Pharmacokinetics of Flunixin after Intravenous Administration in Healthy and Endotoxaemic Rabbits

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ABSTRACT

The pharmacokinetics of flunixin were determined after intravenous bolus injection at a single dose (2.2 mg/kg) in healthy rabbits and diseased rabbits with *Escherichia coli* lipopolysaccharide-induced septic shock. Six adult New Zealand White rabbits were used. Concentrations of drug in plasma were determined by HPLC. Pharmacokinetics were best described by a two-compartment open model. In healthy rabbits, there was a high plasma clearance (0.62 L/(h kg)), and a relatively short elimination half-life (1.19 h). In endotoxaemic rabbits, total plasma clearance (0.43 L/(h kg)) was significantly lower (*p* < 0.05), and elimination half-life (1.90 h) and AUC₀₋∞ (5.29 (µg h)/ml) were significantly higher (*p* < 0.05) than in healthy animals. The changes of pharmacokinetics of flunixin in rabbits with septic shock could be of clinical significance, and may require monitoring of plasma flunixin levels in endotoxaemic status.

*Keywords:* endotoxaemia, flunixin, lipopolysaccharide, pharmacokinetics, rabbits

*Abbreviations:* ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration–time curve; Cl₁, total plasma clearance; FM, flunixin meglumine; GGT, γ-glutamyltransferase; Kᵣ₀, elimination rate constant; Kᵣ₂, distribution rate constant for transferring the drug from the central to peripheral compartment; Kₑ₂, transfer rate constant from peripheral to central compartment; LPS, lipopolysaccharide; MRT, mean residence time; Tbilirubin, total bilirubin; Tprotein, total protein; t₁/α, the half-life of the α phase; t₁/β, the half-life of the β phase; Vᵣ, volume of distribution

INTRODUCTION

*Escherichia coli*-derived lipopolysaccharide has been used extensively to establish a model of septic shock. Advantages of this model system are the ease with which it can be produced and its relative similarity to systemic bacteraemia (*Post et al.*, 2003). Lipopolysaccharide (LPS), which is a component in the outer membrane of Gram-negative bacteria, is known for a wide range of biological and immunological activities. LPS induces various changes: circulatory changes, disseminated intravascular coagulation, and damage to many organs such as the central nervous system, liver, kidneys, heart, gastrointestinal tract and lungs (*Hewet and Roth*, 1993; *Haghoorn et al.*, 1995; *Yazar et al.*, 2004).
Flunixin meglumine (FM) is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs act by inhibiting the synthesis of prostanooids (Higgins et al., 1986, 1987; Landoni et al., 1995a,b) and their unique analgesic effect is mediated through prostaglandin inhibition (McKellar et al., 1989; Kallings, 1993; Cheng et al., 1998b). As FM has anti-inflammatory, analgesic and antipyretic properties, it has been used extensively to treat a number of conditions in various species, viz. fever and mastitis in cows (Anderson et al., 1986; Rantala et al., 2002), and endotoxaemia in calves and horses (Luthman et al., 1989; Daeus et al., 1991; Toutain et al., 1994).

At the present time, dosage recommendations of drugs are generally based on empirical or microbiological and physiological considerations taken in conjunction with pharmacokinetic characteristics studied in healthy animals (Pijpers et al., 1990). However, drug disposition, metabolite formation and the excretion of the active ingredient and its metabolites may be markedly altered in diseased animals owing to organ dysfunction (kidney, liver, heart, etc.) or diarrhoea (dehydration), for example, or as a consequence of the acute-phase response to infections (Sarwari and Mackowiak, 1996; Saith et al., 1999, 2000; Monshouwer and Witkamp, 2000; Rao et al., 2000; van Miert, 2000).

Characterization of the pharmacokinetics of FM have been established in healthy animals of most species (McKellar et al., 1989; Landoni et al., 1995a; Cheng et al., 1998a; Wasil et al., 1998; Baert and De Backer, 2002, 2003) and in healthy rabbits (Miyazaki et al., 2001; Elmas et al., 2005). On the other hand, few articles are available on the pharmacokinetics of FM in diseased animals (Toutain et al., 1994; Rantala et al., 2002).

The aim of this study was to determine the pharmacokinetics of FM, which is used for treatment of septic shock with a single intravenous dose (2.2 mg/kg) in healthy and *E. coli* LPS-induced endotoxaemic rabbits.

**MATERIALS AND METHODS**

**Animals**

Six male New Zealand White rabbits were used (age 6–8 months; body weight 2.88 ± 0.05 kg; Experimental Medicine Research Centre, Faculty of Meram Medicine, Selcuk University, Konya, Turkey). The rabbits were housed individually in cages one week prior to the study and throughout the study and had access to food and water. All animals were clinically normal and had not received any drugs within 2 months of beginning the study. The Ethics Committee of the Faculty of Veterinary Medicine (University of Selcuk, Konya, Turkey, report no. 04/06) approved the study protocol.

**Experimental design**

A crossover pharmacokinetic design was used. The washout interval between the phases of the study was 2 weeks. FM (Fluvin injection, 50 mg/ml, Vilsan, Ankara,