Pharmacokinetics and Pharmacodynamics of Dexamethasone after Intravenous Administration in Camels: Effect of Dose

N.A. Al Katheeri1, I.A. Wasi1*, M. Lambert2, and A. Saeed3
1Camelracing Laboratory, Forensic Science Laboratory, PO Box 253, Abu Dhabi, United Arab Emirates; 2Equine Forensic Unit, Department of Pharmacology and Therapeutics, Trinity College, Dublin, Ireland; 3Veterinary Research Centre, Sweihan Road, Abu Dhabi, United Arab Emirates
*Correspondence: E-mail: iawasi@emirates.net.ae


ABSTRACT

The pharmacokinetics and pharmacodynamics of dexamethasone were evaluated in healthy camels after single intravenous bolus doses of 0.05, 0.1 and 0.2 mg/kg body weight. Dexamethasone showed dose-independent pharmacokinetics. The pharmacokinetic parameters of the two-compartment pharmacokinetic model for the lowest intravenous dose (mean ± SD) were as follows: terminal elimination half-life 8.17 ± 1.79 h; total body clearance 100.7 ± 52.1 (ml/h)/kg; volume of distribution at steady state 0.95 ± 0.23 L/kg; and volume of the central compartment 0.22 ± 0.07 L/kg. The extent of plasma protein binding was linear over the concentration range 5–100 ng/ml and averaged 75% ± 2%

Pharmacodynamic effects were evaluated by measuring endogenous plasma cortisol concentrations, numbers of circulating lymphocytes and neutrophils and plasma glucose concentrations and were analysed using indirect pharmacokinetic/pharmacodynamic models. The cumulative systemic effect increased with dose for markers of pharmacodynamic activity. The estimated IC50 of dexamethasone for cortisol and lymphocytes for the lowest dose were 3.74 ± 2.44 and 5.58 ± 8.37 ng/ml, respectively and the EC50 values for neutrophils and glucose were 45.8 ± 36.9 and 1.17 ± 0.71 ng/ml, respectively.

Keywords: camels, clearance, dexamethasone, doses, pharmacodynamics, pharmacokinetics, racing

Abbreviations: DXM, dexamethasone; PK, pharmacokinetics; PD, pharmacodynamics; i.v., intravenous; LOQ, limit of quantitation; LOD, limit of detection; WBC, white blood cells

INTRODUCTION

Synthetic corticosteroids such as dexamethasone (DXM), methylprednisolone and prednisolone possess anti-inflammatory effects and are widely used in veterinary practice (Pugh, 1991; Ferguson and Hoenig, 1995). DXM has the highest anti-inflammatory potency among synthetic corticosteroids and has been in use for many years in various species: dogs (Eiler and Oliver, 1980; Toutain et al., 1983; Eiler, 1986; Young et al., 1989; Greco et al., 1993; Kemppainen and Peterson, 1993); horses (Jones, 1942; Cross, 1966; Abrams and Brooks, 1990; Lane et al., 1990; Spiess et al., 1999); and
cattle (Toutain et al., 1982). DXM and other long-acting corticosteroids are used to treat lameness attributable to joint injury or swollen bursae and tendon sheaths (Friederich et al., 1992), as well as immune based conditions such as immune-mediated haemolytic anaemia (Grundy and Barton, 2001).

Administration of synthetic corticosteroids results in lymphocytopenia and suppresses the secretion of cortisol. The DXM suppression test has been used extensively as a probe of hypothalamic pituitary-adrenal function (Nugent et al., 1965). Suppression of the release of endogenous cortisol and the presence of lymphocytopenia are used as surrogate markers for the systemic effects of corticosteroids. Several pharmacokinetic/pharmacodynamic (PK/PD) modelling approaches have successfully been used to describe the effect of exogenous corticosteroids on lymphocytes by linking steroid serum levels directly to their effects on lymphocytes, neglecting the effect of the circadian rhythm of endogenous cortisol (Oosterhuis et al., 1983; Wald et al., 1991; Möllmann et al., 1995; Hochhaus et al., 2001). However, others have also successfully modelled corticosteroid-induced lymphocytopenia as a joint effect of exogenous and endogenous corticosteroids (Braat et al., 1992; Milad et al., 1994; Meibohm et al., 1999).

The pharmacokinetics (PK) of DXM have been reported in dogs (Toutain et al., 1983; Greco et al., 1993), horses (Toutain et al., 1984; Cunningham et al., 1996), cattle (Toutain et al., 1982) and humans (Hare et al., 1975; Tsuei et al., 1979; Brady et al., 1986; Workman et al., 1986; Young et al., 1989; Hochhaus et al., 2001) but not in camels. There are very few reports on the pharmacodynamics (PD) of DXM in farm animals: a preliminary report on camels (Wäscher et al., 1989) and one on dogs (Kemppainen and Peterson, 1993). The action of DXM in an equine model of acute non-immune inflammation has also been reported (Lane et al., 1990).

Integrated PK/PD modelling of DXM in camels has not previously been studied. Characterization of these parameters in camels, together with controlled clinical efficacy trials, is one important factor that would allow development of appropriate dosage regimens provided that the obtained PK/PD parameters are for clinical end-points or for surrogate end-points (biomarkers) that are objectively measured and validated to substitute for clinical end-points (Toutain, 2002). In addition parameters obtained from PK/PD modelling will be helpful for different bodies in the racing industry. Regulatory bodies will be able to make appropriate decisions on ineffective trace concentrations of drugs, while animal trainers and veterinarians would be better advised when to discontinue such drugs before racing in order to avoid penalties imposed by the racing commissioners if an animal tests positive for a foreign substance.

The aims of the present study were therefore to characterize the PK parameters of DXM in camels after intravenous (i.v.) administration and to evaluate the effect of dose. A further goal was to evaluate the PD parameters of DXM by applying PK/PD modelling using cortisol, lymphocytes, neutrophils and glucose as PD parameters.