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PBA-ω-Lys as Sustained Phenylbutyrate-Releasing Prodrug

Chun-Li Wang（王群力）[1], Po-Ren Hsuen（薛博仁）[2], Meng-Jie Sun（孫孟傑）[4], Yann-Lii Leu（呂彥禮）[4], Feng-Shou Chang（張峯碩）[3], Shu-Wei Yang（楊書瑋）[1], Jang-Feng Lian（連掌鋒）[1], and Hui-Po Wang（王惠珀）*[1,3]

[1]*College of Pharmacy, Taipei Medical University, Taipei, Taiwan, R.O.C.*
[2]*Department of ENT, Taipei Medical University Hospital, Taipei, Taiwan. R.O.C.*
[3]*Center of Excellence for Cancer Research, Taipei Medical University Hospital, Taipei, Taiwan. R.O.C.*
[4]*Graduate Institute of Natural Products, Chang Gung University, College of Medicine, Tao-Yuan,Taiwan, R.O.C.*

Lysine was attached to phenylbutyric acid (PBA) to form PBA-α-Lys and PBA-ω-Lys as PBA prodrugs for treating chemotherapy-associated mucositis. Pharmacokinetic studies were conducted in Wistar rats for determining the systemic bioavailability of both prodrugs and the released PBA. The systemic bioavailability of PBA after oral administration of PBA-α-Lys or PBA-ω-Lys was higher than from i.v. administration, indicating that first pass effect is responsible for the transformation from the prodrugs to the parent drug. Lack of stability in the intestine made PBA-α-Lys unsatisfied as an oral prodrug of PBA. Oral administration of PBA-ω-Lys, on the other hand, led to a slow PBA-releasing profile in circulation. Although the $AUC_{0\rightarrow t}$ of systemic released PBA from oral administration of PBA-ω-Lys was lower than from oral administration of PBA *per se*, MRT_{inf} was 5 times longer (9.64 ± 2.16 vs 1.81 ± 0.28 hr), $t_{1/2}$ was 4 times longer (6.18 ± 2.09 hr vs 1.50 ± 0.17 hr), and $AUMC_{inf}$ was 2 folds higher (168.7 ± 67.7 hr*hr*μg/mL vs 88.8 ± 12.4 hr*hr*μg/mL). In conclusion, oral administration of PBA-ω-Lysine exhibited a sustained PBA-releasing pharmacokinetic profile in rats. The bioavailability of PBA released in inflammatory tissues and anti-mucositis activity need to be further investigated for the evaluation of PBA-ω-Lysine as an effective targetable anti-mucositis agent.

Key words: phenylbutyric acid, PBA-α-Lys, PBA-ω-Lys, pharmacokinetics