Theme: Pre-clinical Research and Mechanisms of Disease

Intranasal administration of histone deacetylase inhibitors: bioanalysis and pharmacokinetic studies

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Abstract:
Histone deacetylase inhibitors (HDACi) are approved for cancer treatment. Their repurposing for central nervous system (CNS) disorders is being investigated, although the blood-brain barrier poses an obstacle for brain targeting. Intranasal (IN) administration emerges as a promising route due to potential nose-to-brain transport and non-invasiveness.
A high-performance liquid chromatography method with diode-array detection was developed and validated for HDACi 1-4 in mouse plasma, brain and lung, according to the ICH M10 guideline. Chromatographic separation was achieved with a mobile phase of water and ortho-phosphoric acid (pH = 2.04) and acetonitrile. Samples were prepared by protein precipitation (acetonitrile) and liquid-liquid extraction (ethyl acetate) with recoveries >94.4% (plasma), 76.6% (brain) and 75.9% (lung). Calibration ranges were 0.0625–12.5 (HDACi 1 and 2), 0.1–15 (HDACi 3) and 0.15–15 (HDACi 4) µg/mL in plasma; 0.035–7 (HDACi 1), 0.025–5 (HDACi 2), 0.05–10 (HDACi 3) and 0.1–10 (HDACi 4) µg/mL in brain; and 0.06–12 (HDACi 1), 0.07–14 (HDACi 2 and 3) and 0.18–18 (HDACi 4) µg/mL in lung. The method showed inter- and intra-day accuracy (-14.37 to 12.75%) and precision (CV<18.36%).
Pharmacokinetic studies were performed in CD1 mice for HDACi 2 and HDACi 3 with ethics committee approval (01-2023). Both were administered by IN route in single equimolar dose (0.15 mmol/kg) and samples were harvested at 2 min, 5 min, 15 min, 1h and 4h (n=3-5). HDACi 3 displayed higher brain exposure (AUCt of 0.092 vs. 0.029 µg/mL.h) and slower brain elimination than HDACi 2 (t1/2 of 0.55 vs. 0.072 h). Brain-plasma ratios were higher for HDACi 3 (0.012 vs. 0.008) whereas lung-plasma ratios were higher for HDACi 2 (0.371 vs. 0.365).
Overall, HDACi 3 exhibited greater potential to reach the brain than HDACi 2 following IN dosing. In future studies, HDACi 3 will be administered to an animal model of disease by IN route, to assess its capacity for the treatment of CNS disorders.

Keywords: High performance liquid chromatography; histone deacetylase inhibitors; intranasal administration; pharmacokinetics