

PHARMACOKINETICS OF METOCLOPRAMIDE AFTER INTRAARTERIAL, INTRAMUSCULAR, SUBCUTANEOUS, AND PERRECTAL ADMINISTRATION IN RABBITS

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Abstract

The objective of this investigation was to compare the pharmacokinetics of metoclopramide (MET) after intraarterial (IA), intramuscular (IM), subcutaneous (SC), and perrectal (PR) administrations to normal rabbits. In this study, 6 normal New Zealand white rabbits were used in a random crossover design (4 × 4 Latin square) with a 1-week washout period between trials. Each rabbit had been administered MET at a dose of 2 mg/kg IA, IM, and SC, and 4 mg/kg PR. The plasma concentrations of MET were determined by high-performance liquid chromatography. The mean plasma profiles of MET after IA, IM, and SC administrations were similar. The bioavailability of MET when administered IM and SC was 96% and 112%, respectively. The plasma concentrations within the PR group were quite variable, resulting in an extremely low and variable bioavailability with an average of 12%. IM and SC administrations of MET may be useful in treating gastrointestinal disorders in rabbits when arterial or venous access is not available, but PR administration is likely to be unreliable. Copyright 2015 Elsevier Inc. All rights reserved.

Key words: metoclopramide; pharmacokinetics; rabbits; bioavailability; injection; rectal

Metoclopramide (MET) (4-amino-5-chloro-2-methoxy-N-[2-diethylaminoethyl] benzamide) was first synthesized in 1964. It is a relatively nonpolar, lipophilic drug that was originally developed as an antiemetic. Despite its main use to reduce emesis, an unforeseen effect of the drug (potent gastric stimulation) has resulted in this active ingredient also being used as a prokinetic in both monogastric¹ and polygastric² species. The drug's action results from antagonism at dopamine-2 (D₂) receptors³ and serotonin (5-HT₃) receptors.⁴ MET also sensitizes gastric and colonic longitudinal muscle to acetylcholine, speeds gastric emptying, relaxes the pyloric sphincter, and promotes aboral movement of stomach chyme.⁵⁻⁷ Central nervous side effects (e.g., shaking and muscle stiffness) have been reported in humans and goats after administration of MET,^{1,4,8} as this agent readily crosses the blood-brain barrier.⁹

Although there are ample pharmacokinetic (PK) data available for humans,¹⁰⁻¹⁵ there are very few published data for rabbits.¹⁶ Recent studies have focused on an experimental intranasal

formulation of MET in rabbits.¹⁷⁻¹⁹ However, intranasal MET is unlikely to be commercially released for some time and is intended for human use.

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As a monogastric herbivore, gastric motility of rabbits has a significant influence on nutritional absorption. Gastrointestinal (GI) motility disorders are commonly diagnosed in rabbits and discussed in detail elsewhere.²⁰⁻²³ Without medical attention, these disorders can result in serious, life-threatening illnesses.²⁴ Pet rabbit medicine is a relatively new area of veterinary interest distinct from laboratory and farm rabbit medicine, and given the medical practice differences between these groups, there is a requirement for increased information that is specific for the companion animal.²⁴

Therapeutic blood levels are most rapidly achieved by direct vascular administration (intraarterial (IA), intravenous [IV] or intraosseous). In clinical practice, it may be challenging to obtain vascular access, especially in debilitated, very small, or highly stressed rabbit patients. This could result in a delay in drug delivery. Intravenous access is also impractical in the home setting when patients are released from the hospital. Moreover, perrectal (PR) administration may also be helpful in avoiding/reducing the first-pass effect caused by high hepatic clearance.²⁵

Hence, the objective of the present research was to compare the PKs of MET after IA, intramuscular (IM), subcutaneous (SC), and PR administration in normal rabbits.

MATERIALS AND METHODS

Animal Treatment and Sampling

For this PK investigation, 6 normal male New Zealand white intact rabbits weighing 3.1 to 4.1 kg were used. The rabbits 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 Department of Veterinary Sciences (University of Pisa). Animal care and handling was 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 (CEASA) and transmitted to the Italian Ministry of Health (protocol 001 4896).

Animals were randomly assigned to 4 treatment groups, using an open, single-dose, 4-treatment, 4-period, unpaired, crossover design (4 × 4 Latin square). During the first period, each subject in group 1 (*n* = 2) received a single dose of 2 mg/kg of MET hydrochloride (Plasil vial 10 mg/2 ml;

Sanofi Aventis, France) injected IA into the central artery of the left ear. Animals in group 2 (*n* = 2) received the same dose IM; it was given into the rectus femoris portion of the quadriceps femoris muscle. Animals in group 3 (*n* = 1) received the same dose SC. Animals in group 4 (*n* = 1) received MET at a dose of 4 mg/kg PR. The volume administered was in the range 2.5 to 3.3 ml. Before PR drug administration, the distal rectum was evacuated with a cotton swab. Rabbits were laid in lateral recumbency and restrained facing downward on a flat surface at a 25° angle. A urethral catheter (sterile urethral catheter 1.0 × 130 mm², Buster cat catheter; Buster, Langeskov, Denmark) with a smooth bullet tip and 2 lateral eyes was marked from the tip every 1 cm for a length of 5 cm and connected to a 3-way Stopcock (3-Way Hi-Flo; Delta Med, Mantova, Italy). The tip of the catheter was lubricated (Surgilube; Savage Laboratories, Melville, NY USA) and inserted 3 cm into the rabbit's rectum. The drug was injected, and to ensure complete administration was followed by 3 mL of air before removing the catheter from the rectum. Rabbits were monitored for potential drug leakage from the rectum for 2 minutes following administration; none was observed with this technique. Given the small volumes administered, further leakage beyond a period of 2 minutes was deemed unlikely. A catheter was placed into the right ear central artery to facilitate blood sampling. The washout period was 1 week. This interval time was estimated as the period exceeding 10 times the half-life of the drug. For the other experimental periods, the groups were rotated and changed in number of animals and the administrations repeated. After 4 weeks, each rabbit had been administered MET by the 4 routes—SC, IM, IA, and PR. Blood samples (2 mL) were collected at 0, 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 24, and 34 hours after administration of MET and placed in collection tubes containing lithium heparin. The blood samples were centrifuged at 3000g (rotor radius 10 cm) within 30 minutes of collection, and the harvested plasma was stored at -20°C until evaluated within 30 days of collection.

CHEMICALS AND REAGENTS

Pure powders of MET (>99.0% purity) and sulphiride (internal standard [IS]) were sourced from Sigma-Aldrich (St. Louis, MO USA). High-performance liquid chromatography (HPLC)-grade acetonitrile, ethyl acetate, methanol (MeOH), and methylene chloride (CH₂Cl₂) were

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