DEVELOPMENT OF NOVEL LACTATE-NA2EDTA BUFFER-BASED F-DOPA FORMULATIONS: TOXICOLOGICAL INVESTIGATION IN RATS AND MICE

1)Maqoud1 F. 2)Denora N. 3)Mele A. 4)Curci A. 5)Camerino GM. 6)Lopedota A. 7)Cutrignelli A. 8)Laquintana A. 9)Franco M. 10)Dimiccoli V. 11)Tolomeo A. 12)Scilimati A. 13)Tricarico D.

Dept. of Pharmacy- Pharmaceutical Sciences, University

The [18F]F-DOPA is used in the diagnosis of neurodegeneration and cancer. Its use is limited by its instability and injection-site adverse reactions. Novel [19F]F-DOPA lactate-based formulations were developed. “In vitro” study on ND1 (lactate/NaCl/Na2EDTA/F-DOPA), ND2 (lactate/Na2EDTA/F-DOPA) and ND3 (acetic acid/F-DOPA) formulations and in “in vivo” tolerability studies in rats (i.v./i.m. 0.025-5 mg/kg) and mice (i.v. 50 mg/kg) were performed. In cell viability experiments, the rank order of potency in inducing cell mortality, at 0.005-0.5 mg/ml of the different formulations was: F-DOPA ≥ ND3 > ND1 ≥ ND2 in mouse skeletal muscle fibers, ND3 > ND1 > ND2 in SHSY5H cells, ND1 > ND3 > ND2 in tsA201 cells. The i.m. injection of ND3 (5 mg/kg) and ND3-vehicle to rats caused a local reaction, loss of fibers with up-regulation of the autophagic Lc3 and Bnip3, apoptotic Caspase 3, 8 and 9, mitochondrial Pgc1□, and inflammatory Mapk3, Cgrp, TNF□□□genes. Mapk3 and Pgc1□ were also up-regulated in the ND2 (5 mg/kg) treated rat muscles. The i.v. injection of ND3 (5 mg/kg) after 14 days of follow-up caused a mild reduction of body-weight in rat; the ND3 (50 mg/kg) and the ND3-vehicle caused a loss of body-weight of -17.8 ± 1% and -12.3 ± 2% vs controls, respectively, in mice. No effects were observed following the ND2 and the ND2-vehicle treatments in rat (5 mg/kg) and mice (50 mg/kg). The F-DOPA acetic acid-based formulation affects skeletal muscle by apoptotic and autophagic mechanisms. The F-DOPA lactate/Na2EDTA-based (ND2) formulation is better tolerated than acetic acid-based formulation.

Keywords: radiopharmaceuticals formulation, F-DOPA, brain tumor, neurodegeneration.