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Effects of slowed gastrointestinal motility on levodopa pharmacokinetics

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ABSTRACT

Autonomic disorders are often seen in Parkinson's disease, with disturbances of the gastrointestinal tract occurring most frequently. These disorders, mainly a delay in gastric emptying and slowed gastrointestinal motility, can modify the pharmacokinetics and effectiveness of drugs used to treat Parkinson's disease and administered orally. In this study, we evaluated in a rabbit model the pharmacokinetics of levodopa (administered with carbidopa) in the context of gastrointestinal motility slowed by the administration of an anticholinergic drug. Levodopa + carbidopa (20:5 mg/kg) and the anticholinergic biperiden (100 μg/kg) were orally administered to rabbits over one of two time periods (7 or 14 days) to verify the stabilization of levodopa concentrations. The values of the area under the curve (AUC) and C_{max} were higher on the final day of treatment with an increase in AUC of 25% on day 7 and 33.4% on day 14; for C_{max}, the increase was 15% on day 7 and 12.8% on day 14. The values of AUC and C_{max} were lower than those obtained when levodopa was administered to rabbits with normal gastrointestinal motility. The values obtained for C_{min} (baseline sample obtained before administration) also increased with treatment duration (24% and 47.4% on days 7 and 14, respectively). These values were higher than those obtained in the absence of anticholinergic administration. We conclude that, under our experimental conditions of slowed gastrointestinal motility, levodopa absorption diminishes, and final concentrations and C_{min} are higher than under conditions of normal motility.

1. Introduction

Parkinson's disease remains one of the most common neurodegenerative disorders, affecting 1% of the population over age 65 (Wilk and Lash, 2007). Autonomic disorders are often seen in idiopathic Parkinson's, especially in the advanced stages of the disease. Disturbances of the gastrointestinal tract are the most frequent autonomic disorders, including abnormal salivation, difficulty in swallowing (dysphagia), early feeling of satiety (abdominal bloating–distension), disorders of gastric emptying, and constipation (Korczyn, 1989; Edwards et al., 1993). These symptoms may affect the quality of life of patients with Parkinson's and modify the pharmacokinetics as well as the effectiveness of drugs used to treat this disease.

Levodopa (usually combined with carbidopa) is the most frequently used medication for treating Parkinson's. This drug is absorbed in the duodenum, jejunum and proximal ileum and metabolized to dopamine through decarboxylation in the stomach (Nutt and Fellman, 1984); thus, the rates of gastric emptying and gastrointestinal motility are important variables that may affect the amount of drug absorbed. Some fluctuations in clinical response in the context of motor performance (e.g., wearing-off and on–off) are that patients with advanced Parkinson's disease experience are partially related to the peripheral pharmacokinetics of levodopa (Bredberg et al., 1990; Kempster et al., 1989; Shoulson et al., 1975).

Age-related delayed gastric emptying, dietary factors, variable transit time, and erratic absorption of the drug at the proximal intestine are some of the contributing factors to the decreased bioavailability of levodopa, leading to unpredictable patterns of motor fluctuation (Hardoff et al., 2001). In addition, these motor response fluctuations can be improved by bypassing the stomach via a non-oral administrative route, such as delivering levodopa directly into the small intestine or intravenously (Mouradian et al., 1990; Nyholm et al., 2003).

In this study, we evaluated the pharmacokinetics of levodopa (administered with carbidopa) under conditions of slowed gastrointestinal motility, a frequent scenario for patients with Parkinson's. To verify the stabilization of levodopa concentrations, we administered the treatment for two different periods of time, 7 or 14 days.

To reduce gastrointestinal motility and produce conditions that lead to constipation, we administered biperiden in a rabbit model. Biperiden is an antimuscarinic anticholinergic drug used in the symptomatic treatment of parkinsonism including the alleviation of the extrapyramidal syndrome induced by drugs, such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. Anticholinergics may decrease the amount of levodopa absorbed by

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delaying gastric emptying and therefore increasing the metabolism of levodopa, but we have not found any study about the interaction between levodopa and biperiden.

2. Materials and methods

For this study, we used 12 healthy New Zealand white rabbits weighing 2.94 to 3.28 kg. The animals were housed in individual metal cages, which allowed the isolation of faeces in a lower container to avoid coprophagia. The environmental conditions were humidity (55 ± 10%), temperature (19 ± 2 °C), and a 12 h light–12 h dark cycle. Rabbits were maintained under these conditions at least one week before the assay, with free access to water and standard laboratory chow.

The rabbits were randomly divided into two groups of six rabbits each. Both groups of animals received orally 20:5 mg/kg levodopa + carbidopa (Sinemet®) and 100 μg/kg biperiden (Akineton®) daily for 7 days (Group 1) or 14 days (Group 2).

