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Assessing the cytotoxic and metabolic impact of cebranopadol in a panel of cell lines

Luísa Silva [1,2,3], Beatriz Diogo [3], Joana Rocha [3], Margarida Almeida [3], Ricardo Jorge Dinis-Oliveira [1,2,3,4,5], Juliana Faria [1,2,3,ǂ] and Joana Barbosa [1,2,3,ǂ,*]

[1] Laboratory i4HB—Institute for Health and Bioeconomy, University Institute of Health Sciences—CESPU, 4585-116 Gandra, Portugal
[2] UCIBIO—Applied Molecular Biosciences Unit, Translational Toxicology Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 4585-116 Gandra, Portugal
[3] University Institute of Health Sciences (IUCS-CESPU), 4585-116 Gandra, Portugal
[4] Department of Public Health and Forensic Sciences, and Medical Education, Faculty of Medicine, University of Porto, 4200 319 Porto, Portugal
[5] FOREN-Forensic Science Experts, Av. Dr. Mário Moutinho 33-A, 1400-136 Lisboa, Portugal
[ǂ] these authors contributed equally to this work

* Correspondence: joana.barbosa@iucs.cespu.pt

Abstract

Background: Cebranopadol is a novel, first-in-class analgesic with a unique pharmacological profile. It acts as a full agonist at the μ-opioid (MOP) and nociceptin/orphanin FQ peptide (NOP) receptors [1]. This dual mechanism shows potential for preserving analgesic potency while reducing adverse effects typical of traditional opioids [2]. Currently, cebranopadol is in phase III clinical trials and has received FDA fast-track designation, reflecting its promise as a next-generation analgesic [3]. Nonetheless, further large-scale studies are necessary to fully establish its safety, long-term efficacy, and comparative advantages over conventional and other emerging opioid analgesics [4]. **Objective:** The present study aimed to assess the metabolic impact of cebranopadol exposure in three cell lines: BV-2 (murine microglia), HepG2 (human hepatocellular carcinoma) and SH-SY5Y (human neuroblastoma). **Methods:** Following 48 hours of exposure to half the respective IC_{50} concentrations, as previously determined through the sulforhodamine B (SRB) assay, BV-2, HepG2, and SH-SY5Y culture medium samples were collected for spectrophotometric quantification of glucose and lactate levels. **Results:** In BV-2 cells, extracellular glucose levels showed a slight decrease, whereas they remained unchanged in SH-SY5Y and HepG2 cells. Lactate levels increased in culture media samples from cebranopadol-treated BV-2 and SH-SY5Y cells compared to those of the controls, while a decrease was observed in HepG2 cells. These results suggest an opioid-induced shift towards anaerobic metabolism in BV-2 and SH-SY5Y cells, whereas fermentative processes may be hindered in HepG2 cells. **Conclusions:** While supratherapeutic concentrations of cebranopadol show low cytotoxicity in BV-2, HepG2, and SH-SY5Y cells, they may affect metabolic processes differently across the three cell lines by interfering with aerobic and anaerobic metabolic fluxes. Further investigation of the molecular and cellular mechanisms behind these metabolic alterations is warranted to fully characterize the safety profile of cebranopadol.

Keywords: cebranopadol; cytotoxicity; cell metabolism

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