水解型單寧 Geraniin 在家兔體內之藥物動力學研究

Pharmacokinetic Studies of Ellagitannin Geraniin in Rabbits

中文摘要

自牻牛兒苗分離出的 geraniin 是一廣泛存在的 ellagitannin，並具有 dehydrohexahydroxydiphenoyl (DHHDP)結構。先前的研究中已發現 geraniin 具有止瀉、腸胃道保護功能、黑色素腫瘤細胞毒殺作用、並能強化巨噬細胞之吞噬作用及酸磷酸酵素、對微粒體具有抗脂質過氧化作用、亦能降低老鼠之 GOT、 GPT、LPO、TG 及 free fatty acid。此外，在老鼠試驗中更發現有降血壓的效果。僅管在藥理作用上已被廣泛研究，但在藥物動力學上的研究卻仍未被研究。爲了對 geraniin 在生物體內的動態，能有更能有完整的瞭解，本實驗將 geraniin 投與至家兔體內，以觀察 geraniin 在家兔體內的藥物動力學表現。

一精確、簡單並具有專一性的 HPLC 分析方法已被發展出來用以偵測生物檢品中 geraniin 的濃度。利用 phenyl 逆相層析管，在 UV 波長 280nm 進行偵測。在血漿濃度 0.1mg 到 100mg/ml 的濃度範圍內，呈現良好之線性關係(Y=0.0008+0.0488X, r2=0.9922)，同日內其與異日內分析的 C.V.值均在可接受範圍內，顯示此爲良好之分析方法。

經由三個不同之劑量(1、2、 5mg/kg)靜脈投予六隻兔子，並分析其血漿濃度，顯示 geraniin 在此劑量下符合二室性模式之藥物動力學性質。排除半衰期分別爲 70.63*14.65、81.76*15.04、81.34 * 4.46 分鐘。清除率爲 2.08*0.81、 2.18*0.62、2.89*0.64 ml/min./kg，各項藥物動力學參數並無統計上差異，顯示 geraniin 在此劑量範圍內呈現良好線性之藥物動力學性質。曲線下面積(AUC)分別爲 551.77*232.72、985.23*296.15、1819.59*504.75 mg*min/ml，與劑量呈現良好之比例關係(Y=297.5460+307.9935X，r2=0.7081，P<0.001.)。而腎清除率分別爲 0.18*0.06、0.12*0.07 及 0.15*0.05 ml/min/kg，佔總清除率的 9.20*3.52 %、5.14*2.04 %及 5.42*1.64 %，顯示 geraniin 之非腎臟排除佔極重要部份。

經口投與 5、50、100、250mg/kg geraniin 至家兔體內並分析其結果，發現血液中 geraniin 濃度於 6 小時內均小於 0.1mg/ml。由安定性試驗中得知 geraniin 在胃液中及鹼性環境下相當不安定。因此口服投與 geraniin 之吸收不良可能是由於腸胃道的不安定所致。

由上述結果可知，geraniin 在 1~5mg/kg 以靜脈投與至家兔體內，呈現非劑量依賴之藥藥物動力學性質特性，並以非腎臟排除爲主要排除途徑。經口投與 5~250mg/kg geraniin 之吸收不良，則可能主要是由於腸胃道的不安定所致。

英文摘要

Geraniin, one of the major components isolated from Geranium thunbergii Sieb. et Zucc., is a widely distributed ellagitannin with a dehydrohexahydroxydiphenoyl (DHHDP) moiety. In previous studies, geraniin has been demonstrated to antidiarrhea and cytoprotective effect; potent cytotoxicity in melanoma tumor cells with ED50=0.35μg/ml; enhancement of phagocytosis and acid phosphatase activity

in macrophage; anti-lipid peroxydation in mitochondria; lowing the GOT, GPT, LPO, TG and free fatty acid in rat; anti-inflammatory, antinociceptive effect, cytoprotective effect and anti-hypertensive action in rat. Although several pharmacological effects has been reported, but the pharmacokinetics of geraniin has not been studied.

An accuracy, simple and specific analytical method based on HPLC was developed to detect the geraniin in the biological sample firstly. A phenyl reversed phase column with UV detection at 280nm was used in chromatographic separation. Under these chromatographic conditions, the calibration curve of plasma shows a good linearity within the concentration range of 0.1mg to 100mg/ml (Y=0.0008+ 0.0488X, r2=0.9922). The validations of this analytical method are within the acceptable criteria.

The pharmacokinetics of geraniin was studied by intravenous administration of three different doses (1, 2, 5mg/kg) to six rabbits, respectively. The plasma concentration-time profiles of geraniin could be described by a bi-exponential equation with each dose. The elimination half-lives are 70.63*14.65, 81.76*15.04, 81.34*4.46 minutes, and the systemic clearance are 2.08*0.81, 2.18*0.62, 2.89*0.64 ml/min./kg. These data show a linear pharmacokinetic property of geraniin in rabbits between 1~5mg/kg with intravenous administration. The area under the curves (AUC) calculated from time zero to infinite are 551.77*232.72, 985.23*296.15, 1819.59*504.75 mg*min/ml. A good linear relationship between dose and AUC is obtained, Y=297.5460+307.9935X, r2=0.7081, P<0.001.The renal clearance are 0.18*0.06, 0.12*0.07 and 0.15*0.05 ml/min/kg, they are 9.20*3.52%, 5.14*2.04 % and 5.42*1.64 % of total clearance, respectively. It indicated that the nonrenal clearance of geraniin play an important role in elimination.

After oral administration of geraniin 5, 50, 100, 250mg/kg to rabbits, the concentration of geraniin in plasma is lower than 0.1mg/ml. According to the stability test, geraniin is quite unstable in gastric acid and basic conditions. It is suggested that unstable in gut results in poor absorption after oral administration of geraniin.

From these data in above, geraniin shows a dose-independent pharmacokinetic property with mainly nonrenal clearance elimination after I.V. administration of 1~5mg/kg geraniin to rabbits. The unstability of geraniin in gut may be the major reason of poor absorption after P.O. administration of 5~250mg/kg geraniin to rabbits.