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Cetirizine in horses: Pharmacokinetics and pharmacodynamics following repeated oral administration

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Abstract

The pharmacokinetics of the histamine H_1-antagonist cetirizine and its effect on histamine-induced cutaneous wheal formation were studied in six healthy horses following repeated oral administration. After three consecutive administrations of cetirizine (0.2 mg/kg body weight, bw) every 12 h, the trough plasma concentration of cetirizine was 16 ± 4 ng/mL (mean $\pm$ SD) and the wheal formation was inhibited by $45 \pm 23\%$. After four additional administrations of cetirizine (0.4 mg/kg bw) every 12 h, the trough plasma concentration was 48 ± 15 ng/mL and the wheal formation was inhibited by $68 \pm 11\%$. The terminal half-life was about 5.8 h. A pharmacokinetic/pharmacodynamic link model showed that the maximal inhibition of wheal formation was about 95% and the EC_{50} about 18 ng/mL. It is concluded that cetirizine in doses of 0.2–0.4 mg/kg bw administered at 12 h intervals exhibits favourable pharmacokinetic and pharmacodynamic properties without causing visible side effects, and the drug may therefore be a useful antihistamine in equine medicine.

Keywords: Horse; Antihistamine; Cetirizine; PK/PD link model

Introduction

Histamine is an important chemical mediator, which is involved in the aetiology of various hypersensitivity manifestations via interactions with histamine H_1-receptors. Specific IgE antibodies attached to mast cells cross-bind antigens and induce release of histamine and other immunological mediators. This results in type 1 allergic reactions, which are characterised by dilatation of vascular smooth muscle, increased permeability of capillary endothelium and contraction of bronchial smooth muscle.

In equine therapy, histamine H_1-antagonists (antihistamines) such as tripelennamine, promethazine and chlorphentamine have been used in conditions in which histamine is a critical mediator, such as allergic reactions to venoms and other antigens and drug-related immunological reactions, including anaphylactic shock (Morrow et al., 1986; Adams, 1995; Rosenkrantz, 1995; Foster et al., 1998). Antihistamines may also be useful to treat the syndrome called ''sweet itch'', ''summer eczema'' or ''allergic urticaria''. This is a worldwide chronic seasonally recurrent pruritic allergic skin disease in horses hypersensitive to antigens in the saliva of biting flies, in particular midges of the genus *Culicoides*, and sometimes also black flies from the genus *Simulium* (Baker and Quinn, 1978; Braverman et al., 1983; Quinn et al., 1983; Broström et al., 1987; Greiner et al., 1988, 1990; Hallorsdottir et al., 1989; Fadok and Greiner, 1990; Anderson et al., 1991, 1993; Marti et al., 1999; Mullens et al., 2005; Baselgia et al., 2006).

It is known that IgE plays a role in the pathogenesis of this syndrome (Matthews et al., 1983; Van der Haegen et al., 2001; Wilson et al., 2001, 2006; Rüfenacht et al.,

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2005; Hellberg et al., 2006; Wagner et al., 2006; Ferroglio et al., 2006). IgE and mast cell activation are also involved in the pathogenesis of equine heaves, chronic bronchitis/bronchiolitis, chronic obstructive pulmonary disease (COPD) and recurrent airway obstruction (RAO). These syndromes show similar clinical signs, but can be mediated by varying immunological mechanisms (McGorum et al., 1993; Halliwell et al., 1993; Schmallenbach et al., 1998; Franchini et al., 1998; Olszewski et al., 1999; Eder et al., 2000; Bowles et al., 2002; Van der Haegen et al., 2005; Horhov et al., 2005). Antihistamines may also be useful in treating these conditions.

Cetirizine, a metabolite of hydroxyzine, is a non-sedative second-generation histamine H_1-antagonist, widely used in human medicine to treat seasonal/perennial allergic rhinitis and chronic idiopathic urticaria (Zuberbier and Henz, 1999; Simons, 2001). In man, cetirizine is well tolerated and has been shown not to alter memory, attention, alertness or performance (Pagliara et al., 1998; Benedetti et al., 2001; Curran et al., 2004; Theunissen et al., 2004, 2006). Cetirizine also displays high and selective affinity for cloned human H_1-histamine receptors and it has very little or no anti-cholinergic activity (Gillard et al., 2002; Orzechowski et al., 2005).

We have recently studied the pharmacokinetics of cetirizine in horses given a single oral dose of the drug (Olsén et al., 2007). The result showed that cetirizine had a favourable pharmacokinetic profile. Previously examined antihistamines, such as clemastine and fexofenadine, were shown to have very low oral bioavailability (Törneke et al., 2003; Olsén et al., 2006). The aim of the present study was to examine the pharmacokinetics and the antihistaminic effect of cetirizine in horses following repeated oral administrations.

Materials and methods

Horses

Six healthy Standardbred trotters (mares), 5–21 years old, weighing 490–570 kg were used. They were fed hay, straw, sugar-beet and oats during the experiment. Water was available ad libitum. The study protocol was approved by the Animal Ethics Committee, Uppsala, Sweden (C65-03).

