Quantification of CYP3A and drug transporters activity in healthy young, healthy elderly and chronic kidney disease elderly patients by a microdose cocktail approach

Punyabhorn Rattanacheeworn[1], Stephen Kerr[2], Wonngarm Kittanamongkolchai[2], Natavudh Townamchai[2], Suwasin Udomkarnjananun[2], Kearkiat Praditpornsilpa[2], Thanundorn Thanusuwannasak[3], Udomsak Udomnilobol[1], Suree Jianmongkol[3], Boonsri Ongpipattanakul[3], Thomayant Prueksaritanont[1], Yingyos Avihingsanon[1], and Pajaree Chariyavilaskul[1]

[1]Chulalongkorn University
[2]Chulalongkorn University Faculty of Medicine
[3]Chulalongkorn University Faculty of Pharmaceutical Sciences

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Abstract

Aims: Ageing and chronic kidney disease (CKD) are known to affect pharmacokinetics (PK) parameters. Since mechanisms are related and remain unclear, cytochrome P450 (CYP)3A and drug transporter activity were investigated in the elderly with or without CKD and compared to healthy adults using a microdose cocktail. Methods: Healthy young volunteers (n = 20), healthy elderly volunteers (n = 16) and elderly with CKD (n = 17) received a single dose of microdose cocktail probe containing 30 µg midazolam, 750 µg dabigatran etexilate, 100 µg atorvastatin, 10 µg pitavastatin, and 50 µg rosuvastatin. After a 14-day washout period, healthy young volunteers continued to study period 2 with the microdose cocktail plus rifampicin. PK parameters including area under the concentration-time curve (AUC), maximum plasma drug concentration (Cmax) and half-life were estimated before making pairwise comparisons of geometric mean ratios between groups. Results: AUC and Cmax of midazolam, a CYP3A probe substrate, were increased 2.30 and 2.90 fold in healthy elderly and elderly with CKD, respectively, leading to a prolonged half-life. AUC and Cmax of atorvastatin, another CYP3A4 probe substrate, was increased 2.14 fold in healthy elderly and 4.15 fold in elderly with CKD, indicating decreased CYP3A4 activity related to ageing. Association with PK changes in probe drugs representing activity of OATP1B1, intestinal P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) transporters was noticed, but were inconclusive. Conclusions: CYP3A activity is reduced in ageing. There is a trend in changes of OATP1B1, P-gp, and BCRP activity measured by microdose cocktail probe drugs.

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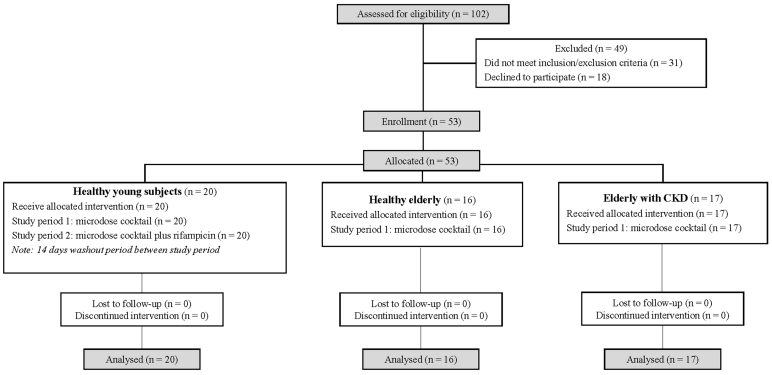

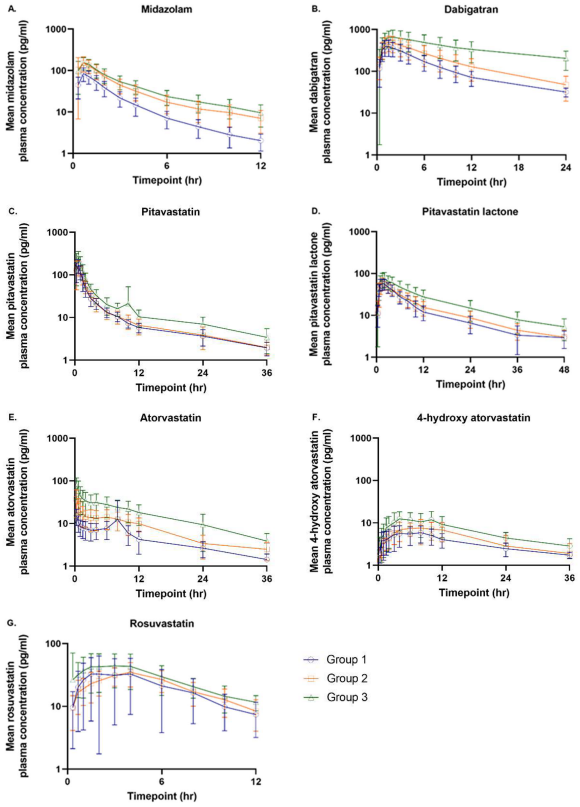

Figure 2 The plasma concentration-time curves of microdose cocktail probe substrates in 3 groups of participants.
Group 1: healthy young volunteers
Group 2: healthy elderly volunteers
Group 3: elderly patients with chronic kidney disease