行政院國家科學委員會專題研究計畫成果報告

Fluconazole 對 Methotrexate 藥動學性質影響之探討

Interaction between Fluconazole and Methotrexate in Rabbits

計畫編號：NSC 90-2320-B-002-090
執行期限：90 年 8 月 1 日至 91 年 7 月 31 日
主持人：林君榮　台大醫學院臨床藥學研究所

一、中文摘要

未樂探討 CYP3A4/P-gp 與抗癌藥品在腎臟與腸道可能的作用關係， 在併用或未併用 fluconazole 下，以靜脈注射及口服的方式投與 methotrexate 到兔子體內。實驗的結果顯示併用 fluconazole 後，靜脈注射 methotrexate 的半衰期及分佈體積延長。7-hydroxy methotrexate 的血中濃度-時間曲線下的面積成下降的現象。相似的結果也在口服投藥後發現。這些結果顯示 fluconazole 的確會與 methotrexate 作用，且其可能位置及可能在腸道及腎臟部位，進一步的試驗是必須的。

關鍵詞：Fluconazole, Methotrexate

二、英文摘要 (Abstract)

To investigate the interaction of CYP3A4/P-gp and antineoplastics in both the intestine and the kidneys, methotrexate was given orally and intravenously to rabbits with or without the presence of fluconazole. As a result, the concomitant used of fluconazole significantly increase the half-life and volume of distribution of methotrexate after intravenous administration. The area-under-the curve of 7-OH methotrexate also decreased after the fluconazole treatment. However, the extent did not reach statistical significance. After oral administration, the area-under-curve of methotrexate also decrease after the administration of fluconazole. Our results indicate that the fluconazole reduce the bioavailability of methotrexate from both intravenous and oral routes, which also suggests that the interaction lies in both renal and intestinal levels.

Keywords: Fluconazole, Methotrexate

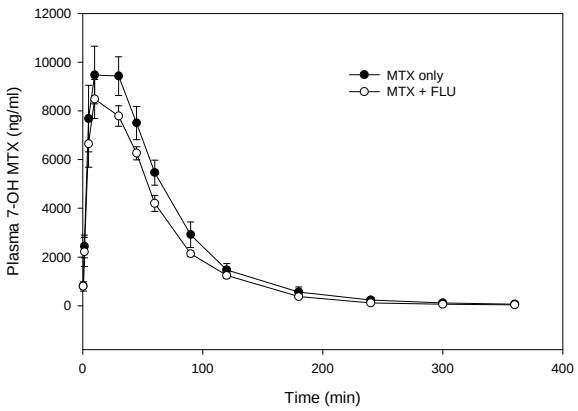
三、緣由與目的

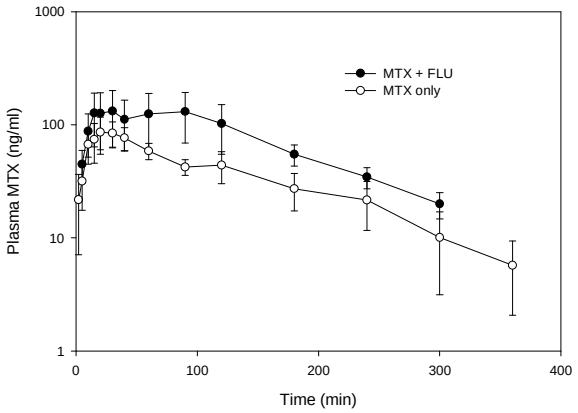
It has been proposed that P-gp and CYP3A4 act in a coordinated manner to determine pharmacokinetic variability and play a role in drug interaction (Soldner et al. 1999). Using human P-gp overexpressing renal cells, LLC-GA5-COL150, it was shown that itraconazole, a CYP3A4 inhibitor, was able to reverse the P-glycoprotein-mediated resistance of vinblastine, daunorubicin and doxorubicin (Takara et al. 1999). In addition, itraconazole has also been shown to decreased renal clearance of digoxin by the inhibition of P-glycoprotein-mediated digoxin secretion in the renal tubular cells (Jalava et al., 1997). However, since these studies were performed using in vitro models, the in vivo consequences of this barrier system is still unknown. In addition, despite numerous studies being reported regarding the role of intestinal CYP3A4 and P-gp as barriers to oral drug delivery (Benet et al. 1999), the renal scenario of this concerted barrier is still not clear. Kidney is an important organ not only in the disposition but also in the reabsorption of given compounds. The renal handling of renal excreted compounds may contribute significantly to the pharmacokinetics of given drugs. In order to see whether it would be significant in vivo. The purpose of this study is to evaluate the influence of CYP3A4

