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• 中文摘要

Pentoxifylline(PTX)爲目前臨床用於促進血流循環之藥物,構造式含 Ketone 基之 Xanthine,在體內還原代謝成爲 Penthydroxifylline(PTH),二者皆具有血液循環、增加紅血球變形能力、減少血液黏滯性。本研究之目的是欲利用化學合成(.plmin.)-PTH 經光學分割製備(+)-PTH 及(-)-PTH。並同時研發 PTH 光學異構物於血漿中定量方法,用於探討 PTX 於人體還原代謝成 PTH 時是否具立體選擇現象存在。 以 NaBH/sub 4/將 PTH 還原成(.plmin.)-PTH,再與 Carbobenzyloxy-L-proline(L-CBP)反應衍生成爲酯類之 Diastereoisomers,經製備級 HPLC 來分離並分別收集後,在強鹼下水解,可得光學活性之(-)-及(+)-PTH,經光譜分析及旋光測定,確定其構造及光學純度。藉 HPLC 方法進行定量血漿(+)-及(-)-PTH 之濃度;取 0.5mL 的血漿,先以 n-hexane 沖洗,再以 CHCl/sub 2/萃取後,再與 L-CBP 反應,並以 Carbonyldiimidazole 爲催化劑,於 40.degree.C 下反應二小時後,注入 HPLC,應用 C/sub 18/之層析管並以 CH/sub 3/OH :CH/sub 3/CN:H/sub 2/O(60/1/39)當移動相, UV 檢測器波長定於 275nm 下進行偵測,此方法之線性關係良好(血漿濃度範圍爲 45-750ng/mL), S-(+)-及 R-(-)-PTH 之分離度(.alpha.=1.13)和分析定量之精確度方面皆有不錯的結果 C.V.%<10%)。溶媒萃取回收率約 80-90%。當 PTX 緩效釋出製劑(400mg)口服頭予八位健康男性志願者,連續五天,每天二次,測其血漿於 24, 48,72,96 小時之 S-(+)-及 R-(-)-PTH 個別濃度,發現八位志願者的血漿所含的皆爲 S-(+)-PTX ;並未檢測出任何的 R-(-)-PTH,本研究顯示 Pentoxifylline 在人體還原代謝具立體專一性。

• 英文摘要

Pentoxifylline (PTX), an orally active haemorhealogical agent is primarily metabolized to pharmacologically active penthdroxifylline (PTH) in man. Both PTX and PTH could enhance blood microcirculation, increase erythrocytes flexibility and lower blood viscosity.

It would be of interest to know the stereochemical course of reduction of pentoxifylline in man. The present research will report on the metabolic stereoselectivity in pentoxifylline reduction in man. (.plmin.)-PTH was prepared from PTX by NaBH/sub 4/ and derivatized with carbobenzyloxy-L-proline (L-CBP) to form diastereoisomeric esters which were separated by preparative silica gel HPLC. Each PTH enantiomer was obtained after alkaline hydrolysis. Human plasma (0.5mL), washed with n-hexane was extracted with methylene chloride and then reacted with L-CBP and carbonyldiimidazole (CDI) at 40.degree.C for 2 hours. A C/sub 18/ column was used to assay the PTH enantiomers with methanol/acetonitrile/water (60/1/39) as the mobile phase. UV detection was used to monitor at 275nm. This assay method show a good linear relationship over the range of 45-750ng/mL and satisfactory resolution (.alpha.=1.13) and presision (C.V.<10). The recovery of (+)-PTH and (-)-PTH by organic solvent extraction is 80-90%. Sustained release product of PTX (400mg) was administrated to eight healthy male volunteers every 12 hours for 5 days, and their plasma concentrations of (+)-PTH and (-)-PTH at 24, 48, 72, 96 hrs were measured. The results demonstrated that only the S-(+)-PTH isomer was found in each one of all volunteer plasma. The present study concluded that the stereochemistry of pentoxifylline reduction is stereospecific in man.