals include tachycardia, hypotension, reduced central venous pressure, respiratory acidosis, hypoxemia, reduction in arteriovenous oxygen tension difference and increased post recovery concentration of urea nitrogen and plasma creatinine (43). However, continuous administration of oxygen in the immediate post anesthetic period should be considered to avoid arterial hypoxemia (56).

Ketamine hydrochloride

Ketamine, a derivative of phencyclidine, induces a rapid onset of a peculiar state of unconsciousness often described as dissociative anesthesia characterized by profound somatic analgesia but poor visceral analgesia. Muscle tone is increased resulting in an involuntary movement. The eyelids remain open, oral and upper

respiratory reflexes remain intact. Excitement during the recovery period is common. Excitement may be prevented by xylazine. Respiratory function may be depressed and rapid I.V. administration often results in apnea (44). Mild signs of central nervous system irritability, consisting of fine tremors of lip muscles, nostrils and limbs have been observed (63).

White *et al.* (62) found that a mixture of ketamine (25 mg/kg) and xylazine (0.15 mg/kg) is superior to either drug used alone. Muscle rigidity and central nervous system irritability are prominent side effects of ketamine anesthesia. Hypertonicity, incoordination and excitement during recovery from ketamine can be eliminated by xylazine. Another advantage of the mixture is the deeper level of analgesia obtained. Xylazine appears to potentiate the analgesic properties of ketamine thereby lowering the dosage. Expediency may require the drugs to be combined in the same syringe for a single injection by remote administration (27, 47). However, this is not pharmacologically sound. Ketamine has a much more rapid induction (2 to 5 min) than xylazine (10 to 20 min) (14). Xylazine should be administered 15 min prior to ketamine to obtain the maximum synergic effects of both drugs.

Halothane

Halothane is the most commonly used inhalation anesthetic in the camel (12, 26, 47). It is a potent dose-dependent cardiopulmonary depressant. Because of its high vapor pressure and high cost, it is best administered from a precision vaporizer located out of the re-breathing circuit using closed or semi-closed systems. Significant changes during halothane anesthesia also include a slightly increased central venous pressure. About 20% decrease in arterial pressure and respiratory acidosis (43). These changes are taken as evidence of myocardial depression. Continuous administration of oxygen should be considered to avoid arterial hypoxia (56).

Neuroleptanalgesia

Etorphine hydrochloride may be used alone or in combination with tranquilizers for the chemical restraint of camels (61). Etorphine may cause severe side effects such as muscle rigidity and tremors, severe opisthotonos, tachycardia and respiratory depression, regurgitation and possible pulmonary aspiration (3, 51). The effect of etorphine could be reversed by 20 mg of the antagonist "diprenorphine." Full re-mobilization takes 1.5 to 3 min. Utmost care should be taken when considering etorphine for treatment as this drug is dangerous to veterinarians (14).

■ ANTIPROTOZOAL DRUGS

Chemotherapy of trypanosomosis in man and animals depends on a few drugs. The safety margin of these drugs is very narrow (35).

Suramin is used at a dose rate of 5-10 g/camel I.V. A perivenous injection leads to thrombophlebitis and abscesses especially if the prepared solution concentration is more than the recommended 10% (52). The drug may cause delayed toxicity including nephritis and has been shown by Smeesters and Jacques (58) to aggregate in lysosomes. Williamson (64) suggested that the granules of suramin occurring in the epithelium of the kidney tubules may be lysosomal depots of the drug. The aspartate aminotransferase (AST) and alanine aminotransferase activities in serum are increased by suramin administration as well as serum globulin (17).

Isometamidium chloride can be used for cure of *T. evansi* infection in the camel but the drug has no prophylactic effects (7, 60). Adverse effects of the drug include inhibition of cholines-

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terase (5). The enzyme activity is reduced by 71% two hours after drug treatment (1 mg/kg) accompanied by salivation, diarrhea, frequent urination, defecation, trembling, hind leg weakness and recumbency (5, 52). Samorin^{TM} also increases AST activity and decreases bilirubin concentration in treated camels (17).

Diminazene aceturate is well tolerated by domesticated species but severe toxic reactions can occur in camels (28). The signs of toxicity include salivation, frequent urination, defecation, convulsions, sweating, recumbency and regurgitation. Postmortem findings have shown hemorrhages in the heart, liver, kidney, urinary bladder and brain. The reason for the greater susceptibility of camels to these trypanocidal drugs is not known. Their effects may be direct or *via* their metabolites. It has been shown that diminazine aceturate is a potent inhibitor of diamine oxidase and S-adenosyl-l-methionine decarboxylase activities in laboratory animals (13). Whether such inhibition also occurs in camels and is responsible for the toxic nervous signs remains to be determined.

Symptomatic treatment including atropine, antihistamines and fluid therapy may be of value during the course of toxicity by the trypanocidal drugs.

Specific clinical signs may stimulate a veterinarian to report a reaction. However, the sensitivity of the reporting system for detecting subtle or delayed reactions, depressed growth rate, lowered fertility and unacceptable tissue residues is not known yet. Examples of clinical sign types that might be missed are the possible renal effects of nonsteroidal anti-inflammatory drugs (33, 48). Any observable deficiency in safety or efficacy should be considered as an adverse reaction to the drug in question, and careful designed surveys of all adverse reactions in the camel is of paramount importance to establish proper incidence baselines (36).

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Adverse effects of drugs in camels

Résumé

Al-Dughaym A.M., Afaleq A.I., Homeida A.M. Synthèse sur les effets indésirables de certains médicaments chez le chameau

Cette synthèse fait le point sur les données pharmacologiques de base concernant le métabolisme de médicaments, les réactions indésirables et autres effets toxiques secondaires provoqués chez le chameau par des agents anti-infectieux courants ainsi que des dépresseurs du système nerveux central et des antiprotozoaires. Certaines caractéristiques du chameau, telles qu'un taux de filtration glomérulaire relativement faible, un long néphron, un faible taux de renouvellement de l'eau, des hématies avec des formes particulières et une faible activité enzymatique du métabolisme des médicaments, peuvent modifier le comportement pharmacocinétique des médicaments chez cette espèce.

Mots-clés : Chameau - Médicament - Toxicité - Effet secondaire.

Resumen

Al-Dughaym A.M., Afaleq A.I., Homeida A.M. Revisión de los efectos adversos de algunas drogas en camellos

El presente artículo revisa datos farmacológicos básicos sobre el metabolismo de las drogas, efectos adversos y otras reacciones tóxicas de los agentes antibacterianos más frecuentes, depresores del sistema nervioso central y agentes anti protozoarios en el camello. Algunas especificidades del camello, como una tasa de filtración glomerular relativamente baja, nefrones largos, baja tasa de circulación de agua, cambios en la forma eritrociataria y baja actividad de la enzima metabolizadora de las drogas pueden modificar el comportamiento farmacocinético de las drogas en estas especies.

Palabras clave: Camello - Medicamento - Toxicidad - Efecto secundario.

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