PHARMACOKINETICS OF ANTI-SARS-COV AGENT NICLOSAMIDE AND ITS ANALOGS IN RATS

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Niclosamide has been demonstrated with inhibitory activity on the replication of SARS-CoV in Vero E6 cells. This study examined the pharmacokinetics and oral bioavailability of niclosamide and its two analogs, BPR1H366 and BPR1H369, in male Sprague-Dawley rats. After single 2-mg/kg intravenous dose, the total body clearance of niclosamide, BPR1H366 and BPR1H369 was 20.0 ± 2.9, 26.7 ± 4.4 and 39.4 ± 6.7 mL/kg/min, and the volume of distribution at steady state was 0.9 ± 0.4, 0.3 ± 0.1 and 1.1 ± 0.2 L/kg, respectively. The half-life of BPR1H366 and BPR1H369 was 2.6 ± 0.3 and 3.7 ± 1.1 hr, respectively, shorter than 6.7 ± 2.0 hr of niclosamide. The AUC were 1413 ± 118 for niclosamide, 1019 ± 203 for BPR1H366, and 750 ± 113 (ng/mL×hr) for BPR1H369, respectively. After a single 5-mg/kg oral dose, all three compounds were rapidly absorbed. Niclosamide showed the highest Cmax of 354 ± 152 ng/mL within 30 min after oral gavage. The oral bioavailability of niclosamide, BPR1H366 and BPR1H369 were 10%, 12% and 15%, respectively. Our results demonstrated that the extent of drug exposure of the three compounds were comparable in rats. The pharmacokinetic properties of the compounds in humans are needed to be determined before their possible future uses in SARS-CoV infected patients.

CAPILLARY ELECTROPHORESIS WITH LASER-INDUCED FLUORESCENCE DETECTION FOR THE DETERMINATION OF CAFFEIC ACID IN SMALL VOLUMES OF RAT PLASMA

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A simple and sensitive capillary zone electrophoresis method has been developed for the determination of caffeic acid in 50 µl of rat plasma. Caffeic acid and the internal standard were extracted with 0.5 ml of tert-butyl methyl ether, after the samples acidified with 50 µl of hydrochloric acid (1 N). The analytes were detected using laser-induced fluorescence (LIF) detection with a HeCd laser operating at the excitation wavelength of 325 nm and the emission wavelength of 520 nm. Sodium tetraborate was chosen as the background electrolyte. The electrophoretic conditions and the fluorescence response were examined and optimized by varying the pH and ionic strength of the background electrolyte, and the applied voltage. Samples were introduced by pressure injection (0.5 psi, 10s). Calibration curves were linear from 0.05 to 50 µg/ml. The average recovery of caffeic acid was greater than 76%. The limit of quantitation was 0.05 µg/ml. The intra- and inter-day relative standard deviation (C.V.) did not exceed 17.8%, and the accuracy was within 6.2% deviation of the nominal concentrations. No endogenous substances were found to interfere. The method was successfully applied to assess the disposition kinetics of caffeic acid following intravenous bolus doses of 5-50 mg/kg administered to rats.