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Original Research

Pharmacokinetics of Sulpiride After Intravenous, Intramuscular, and Oral Single-Dose Administration in Nurse Mares

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ABSTRACT

Sulpiride (SLP) is an antipsychotic drug used in humans. Although no pharmacokinetic data are available for horses, it is commonly used to encourage ovulation in noncycling mares and to stimulate lactation in adoptive mares. The aim of this study is to assess the pharmacokinetics profile of SLP after intravenous (IV), intramuscular (IM), and oral (PO) administrations in normal horses. Animals (n = 6) were treated with 1 mg/kg SLP, administered by IV, IM, and PO routes according to a randomized crossover design (3 × 3 Latin square). Blood samples (5 mL) were collected at a programmed time and analyzed using a validated with fluorescence detection method. SLP was present at a detectable concentration up to 24 hours postadministration for all routes, except for one animal in the PO group. IV and IM administrations gave similar curves, with an IM average bioavailability of 118.0%. These high values were mainly the result of the profile generated by two horses, in which a secondary concentration peak occurred in the terminal phase of the curve. After PO administration, $AUC_{0-\infty}$, and consequently bioavailability (20.4%), was low. This finding could be owing to the physicochemical features of the drug. Indeed, considering that SLP is a weak base, existing in the ionized form at gastric and physiological pH, it is unsurprising that it is poorly absorbable, especially in horses with a particularly acidic gastric pH. In conclusion, injective routes are definitely preferable to PO dosing because of the low bioavailability using this route.

1. Introduction

Sulpiride (SLP) belongs to a special class of antipsychotic drugs, the substituted benzamides, which possess a more specific pharmacological profile than the conventional neuroleptics. SLP selectively blocks the so-called dopamine receptors and probably does not interact with noradrenergic or serotonergic receptor mechanisms. SLP is widely used in humans as a behavior regulator to treat mental disorders and for the psychopathology of senescence, depression, and schizophrenia; the daily dose for these indications is 200-800 mg [1]. It is also used at doses of 50-150 mg/human for the treatment of gastric or duodenal ulcers [2], in the treatment of an irritable colon due to psychosomatic stress [3], and for treating various vertigo syndromes [4]. Tolerance to SLP at this lower dose is good, and extrapyramidal, neurovegetative, and endocrine side effects are rare [5].

The earliest application of this molecule in equine reproduction was to treat fescue toxicosis (3.3 mg/kg): in this application, a stimulation of endogenous prolactin level and/or induction of galactopoiesis in agalactic mares was observed [6]. In subsequent studies, SLP has been used to induce lactation in cycling and noncycling mares (0.5-1 mg/kg twice a day) [7] or to hasten the first ovulation of the breeding season in noncycling mares (1 mg/kg once a day) [8-11].

Although the effectiveness of SLP in transitional mares is still controversial [8,11], SLP is widely used in equine

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practice. To the best of the authors' knowledge, no pharmacokinetic data have been generated for horses. Optimization of treatment with SLP requires knowledge of its bioavailability, pharmacokinetics, and metabolism in the target species. The pharmacokinetic parameters determined after a single-dose administration can then be used for dosage regimen adjustments and individualization of therapy. Hence, the aim of this study is to assess the pharmacokinetics profile of SLP after intravenous (IV), intramuscular (IM), and oral (PO) administration in normal horses.

