Warfarin 與銀杏葉萃取物(EGb 761)交互作用之評估

Evaluation of the Interaction between Warfarin and Ginkgo biloba extract (EGb 761)

中文摘要

中草藥的使用愈趨廣泛，因此在探討中草藥與西藥合併使用後，是否會產生交互作用就成爲重要課題。目前已有 6 個因服用銀杏葉萃取物而造成出血之臨床案例報告，其中一例爲病人併服 warfarin 後產生。因此本研究以下列 3 項結果評估 Warfarin 與標準規格之銀杏葉萃取物(EGb 761)的交互作用存在與否，並確立 EGb 761 在血液學上的安全性；以做爲臨床醫療人員及研究者解決此一課題的基礎：(1)大白鼠模式下，看 EGb 761 對 warfarin 藥物動力學及臨床監測參數 PT、INR 值的影響(2)收集臨床實例分析 EGb 761 對 warfarin 監測參數 INR 數值的影響(3)利用健康志願受試者服用 EGb 761 觀察凝血功能檢驗數值(platelet counts, INR, bleeding time, clotting time)之變化。藥物動力學多重劑量模式下，EGb 761 明顯降低 warfarin 濃度曲線下面積(AUC)、增加清除率(CL/F)及分佈體積(Vd/F)；相同的，最大 PT 值及 PT 曲線下面積在 EGb 761 存在下之結果亦明顯降低。共 21 個臨床實例之分析結果顯示 EGb 761 對已服用 warfarin 病患之 INR 值影響並無影響。而 12 位健康受試者在連續服用臨床治療建議劑量下之 EGb 761(120 mg/d) 28 天，所有凝血功能指標變化皆未達到臨床上意義。因此治療建議劑量下之 EGb 761 不會干擾正常人凝血功能；但因爲在大白鼠模式下觀察到長期服用高劑量之 EGb 761 對 warfarin 存在有藥物動力學交互作用及對 warfarin 臨床監測參數 PT、INR 值有下降之影響，所以在產生交互作用機制尚未確定及無完整人體臨床試驗結果報告之情況下；建議在二藥併用後密切監測 PT、INR 是必須的。

英文摘要

The potential herb-drug interaction should be screened since the usage of herbal products became popular. Six bleeding cases have been reported with the use of Ginkgo biloba extract, and one was linked to concurrent use of warfarin. The objective of the study was to evaluate the effect of EGb 761, a standardized Ginkgo biloba extract, on warfarin and coagulation function. To recognize the influence of EGb 761 on pharmacokinetics and pharmacodynamics of warfarin, changes in warfarin plasma concentration and prothrombin time (PT) after coadministration with EGb 761 were studied in a Sprague Dawley model. Clinical cases with concurrent use of two drugs were also retrospectively reviewed to evaluate the relationship between EGb 761 and international normalized ratio (INR). Changes of coagulation parameters, including platelet counts, INR, bleeding time, clotting time, was determinated in twelve healthy volunteers taking EGb 761 120 mg once daily for 28

days. A significant decrease in the area under plasma concentration-time curves (AUC) from 22.54±2.67 to 17.27±1.64 μg·hr/ml, was detected with coadministration of EGb 761 under a multiple dosing design ($p=0.002$). Similarly, maximal PT and area under the PT versus time curve were significantly reduced with EGb 761 treatment group ($p=0.001$). There was no significant change in INR after adding EGb 761 in 21 clinical cases ($p=0.551$). No clinically significant change in coagulation parameters was observed when finishing the regimen. No clinically significant influence of EGb 761 on warfarin was found on clinical cases and healthy volunteers. As the animal results of decreased pharmacokinetic and pharmacodynamic effects of warfarin, careful monitoring of PT was recommended with concurrent use of EGb 761 and warfarin.