非瑟素動力學及黃酮類化合物
對於環孢靈動力學影響之構效關係

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摘要

非瑟素(Fisetin)**為一具許多優越活性之天然黃酮類化合物，本研究以大白鼠為模型，探討非瑟素靜脈注射及口服給藥後之動力學行為。血清中非瑟素代謝物之定量，係將檢品於** 37**℃下以** β-glucuronidase **水解** 6 **小時或以** sulfatase **水解** 4 **小時後，利用高效液相層析法定量。非瑟素靜脈注射給藥後，非瑟素** sulfates **之平均血藥面積為** glucuronides **之** 4.6 **倍，而原形藥僅為** glucuronides **之三分之一，顯示非瑟素靜脈注射給藥後主要係以** sulfates **結合態代謝物存在於全身循環中。**

非瑟素口服給藥後吸收迅速，原形藥平均 T_{max} **為** 5 **分鐘，絕對生可用率為** 44.1 % **非瑟素** sulfates **之平均血峰濃度為** glucuronides **之** 2.6 **倍，平均血藥面積為** glucuronides **之** 2.2 **倍，顯示非瑟素口服給藥後主要亦**

以 sulfates 之結合態代謝物形式存在於體內。本研究結果顯示，此類結合態代謝物於體內發揮藥理作用之重要性不可忽略。

環孢靈為一強效免疫抑制劑，治療指數極小，任何改變環孢靈吸收之因素，皆可能危及患者之生命安全。本研究以特定結構之黃酮類化合物 5-hydroxyflavone、flavone、quercetin、fisetin 及 morin，探討其對於環孢靈動力學之影響，並探討其構效關係。結果顯示，各黃酮類化合物與環孢靈併用後，導致增加或降低環孢靈吸收之作用。於 40 mg/kg 或 50 mg/kg 劑量時，黃酮類結構中 A 環第五位之酚基存在與否，不影響其與環孢靈之交互作用，B 環上 3'與 4'鄰位酚基較 2'與 4'間位酚基，更明顯降低環孢靈之吸收。於 20 mg/kg 劑量時，A 環第五位酚基明顯增強對環孢靈吸收增加之影響，B 環上 2'與 4'間位酚基顯著增加環孢靈之吸收，而 3'與 4'鄰位酚基反而顯著降低環孢靈之吸收。

本研究利用體外翻腸試驗，探討 5-hydroxyflavone、flavone 及 morin 等黃酮類化合物影響環孢靈生可用率之機轉，是否與影響腸內 Pgp 之活性有關。實驗結果顯示，對腸道 Pgp 的作用無法解釋 5-hydroxyflavone、flavone 降低環孢靈吸收之現象，推測可能尚有其他機轉。影響環孢靈吸收之體內機制極為複雜，尚待更進一步研究以釐清交互作用之主要機轉。吾人建議為確保環孢靈之療效與安全，器官移植患者應避免併服富含黃酮類之中草藥或保健食品。

Pharmacokinetics of Fisetin and Structure-Activity Relationship for the Effect of Flavonoids on the Cyclosporine Pharmacokinetics

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ABSTRACT

Fisetin is a bioactive natural flavonoid. In this study, the pharmacokinetics of fisetin was investigated in rats. The serum concentrations of fisetin were assayed by HPLC method after incubation at 37℃ for 6 hours with glucuronidase or 4 hours with sulfatase. After intravenous administration of fisetin, the AUC of fisetin sulfates was 4.6-fold glucuronides, whereas the parent form only one-third of glucuronides, suggesting that the major molecules circulating in blood were fisetin sulfates.

When fisetin was administered orally, T_{max} of the parent form was 5 minutes, indicating that fisetin was absorbed rapidly. The absolute bioavailability of fisetin was 44.1 %, and the major molecules circulating in bloodstream were fisetin sulfates. The C_{max} of fisetin sulfates was 2.6-fold of

glucuronides, and the AUC was 2.2-fold of glucuronides. It is suggested that sulfates of fisetin be more focused than fisetin for *in vitro* pharmacological studies in order to have a more accurate model for *in vivo* systems.

Cyclosporine is a widely used immunosuppressant with a narrow therapeutic window. Any factor affecting the absorption or disposition of cyclosporine is therefore of therapeutic importance. The present study attempted to measure the influence of coadministration of flavonoids including 5-hydroxyflavone, flavone, quercetin, fisetin and morin on the pharmacokinetics of cyclosporine in rats, and the structure-activity relationship was explored.

Our results showed that each flavonoid investigated resulted in alteration of cyclosporine pharmacokinetics. The structure-activity relationship was established. At dose of 40 mg/kg or 50 mg/kg, the presence of 5-OH didn't affect the interaction with cyclosporine, the presence of 3',4'-dihydroxy groups significantly decreased cyclosporine bioavailability in greater extent than 2',4'-dihydroxy groups. At dose of 20 mg/kg, the presence of 5-OH significantly reinforced the increase of cyclosporine bioavailability, the presence of 2',4'-dihydroxy groups significantly increased cyclosporine bioavailability, whereas the presence of 3',4'-dihydroxy groups significantly decreased that.

A study using the everted intestinal sac was carried out to dissect the mechanisms of flavonoids-cyclosporine interaction. Our results showed that the *in vitro* evidence could not explain the *in vivo* effects of 5-hydroxyflavone and flavone on the fate of cyclosporine. It was conjectured that there were other mechanisms involved. It is suggested that concurrent use of flavonoids-containing herbs or dietary supplements with cyclosporine or other CYP3A4/P-gp substrates should be avoid.