2. Materials and Methods

2.1. Animal Treatment and Sampling

Six nurse mares aged 8-12 years and weighing 440-570 kg were used. The horses were previously determined to be clinically healthy based on a physical examination and full chemistry and hematological analyses. Animal experiments were conducted at the animal experimental facility of the Faculty of Veterinary Medicine (University of Pisa). Animal care and handling were performed according to the provision of the EC Council Directive 86/609 EEC. The study protocol was approved by the University of Pisa's Ethics Committee for Animal Welfare (ECAW) and transmitted to the Italian Ministry of Health. Animals were randomly assigned to three treatment groups, using an open, single-dose, three-treatment, three-period, paired, randomized crossover design (3×3 Latin square). Each subject in group I ($n = 2$) received a single dose of 1 mg/kg SLP (Championyl, Sanofi Aventis, France) injected IV over 1 minute into the left jugular vein in the morning after fasting for 12 hours overnight. Animals in group II ($n = 2$) received the same dose but by IM route, injected in the middle quadrant of the neck muscle, after fasting for 12 hours overnight. Animals in group III ($n = 2$), after overnight fasting, received the same dose via nasogastric tube. For this route, tablets of SLP were used (Championyl 50 mg/tab, Sanofi Aventis, Milan, Italy). After administration, the nasogastric tube was rinsed with 300 mL of distilled water to ensure complete delivery of the drug into the stomach. A catheter was placed into the right jugular vein to facilitate blood sampling. The washout period was 1 week. The groups were rotated and the administrations repeated. After 3 weeks, each horse had been administered with SLP by the three routes. Unfortunately, the day before the last experiment, one horse from group 3 was severely injured in a traumatic event unrelated to the study and was excluded from the experiment. Blood samples (5 mL) were collected at 0, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 4, 6, 8, 10, 24, and 34 hours after administration of SLP, and placed in collection tubes containing lithium heparin. The blood samples were centrifuged at $3{,}000 \times g$ (rotor radius: 10 cm) within 30 minutes of collection, and the harvested plasma was stored at -20°C until use within 30 days of collection.

2.2. Chemicals and Reagents

Pure powders of SLP (>99.0% purity) and metoclopramide (internal standard [IS]) were sourced from Sigma-Aldrich (St. Louis, MO) (Fig. 1). High-performance liquid chromatography (HPLC)-grade acetonitrile, ethylacetate, methanol (MeOH), and methylene chloride (CH_2Cl_2) were purchased from Merck (Darmstadt, Germany). Analytical-grade sodium hydroxide (NaOH), acetic acid, and ammonium acetate were purchased from Carlo Erba (Milan, Italy). Deionized water was produced by a Milli-Q Millipore Water System (Millipore, Billerica, MA). All the other reagents and materials were of analytical grade and supplied from commercial sources. The aqueous and organic components of the mobile phase, degassed under pressure, were mixed by the HPLC. The liquid chromatography mobile phases were filtered through 0.2-μm cellulose acetate membrane filters (Sartorius Stedim Biotech, Aubagne Cedex, France) with a solvent filtration apparatus.

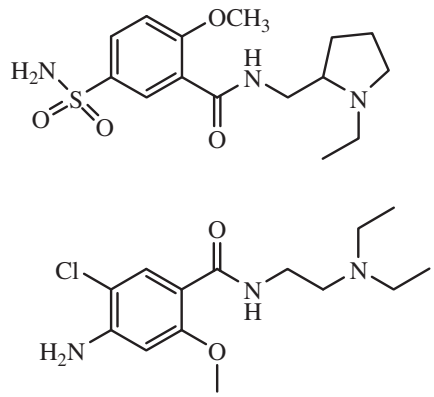

Fig. 1. Molecular structure of sulpiride and metoclopramide (IS).

2.3. Preparation of Solutions

Singular stock solutions of SLP and IS in MeOH were prepared at an individual concentration of 1,000 μg/mL using volumetric flasks; these were stored at -20°C. To reach a final concentration of 100 μg/mL, appropriate dilutions of stock standard solutions were prepared by diluting 1 mL of each solution to 10 mL. Successively, these solutions of SLP and IS were diluted in glass tubes (10 mL) to reach final concentrations of 10, 5, and 1 μg/mL. These were stored at -20°C. This latter concentration (1 μg/mL) was then diluted with MeOH to prepare a five-point calibration curve of the analytes at the following concentrations: 0.200, 0.100, 0.050, 0.025, 0.010, and 0.001 μg/mL. The two analytes were stable for at least 30 weeks if stored at -20°C.

2.4. Instrumentation and Chromatographic Conditions

The HPLC system was a liquid chromatography system (Jasco Inc., Tokyo, Japan) consisting of high-pressure mixer pump (model PU 980 Plus), spectrofluorometric detector (model 2020 Plus), and a loop of 50 μL. Data were processed by Borwin software (Jasco Inc.). Chromatographic separation assay was performed by a Luna C18 ODS2 analytical column (150×4.6-mm inner diameter, 5-μm particle size; Phenomenex, Torrance, CA) maintained at 25°C. The mobile phase consisted of acetonitrile/buffer (10 mM ammonium acetate, adjusted to pH 5.2 with acetic acid) (15:85, v/v%) at a flow rate of 1.2 mL/min. Excitation and emission wavelengths were set at 300 and 356 nm, respectively.