POPULATION APPROACH TO EPLERENONE PHARMACOKINETICS AND SATURABLE PROTEIN BINDING

Yuko Mori¹, Koji Chiba², Harumi Takahashi³ and Hiroyasu Ogata³

¹ Department of Clinical Pharmacology, Pfizer Global R&D, Tokyo Laboratories, Pfizer Japan Inc., 3-22-7, Yoyogi, Shibuya, Tokyo, 151-8589, Japan
² Department of Drug Development Science & Clinical Evaluation Faculty of Pharmacy, Keio University, 1-5-30, Shibakouen, Minato, Tokyo, 105-8512, Japan
³ Department of Biopharmaceutics, Meiji Pharmaceutical University, 2-522-1, Noshio, Kiyose, Tokyo, 204-8588, Japan

Microdialysis study in evaluation of intramuscular lateral distribution profiles of topically administered drugs in rats

Tsukasa Higashionna, Hitomi Murakami, Keiichi Makinodan, Kozue Kanda, Mayu Shibata, Tetsuya Aiba and Yuji Kurosaki

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan

[Purpose] Eplerenone shows deviation from linear pharmacokinetics above, but near, therapeutic dose range. The purpose of the present study was to clarify the factors contributing to the nonlinear pharmacokinetics of eplerenone and to provide a possibility that there is no change of free drug concentration.

[Methods] Plasma concentrations of eplerenone and its metabolite SC-70303 which is converted reversibly from eplerenone were gathered from four phase I studies and used for population pharmacokinetic analysis by NONMEM. A model incorporating protein binding and the reversible conversion was developed.

[Results and Discussion] The observed concentrations of eplerenone and SC-70303 were best described by the model with nonlinear protein binding. The area under the plasma concentration-time curve of eplerenone simulated by the model increased less than proportionally with increasing dose, whereas that of SC-70303 increased proportionally with increasing dose, these results were consistent with observations from the non-compartmental analysis.

[Conclusions] The nonlinear pharmacokinetics of eplerenone and the apparently linear pharmacokinetics of SC-70303 were described well by the present model with nonlinear protein binding, suggesting that nonlinear protein binding caused the nonlinearity of eplerenone. This also indicates no change of free concentration around the therapeutic range.

Microdialysis study in evaluation of intramuscular lateral distribution profiles of topically administered drugs in rats

Tsukasa Higashionna, Hitomi Murakami, Keiichi Makinodan, Kozue Kanda, Mayu Shibata, Tetsuya Aiba and Yuji Kurosaki

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan

[Purpose] To exert localized pharmacological effects rationally in topical DDSs, precise pharmacokinetics of drugs must be clarified. In this study, we determined the concentration-time profiles of antipyrine (ANP) in the muscle using microdialysis (MD) method to clarify the lateral diffusion of ANP in the muscle.

[Methods] ANP was applied into the rat abdominal muscle in the 0-order kinetics through a MD probe. Time courses of intramuscular ANP concentration was monitored by another MD probe inserted parallel to the delivery probe in a fixed distance (2, 5, 10 and 15 mm).

[Results and Discussion] The concentration-time profiles of ANP in the muscle were highly dependent on the distance from the delivery probe. At the steady-state of the diffusion, the ANP concentrations at the 2mm, the 5mm, the 10mm and the 15mm position were 10.27 μg/mL, 3.28 μg/mL, 1.50 μg/mL, and 1.05 μg/mL, respectively. In addition, the concentration-profile in the muscle at the 15mm was in good agreement with that in the plasma suggesting the topical effect would be restricted only in 10 mm area of the administration site.

[Conclusions] MD can be applied to study topical pharmacokinetic in lateral (horizontal) diffusion, the primary process accountable for the supply in adjacent muscular tissue from the delivery site.