腎臟有機陰離子運輸蛋白担體 I 於家兔體內藥物交互作用之藥物動力學研究

Pharmacokinetic Studies of Drug-Drug Interactions by Renal Organic Anion Transporter I in Rabbits

中文摘要

運輸蛋白(transporter)是一種在細胞膜上掌控物質進出的蛋白質，近年來許多臨床上發生的藥物交互作用被認爲可能與其有關。本實驗的目的爲以單劑量與多劑量兩種不同的合併給藥方式來探討兔子腎臟上有機陰離子運輸蛋白担體 I(Organic anion transporter I, OATI)進行交互作用時的藥物動力學變化

本實驗藥物 p-Aminohippuric acid (PAH)、Ibuprofen (IBU)及 Indomethacin (INDO)在血漿中濃度的分析方法皆採用逆向高效液相層析法，其血中濃度檢量線在本實驗濃度範圍內具有良好的線性關係以及準確性與精確性。

口服同莫耳單一劑量的 IBU(21.38mg/kg)或 INDO(37.08mg/kg)至家兔體內，並同時靜脈注射等莫耳數之 PAH(20mg/kg)，可得單劑量給藥後結果。實驗顯示：(1) INDO 血中濃度曲線下面積(AUC)及最高血中濃度(Cmax)相較於對照組有 8.42 至 11.33 倍顯著差異($p<0.01$)；清除率(clearance,CL)有 6.94 倍的顯著下降($p<0.01$)。(2) PAH 之 AUC 及 CL 有稍微上升及下降。(3) IBU 的 AUC 稍微上升且 CL 下降了 3.56 倍($p<0.01$)。(4) PAH 在與 IBU 單劑量合併使用時，AUC 些微上升。

多劑量 IBU 或 INDO 口服給藥後發現：(1) INDO 的 AUC 及 Cmax 有 15.02 至 20.93 倍之顯著上升($p<0.01$)；CL 下降了 19.66 倍($p<0.01$)。(2) PAH 與 INDO 合併給藥時，其 AUC 有 2.07 倍的顯著上升($p<0.01$)；CL 有 1.94 倍的顯著下降($p<0.01$)。(3) IBU 的 AUC 上升且 CL 下降了 5.53 倍($p<0.01$)。(4) PAH 在與 IBU 多劑量合併使用時，AUC 及 CL 都有上升及下降。INDO 經由腎排除的比例有 60%，IBU 則約 45%~75%，但因 IBU 在腎小管的主動分泌比例只有約 1%，而 INDO 則將近 34.4%，故在評估 OATI 對於 IBU 與 INDO 的影響時須考慮此因素。由實驗結果可知，OATI 上發生藥物交互作用時會改變藥物彼此間的排除。

英文摘要

Carrier-mediated processes, often referred to as transporters which located on the membrane, play key roles in the reabsorption and secretion of many endogenous and xenobiotic compounds by the kidney. In recent years, the specific roles of such transporters in drug disposition and drug-drug interactions become more important. The purpose of this study is to estimate the interaction of drugs with the organic anion transporter I (OATI) in the kidney.

An accuracy, precision, simple and specific HPLC method was developed to detect

the concentration of p-aminohippuric acid (PAH), ibuprofen (IBU) and indomethacin (INDO) in plasma.

The drug-drug interaction evaluating of OATI was determined by combining dosing with same molar dose of I.V. of PAH (20mg/kg) and P.O. administration of single or multiple dose of IBU (21.38mg/kg) and INDO (37.08mg/kg) to rabbits. During single dose of INDO or IBU administration, the results were shown below: (1) INDO: significantly increased the AUC and Cmax by 8.42 to 11.33 fold ($p<0.01$) and decreased the CL by 6.94 fold ($p<0.01$). (2) PAH: slightly increased the AUC and slightly decreased the CL. (3) IBU: slightly increased the AUC and Cmax but significantly decreased the CL by 3.56 fold ($p<0.01$). (4) PAH: combination dosing with IBU slightly increased the AUC.

In multiple dose studies, the results were shown below: (1) INDO: significantly increased the AUC and Cmax by 15.02 to 20.93 fold ($p<0.01$) and decreased the CL by 19.66 fold ($p<0.01$). (2) PAH: significantly increased the AUC by 2.07 fold ($p<0.01$) and decreased the CL by 1.94 fold ($p<0.01$). (3) IBU: slightly increased the AUC and Cmax but significantly decreased the CL by 5.53 fold ($p<0.01$). (4) PAH: slightly increased the AUC and slightly decreased the CL. The excretion of IBU in kidney (45%-75%) is equal with INDO (60%), but the tubular excretion of IBU was only 1% compared with 34.4% of INDO.This may result the difference of OATI effect.

In comparison between single and multiple dose administration, the results showed the higher competition level in drug-drug interaction when INDO or IBU multiple administration. The OATI effect the elimination of IBU and INDO.