inhibitors on the pharmacokinetics of antineoplastics in rabbits and the possible clinical relevance. Rabbits are chosen as a model is due to its similarity in the metabolism of methotrexate with humans.

四、結果與討論

After intravenous administration, the half-life of methotrexate increase from 56.5±11.5 min to 124.9±19.8 min in the presence of fluconazole (P<0.001). Volume of distribution also increased from 553±90 ml to 664±59 ml in the presence of fluconazole (P<0.05). The AUC of 7-OH methotrexate decreased from 12.5±3.8 ug*hr/ml to 9.9±1.3 ug*hr/ml. After oral administration, the AUC of methotrexate also decreased while the extent needs to be clarify due to the limited number. Since the bioavailability of methotrexate is dose-dependent. The interaction between fluconazole and methotrexate is also expected to be dose-dependent. Further study is required to further elucidate the extent and mechanisms of interaction between fluconazole and methotrexate.





五、計劃成果自評

本計劃實際執行期間自 2002 年 1 月起，主要的瓶頸典在於 methotrexate 及其代謝物 7-OH methotrexate 於血中濃度的分析。由於兔子口服 methotrexate 後的可用率頗低，因此給予臨床劑量後 methotrexate 的血中濃度幾乎測不到，在增加劑量後，情況則有改善。然而為了日後相關的試驗能順利進行，找出更靈敏的測量方法是必須的。目前我們也正積極往這方面努力進行。無論如何，本研究的姐果顯示 fluconazole 與 methotrexate 確實在腎臟及腸道有作用關係存在，這樣的結果是首次發現的，而且職得以 in vitro 的 models 作進一部機轉的確認及探討。

六、參考文獻

Benet LZ, Izumi T, Zhang Y, Silverman JA, Wacher VJ (1999) Intestinal MDR transport proteins and P-450 enzymes as barriers to oral drug delivery. J Control Release 62: 25-31

Jalava et al., (1997): Itraconazole decreases renal clearance of digoxin. Therapeutic Drug Monitoring. 19(6): 609-613.

Soldner, A., Christians, U., Susanto, M., Wacher, V. J., Silverman, J. A., and Benet, L. Z. (1999) Grapefruit juice activates P-glycoprotein-mediated drug transport. Pharmaceutical Research 16(4): 478-485

Takara, K., Tanigawara, Y., Komada, F., Nishiguchi, K., Sakaeda, T., and Okumura, K. (1999) Cellular pharmacokinetic aspects of reversal effect of itraconazole on P-glycoprotein-mediated resistance of anticancer drugs. Biol. Pharm. Bull. 22(12): 1355-1359.

行政院國家科學委員會補助專題研究計畫成果報告

※※※※※※※※※※※※※※※※※※※※※※※※※※
※　　　　　　　　　　　　　　　　　　　　　　　　※

Fluconazole 對 Methotrexate 藥物動力學影響之探討

※　　　　　　　　　　　　　　　　　　　　　　　　※
※※※※※※※※※※※※※※※※※※※※※※※※※※

計畫類別：■個別型計畫　　□整合型計畫

計畫編號：NSC 90－2320－B－002－090－

執行期間：90 年 8 月 1 日 至 91 年 7 月 31 日

計畫主持人：林君榮

本成果報告包括以下應繳交之附件：

□赴國外出差或研習心得報告一份

□赴大陸地區出差或研習心得報告一份

□出席國際學術會議心得報告及發表之論文各一份

□國際合作研究計畫國外研究報告書一份

執行單位：台大醫學院臨床藥學研究所

中　華　民　國　91　年　10　月　25　日