プロドラッグとしての経口オフロキサシンピバロイルオキシメチルエステルの合成とそのバイオアベイラビリティーに関する研究

前田　頼信*, 面田　恵*, 小西　敏夫*, 高橋　真*,
木平　健治**　日比野　俐, 突合　皐月[1*]

Biol. Pharm. Bull., **16** (6) 594–599 (1993).

Effects of Aluminium-Containing Antacid on Bioavailability of Ofloxacin Following Oral Administration of Pivaloyloxymethyl Ester of Ofloxacin as Prodrug

Yorinobu Maeda*, Kei Omoda*, Toshio Konishi*,
Makoto Takahashi*, Kenji Kihira**, Satoshi Hibino,
and Satsuki Tsukiai*

ABSTRACT We newly synthesized a pivaloyloxymethyl ester of ofloxacin (OFLX-PVM) as prodrug in order to avoid the chelate formation between new quinolone and metal cations such as Al^{3+}, Mg^{2+}, Ca^{2+}, or Fe^{2+} in the gastrointestinal tract. This compound was rapidly hydrolyzed in an incubation experiment by 43% in plasma, by 92% in small intestinal mucosal homogenates, and by 97% in liver homogenates during 0.5h incubation, but was resistant to hydrolysis by pancreatic enzymes. In everted gut sac experiments, this compound was efficiently absorbed even in the presence of aluminium ion, whereas the absorption of ofloxacin (OFLX) was decreased significantly by the presence of aluminium ion. Minimal inhibitory concentoration (MIC) values of OFLX-PVM were far higher than OFLX. Effects of aluminium hydroxide on the oral bioavailability of OFLX and OFLX-PVM were investigated in rabbits. The area under the plasma concentration-versus-time curve from zero to 24h ($AUC_{0\text{-}24h}$) following oral administration of OFLX was decreased significantly by 47.6% by combined administration with aluminium hydroxide, but $AUC_{0\text{-}24h}$ values of OFLX-PVM coadministered with and without aluminium hydroxide were similar to

that of OFLX alone. These observations indicate that this new compound is likely to offer a prodrug for avoidance of interaction between new quinolone and metal cations.

抄録　繁用抗菌剤オフロキサシンは、経口投与においてバイオアベイラビリティーが極度に減少するとの報告がみられる。この経口投与におけるバイオアベイラビリティーの改善を目的とし、オフロキサシンピバロイルオキシメチルエステルを合成し、そのバイオアベイラビリティーを検討した。その結果、この新規オフロキサシンエステル誘導体は、胃腸管部においてキノロン部分と金属イオンとのコンタトを回避することができ、プロドラッグとしての機能を有する化合物であることが判明した。

＊Department of Pharmacy and Surgery Chugoku-Rosai Hospital 中国労災病院薬剤部，外科

＊＊Department of Pharmacy, Hiroshima University Hospital 広島大学医学部附属病院薬剤部