The drugs were administered dispersed in water by gastric intubation every morning at the same hour. A total of 50 ml water was used for administration and cannula cleaning.

The first (day 1) and the last day (day 7 or 14, respectively) of treatment, levodopa concentrations were determined at different sampling times after drug administration. To obtain blood samples, we anaesthetized the rabbits with sodium pentobarbital (30 mg/kg body weight, i.v.) and cannulated the left carotid artery with a silicone catheter (Silastic medical-grade tubing, 1.02 mm inner diameter × 2.16 mm outer diameter). Drug administration was carried out following the achievement of total recovery from anaesthesia. Blood samples (3 ml) were obtained from the left carotid artery through the cannula into heparinised containers, immediately before and at 5, 10, 20, 30, 60, 90, 120, 180, 240, and 300 min after administration.

To study the evolution of the maximum and minimum concentrations through the study, we obtained two blood samples from the marginal ear vein: immediately before (C_{min}) and at 20 min after drug administration (C_{max}) on days 3 and 5 (7-day treatment) and on days 3, 6, 9, and 11 (14-day treatment).

Immediately after blood sample collection, plasma was separated by centrifugation and stored at −20 °C until analysis.

Levodopa extraction from plasma samples was carried out by using a catecholamine kit (Chromsystems®) and was quantified by HPLC with electrochemical detection following the method described by Cummings et al., in 1990, slightly modified.

The mobile phase consisted of 50 mM sodium dihydrogen phosphate buffer adjusted to pH 2.9 with 1 M orthophosphoric acid containing 250 mg/l heptanesulphonic acid and 80 mg/l EDTA and

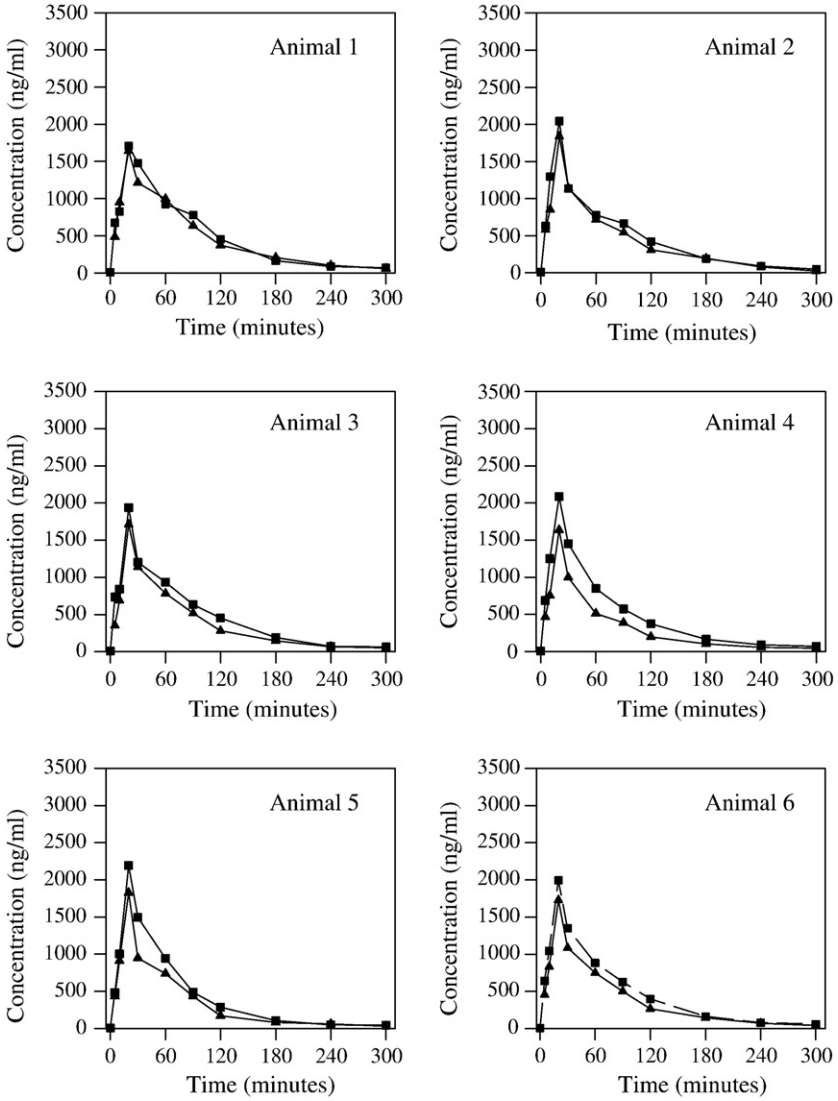

Fig. 1. Individual plasma concentrations of levodopa in rabbits after oral administration of 20:5 mg/kg levodopa + carbidopa with biperiden (100 μg/kg) for 7 days (day 1 –▲–, and day 7 –■–).