芍藥甘在家兔體內之藥物動力學研究

Pharmacokinetic study of paeoniflorin in rabbits

中文摘要

Paeoniflorin 是芍藥(paeoniae radix)的主要活性成份，在過去的報告中，被發現有肌肉鬆弛，緩解痙攣，增強記憶認知，免疫調節，抗發炎，抑制固醇類的蛋白結合，抗凝血，降血糖…等作用。儘管 paeoniflorin 在臨床藥理研究上，已有不少的文獻被發表，但是在藥物動力學的研究卻不甚完善。爲了對 paeoniflorin 在生物體內動態有更完整的了解，本實驗以靜脈注射，腹膜腔以及口服的方式投與至家兔，來觀察 paeoniflorin 在家兔體內之藥物動力學表現，進一步探討 paeoniflorin 於家兔體內之生體可用率。

本實驗之分析方法乃利用逆相高效液相層析管柱配合波長 238nm 之紫外光檢測。在血漿濃度範圍爲每毫升 50-50000ng 內，呈現良好的線性關係，r2 = 0.9993；同日內分析之變異係數爲 0.94?3.70%，異日間分析之變異係數爲 2.26?9.03%。而尿液濃度範圍爲每毫升 0.5-500mg 內，也呈現良好的線性關係，r2 = 0.9992；同日內分析之變異係數爲 1.64?3.27%;異日間分析之變異係數爲 2.60?8.11%，顯示此兩者皆爲良好之分析方法。

本研究先以三種不同劑量 0.5 mg/kg， 5mg/kg，25 mg/kg 之 paeoniflorin 靜脈投與至六隻家兔，分析其血漿中濃度，顯示 paeoniflorin 於家兔體內動態符合二室性模式。而在此劑量範圍下呈 Dose-Independent 之藥物動力學特性，各項藥物動力學參數並無統計上之差異,排除半衰期分別爲 27.45 * 5.23，32.06*6.89，31.73*7.92 分鐘， 清除率分別爲 9.78 * 0.96，8.77*0.49，8.63*0.71 ml/min/kg; 其曲線下面積(AUC)分別爲 51.67*5.50，571.93*33.72，2916.65*246.24 mg*min/ml，與劑量之關係圖呈良好的比例現象。(Y=0.04X-0.012，r=0.977，P<0.001)

以腹膜腔內投與劑量 25 mg/kg 之 paeoniflorin 於六隻家兔，分析其結果，發現其血液內 paeoniflorin 之動態與靜脈注射之結果不相同，屬於一室性模式，而其曲線下面積(AUC) 2992.72*419.54 mg*min/ml 與靜脈注射 25mg/kg 之數據比較，獲得腹膜腔內注射之生體可用率有 1.03*0.16。

另外將 paeoniflorin 以口服投與 25 mg/kg 至家兔體內，分析其結果，發現血液中 paeoniflorin 的含量很低。經由體外十二指腸滲透實驗結果顯示，paeoniflorin 經過 7 小時之滲透率僅 0.124*0.044%。故由此結果印證，口服生體可用率不佳之主因乃是腸胃道吸收不良所造成。

英文摘要

Paeoniflorin is the major constituent of paeoniae radix. In previous papers, paeoniflorin has been demonstrated to release muscle spasm, enhance memory, regulate immunity, anti-inflammatory, inhibit protein binding of steroids, anticoagulative and antihyperglycemic effects. Although paeoniflorin has several pharmacological actions, but the pharmacokinetics of paeoniflorin has not been studied well .

An accuracy, simple and specific HPLC method was developed to detect the concentration of paeoniflorin in biological sample firstly. A reverse phase column with UV detection at 238 nm was used in chromatographic separation. The calibration curve of plasma sample shows good linearity within the concentration range of 50 to 50000 ng/ml (r2=0.9993); the calibration curve of urine sample also shows good linearity within the concentration range of 0.5 to 500 mg/ml (r2=0.9992) The coefficients of variation (C.V.) of the intraday and interday validation are all within 10 % .

The pharmacokinetics of paeoniflorin was studied by intravenous administration of three different doses (0.5, 5, 25 mg/kg) in six rabbits, respectively. The plasma concentration-time profiles of paeoniflorin could be described by a bi-exponential equation with each dose. There are no significant difference in pharmacokinetic parameters of paeoniflorin under these three doses. The elimination half-life are 27.45*5.23, 32.06*6.89, 31.73*7.92 min, and systemic clearance are 9.78 * 0.96, 8.77*0.49, 8.63*0.71 ml/min/kg . The area under the curves (AUC) calculated from time zero to infinite are 51.67*5.50, 571.93*33.72, 2916.65*246.24 mg*min/ml. It is proportional to the dose administrated (Y=0.04X-0.012, r=0.977, P<0.001). It indicated that paeoniflorin may behave dose-independent pharmacokinetics between 0.5?25 mg/kg IV injection .

In addition, 25mg/kg of paeoniflorin was intraperitoneal administered to rabbits . The plasma concentration-time profiles could be also fitted by one-compartment model . The area under the curve (AUC) was 2992.72*419.54 mg*min/ml. Comparing with that of intravenous administration in the dose of 25mg/kg , the absolute bioavailability of paeoniflorin was 1.03*0.16 through the I.P. administration .

After oral administration of paeoniflorin 25 mg/ml , the number of paeoniflorin in plasma was very low . According to duodenum permeability, the ratio of paeoniflorin permeability only was 0.124*0.044% , it is suggested that poor absorption in intestine results low bioavailability from oral administration of paeoniflorin .