

A NEW APOMORPHINE FORMULATION FOR ORAL ADMINISTRATION

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Apomorphine (APO) is a well-known potent short-acting dopamine agonist, used as an antiparkinson drug for patients with refractory motor fluctuations. Despite its favourable characteristics, the clinical use is somewhat limited by its pharmacokinetic profile: short half-life, rapid clearance and poor oral bioavailability. In previous researches we have shown that the incorporation of several drugs in solid lipid nanoparticles SLN can improve their bioavailability, with the increase of AUC and of half-life and the reduction of clearance. The aim of the present work is to evaluate the plasma pharmacokinetics and brain concentrations of a new formulation of apomorphine incorporated in Solid Lipid Nanoparticles (Apo-SLN) in comparison with apomorphine solution (Apo-Sol) after duodenal administration in rats. Methods: male albino rats (Wistar derived strain) weighing 350-450 g. were used. Apo-SLN and Apo-Sol 4 mg/Kg were administered directly into the duodenal lumen through a cannula surgically implanted. Blood samples at different time were collected through an implanted cannula into the jugular vein 24 h after surgery. The drug plasma concentrations were determined by high performance liquid chromatography with electrochemical determination. Results: After duodenal administration the peak plasma concentration after Apo-SLN was about 146,35±20,03 ng/mL, while the peak plasma concentration after Apo-Sol was about 19,32±9,86 ng/mL (P<0.001). The AUC_{tot} after Apo-SLN was significantly higher (P<0.001) than after Apo-Sol (57394,15±24651,60 vs. 2774,39±1577,45 ng/mL/min). We observed a significant increase of the elimination half life after Apo-SLN (319,84±146,00 vs. 144,50±144,93 min).

In the brain after 30 min and 4 h of i.v. injections the drug concentration was significantly higher after Apo-SLN than after Apo-Sol (1308 vs. 845 ng/g and 66 vs. 0 respectively). After duodenal administration Apomorphine was detected only after 30 min following Apo-SLN administration at the dose of 4 mg/kg

In conclusion Apomorphine incorporated in SLN was present in plasma after duodenal administration. The new formulation is absorbed from the gastrointestinal tract and can cross the blood brain barrier. The plasma levels in rats were much higher after administration of Apo-SLN than of Apo-solution. The plasma levels of Apo following duodenal administration in rats are largely above the therapeutic range in Parkinson's subjects after subcutaneous administration.