Diphenidol 在家兔體內之藥物動力學研究

Pharmacokinetic study of diphenidol in rabbits

中文摘要

Diphenidol 是一個合成之抗眩暈劑及止吐劑,具極佳之特異性與療效,上市至今三十多年,已成爲抗眩暈藥物中之首選藥,臨床應用上已非常廣泛及普遍;但是其基礎研究並不甚完善,例如在安定性,分析方法及藥物動力學研究等報告上,至今仍無相關專題之文獻發表。爲了對 Diphenidol 在生物體內動態有基本的了解,本實驗以靜脈注射,腹膜腔以及口服的方式投與至家兔以觀察 Diphenidol 在家兔體內之藥物動力學表現。

本實驗之分析方法乃利用正相高效液相層析管柱配合波長 220nm 之紫外光檢測。在血漿濃度範圍爲每毫升 10-2000ng 內,呈現良好的線性關係,r = 0.9998。同日內分析之變異係數爲 0.91%-5.09%;異日間分析之變異係數爲 1.12%-7.79%,顯示此爲良好之分析方法。

本研究先以三種不同劑量 1 mg/kg,
3 mg/kg, 6 mg/kg 之 Diphenidol 靜脈投與於六
隻家兔,分析其血漿中濃度,顯示 Diphenidol 家兔體內動態符合二室性模式。 劑量 1 mg/kg 和 3mg/kg 之各項藥物動力學參數並無統計上之差異,平均分布相半衰期爲 5.87*3.05 分鐘,排除半衰期爲 69.74 * 11.63 分鐘,分佈體積爲 11.55 * 2.24 liter/kg,清除率爲 123.01 * 31.31 ml/min/kg; 而劑量 6mg/kg 之排除半衰期 96.74*15.00 分鐘與清除率 91.54*23.17 ml/min/kg 則顯示出統計上之差異 (p<0.05) 。而其曲線下面積(AUC)在三個劑量分別爲 9002±2077, 24412±5551, 69279±17979 ng*min/ml 。其與劑量之關係圖亦呈現明顯不成比例的現象 (p<0.001)。

以腹膜腔內投與劑量 6 mg/kg 之 Diphenidol 於六隻家兔,分析其結果,發現其血液內 Diphenidol 之動態與靜脈注射之結果接近, 亦符合二室性模式, 以其曲線下面積(AUC) 9693±1533(ng*min/ml)與靜脈注射 1mg/kg 之數據比較,獲得腹膜腔內注射之生體可用率僅有 0.25。

另外將 Diphenidol 以口服投與至家兔後,發現血液檢品中並無 Diphenidol 存在,僅劑量高達 150mg/kg 時,於 Diphenidol 之滯留時間前約 0.7 分鐘處出現一巨大峰線。此外將劑量 75mg/kg 口服投與之血漿以 β-Glucuronidase 水解後分析,發現於 Diphenidol 滯留時間前 0.7 分鐘亦檢測出同一峰線。由此結果推測, Diphenidol 口服至胃腸道中時,因首渡效應影響,可能經快速的胃腸道生體轉變後,再進行酵素

性轉變而產生其共軛物質,以此形態存在家兔體內,導致口服 Diphenidol 後血中濃度消失之現象。

英文摘要

Diphenidol is a synthetic antivertigo and antiemetic agent. It apparently exerts a specific effect in the therapy of vertigo, nausea and vomiting. Although diphenidol is used broadcast in clinical application for more than thirty years, the relative reports are not available, for example: stability, analytical methods and pharmacokinetic data in past literature are still lacking.

An accuracy, simple and specific HPLC method was developed first to detect the concentration of diphenidol in biological sample. A normal phase column with UV detection at 220nm was used in chromatographic separation. The calibration curve shows good linearity within the concentration range of 10 to 2000 ng/ml. The coefficients of variation (C.V.) of the intraday and interday variation are all within 8 %.

The pharmacokinetics of diphenidol was studied by intravenous administration of three different doses (1, 3, 6mg/kg) in six rabbits, respectively. The plasma concentration-time profiles of diphenidol could be described by a bi-exponential equation with each dose. There are no significant difference in pharmacokinetic parameters of diphenidol under the dose of 1mg/kg and 3mg/kg.The distribution half-life and elimination half-life are 5.87* 3.05 min and 69.74* 11.63 min. The volume of distribution is 11

In addition, 6mg/kg of diphenidol was intraperitoneal (I.P.) administered to rabbits for the bioavailability study. The plasma concentration-time profiles could be also fitted by two-compartment model. The area under the curve (AUC) was 9693±1533(ng*min/ml).Comparing with that of intravenous administration in the dose of 1 mg/kg, the absolute bioavailability of diphenidol was 0.25 through the I.P. administration.

After oral administration of diphenidol, there was no diphenidol appear in the plasma under the dose of 150mg/kg. A giant peak just about 0.7min ahead the retention time of diphenidol in HPLC analysis. This unknown peak was also detectable in the plasma sample of 75mg/kg P.O. dosing rabbit after b-glucuronidase hydrolysis. According to our results, it is suggested that most of diphenidol convert rapidly into a major unknown metabolite and that quickly glucuronidate as the major compound exist in

plasma