Study design

For oral administration, racemic cetirizine dihydrochloride (Cetirizin Biochemie, tablets 10 mg) were mixed with sugar-beet and given to the horses. Cetirizine was administered at times 0, 12, 24, 36, 48, 60 and 72 h (i.e. at 12 h intervals). For the first three administrations the dose was 0.2 mg/kg body weight (bw), and for and the last four administrations the dose was 0.4 mg/kg bw. Blood samples (10 mL; collected in heparinised test tubes) were taken by direct jugular venepuncture at time 0 (pre-dose), and immediately prior to the administrations at time-points 12, 24, 36, 48, 60 and 72 h (i.e. just before the administration of a new dose). Following the last oral administration (at 72 h) blood was also taken via an intravenous catheter at the post-administration intervals 0.5, 1, 1.5, 2, 3, 5, 7, 11, 24 and 30 h. The blood was centrifuged at 1500 *g* for 15 min and the plasma was separated and stored at −20 °C until analyses.

Recording of the pharmacodynamic effect

The antihistaminic effect of cetirizine was recorded using an intra-dermal test. Intra-dermal skin testing is an accepted method for detecting allergen hypersensitivity in atopic humans. Determination of the inhibition of cutaneous reactions following intra-dermal histamine-injections is used to estimate the effect of antihistamines. The protocol applied in the present study was adopted from investigations in humans and has been optimised to horses and used in several previous studies as well as in allergen hypersensitivity detections at horse clinics in Sweden (Simons et al., 1993; Törneke et al., 2003; Olsén et al., 2006; K. Bergwall, personal communication).

The horses were shaved with electric clippers on the lateral neck prior to intra-dermal injections with 7 μg/site of histamine hydrochloride (0.1 mg/mL, Apoteket AB) using 27-gauge needles. The diameter of the skin reaction was measured after 20 min using Vernier callipers. Histamine-injections before administration of cetirizine served as positive controls. Histamine-injections were then performed immediately before each of the consecutive 12 h administrations of cetirizine and in addition at 1, 3, 5, 7, 11 and 24 h after the last cetirizine-administration. Three injections were performed on each occasion and the median value was used for further calculations. Sterile saline (0.07 mL served as a negative control. The negative control mean value was calculated from at least 11 administrations for each horse.

Analysis of cetirizine

Cetirizine dihydrogen chloride (Sigma-Aldrich) and internal standard [$^2H_4$]-cetirizine (C/D/N isotopes) were used as reference standards. Stock solutions of cetirizine and [$^2H_4$]-cetirizine were prepared in methanol–water (50:50) and stored at −20 °C until used. The water was of Millipore quality and had a resistance of 10.0 MΩ cm. All other solvents and reagents were at least of analytical grade. The protocol was adopted from Olsén et al. (2007). Briefly, [$^2H_4$]-cetirizine (9.6 ng base in 100 μL methanol) was added to each plasma sample (1.0 mL), which after the addition of 0.2 M sodium acetate buffer pH 4.0 (1.0 mL) was applied to Bond Elut C18 solid phase extraction columns (3 mL, 200 mg sorbent mass). The columns were sequentially preconditioned with methanol (2 mL), deionised water (2 mL) and 0.2 M sodium acetate buffer pH 4.0 (1.5 mL) and washed with deionised water (2 mL), methanol–water (50:50, v/v, 2 mL) and methanol (1 mL).

After a drying period of 2 min, cetirizine and [$^2H_4$]-cetirizine were eluted from the columns with 50 mM triethylamine in methanol (2.5 mL) and the eluates were evaporated to dryness under nitrogen. The extraction procedure was performed by Gilson ASPEC XL4 instrumentation (Pretech). The residue in each vial was reconstituted in 100 μL of methanol and 0.1 M acetic acid in water (4:6, v/v). The reconstituted samples were quantified by liquid chromatography electrospray tandem mass spectrometry (LC–ESI-MS/MS) using a Finnigan TSQ Quantum Ultra mass spectrometer (Thermo Electron Corporation), with a Surveyor MS pump. The separation was performed with a Zorbax Eclipse XDB C_{18} (Agilent) chromatographic column (length 50 mm, inner diameter 2.1 mm and particle diameter 5 μm). The samples were eluted using a gradient created by mixing phases from two reservoirs comprising respectively of 0.1% acetic acid in water and methanol. The injection volume was 5.0 μL and the volumetric flow-rate 0.2 mL/min.

The ionisation technique was electrospray (ESI) in positive mode. The ESI source voltage was set at 3.5 kV and sheath gas flow-rate and auxiliary gas were 50 and 2 arbitrary units, respectively. When running the collision-induced dissociation (CID) procedure, argon was used as collision gas at a pressure of 1.5 mTorr. For the Selected Reaction Monitoring (SRM) mode, the following transitions were recorded: cetirizine [$M+H^+$] m/z 389 → 201 and [$^2H_4$]-cetirizine [$M+H^+$] m/z 393 → 201 using collision energy 25 V. Different concentration-intervals in the calibration curve were used for different samples: one for 0.11–11 ng/mL and one for 11–179 ng/mL. For evaluation of the accuracy, the quantification precision as percentage relative standard deviation (RSD) and the linearity of the method quality control (QC) samples in three different concentrations (1.0,