精神分裂症病患併用喹;硫平之肝功能及血中濃度監測分析

Liver Function Tests and Therapeutic Drug Monitoring in Schizophrenic Patients on Quetiapine Combination Therapy

中文摘要

過去研究指出服用喹硫平（quetiapine；QTP）患者可能發生無症狀肝功能異常現象，並可造成糖尿病的發生。而經比較原始血糖正常或異常之精神分裂症病患族群服用 QTP 後，兩族群之生化指數變化不同；且同時服用水飛薊（silymarin；SB）與口服降血糖藥物的糖尿病病患之血糖控制情形較佳；然尚未有研究報告監測臺灣地區服用 QTP 之精神疾病患者肝功能及分析 QTP 血中濃度。故本研究欲了解 QTP 對肝功能的影響，並分析併用 SB 一週後對生化代謝指數與 QTP 血中濃度之影響。研究設計：本臨床試驗爲經臺北醫學大學人體試驗委員會核可，於臺北市某私立康復之家依照核可內文執行，並獲得病患簽署之同意書；收錄條件須爲經醫師診斷之精神分裂症病患。給藥設計如下：試驗開始的一週期間逐漸調升劑量至 QTP 300 mg/day，並維持該劑量一週(第 15 日)後，再併用 SB (70 mg/day) 7 日（第 22 日）。分別於試驗第 1、15、22 日檢測血液生化值，並於試驗第 15、22 日抽血進行 QTP 療劑監測（therapeutic drug monitoring）（服藥後第 0 至 8 小時）。共收錄受試者 13 人，平均年齡爲 46.6 ± 10.8 歲，體重爲 66.6 ± 9.5 公斤；經剔除部份同時服用 clozapine 之病患後，此受試群（10 人）平均年齡、體重爲 48.9 ± 11.3 歲、65.9 ± 9.4 公斤；結果顯示：此受試群服用 QTP 兩週後，飯後胰島素值下降、空腹胰島素值上升、quantitative insulin sensitivity check index (QUICKI)下降、aspartate aminotransferase (AST)或 alanine aminotransferase (ALT)上升超過 10%者共 10 人；使用 SB 一週後，空腹胰島素值、QUICKI 數值分別較未併用前之 basal 值下降、上升，且 AST 或 ALT 上升超過 10%者剩 3 人。不論是否有剔除同時服用 clozapine 之病患，併用 SB 前後 QTP 療劑監測與臨床藥物動態學（pharmacokinetics）數值並無顯著差異。再依第 1 日血糖數值，再將病患區分爲原始血糖異常（≧100 mg/dL）或正常二族群；經比較後，原始血糖正常之精神分裂患者在第 15 日呈現 AST 或 ALT 上升超過 10%者共 4 人，但無受試者在第 22 日 AST 或 ALT 上升超過 10%。原始血糖異常者之 QTP 平均最高血中濃度值(Cmax)較原始血糖正常者低（p=0.04），併用 SB 後則兩組之 Cmax 無顯著差異。又原始血糖異常者總膽固醇值比未併用 SB 前高（p=0.04），但未達臨床異常標準；而原始血糖正常者 QTP 分布體積值比未併用 SB 以前低（p=0.03），兩者皆達統計上顯著差異。從上述結果推論：（1）併用 SB 可減少服用 QTP 後觀察到肝功能異常病患之人數，尤其對原始血糖正常之精神分裂患者較爲明顯;（2）血糖正常患者短期併用 SB (70 mg/day)與 QTP 兩藥物無需調整 QTP 劑量；血糖異常者則建議進行療劑監測，作爲 QTP 劑量調整之參考。

英文摘要
It was reported that quetiapine (QTP)-treated patients presented asymptomatic liver dysfunction and new-onset diabetes mellitus. It was also shown that QTP treatment may change metabolic parameters of schizophrenic patients with or without hyperglycemia differently. Blood glucose controls of oral antidiabetics may be improved while diabetic patients co-medicated with silymarin (SB). The purpose of this study was to monitor the liver function changes and therapeutic drug concentrations after QTP treatments, and after QTP co-medicated with SB treatments in Taiwanese schizophrenic patients. This clinical trial was approved by Taipei Medical University Institutional Review Board and each patient's informed consent was obtained. This study was conducted in a private long-term care facility in Taipei, Taiwan, and patients diagnosed with schizophrenia were recruited. Study design: QTP dosage was titrated up to 300 mg/day within one week. Patients were maintained on this dose until the end of the study. SB (70 mg/day) was added on from day 15 to day 22. Blood samples were collected from patients at day 1, 15, and 22 to test metabolic parameters and liver function. Samples of day 15 and 22 were further analyzed for QTP therapeutic drug monitoring (TDM) at 0~8 hours postdose. There were thirteen patients recruited, and their average age and body weight were 46.6 ± 10.8 years old and 66.6 ± 9.5 kg, respectively. After three patients co-treated with clozapine were excluded, patients' (n=10) average age and body weight were 48.9 ± 11.3 years old and 65.9 ± 9.4 kg, respectively. Results: After 2 weeks of QTP treatment (day 15), the patients' average postprandial insulin levels (PPI) decreased significantly (p=0.03) while number of quantitative insulin sensitivity check index (QUICKI) decreased and fasting insulin concentration increased. There were ten patients whose aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased more than 10% at day 15. Fasting insulin concentration and QUICKI of samples collected at day 22 decreased or increased, respectively, when compared to those collected at day 15. There were only three patients whose AST or ALT increased more than 10% at day 22. There were no significant differences in QTP TDM and pharmacokinetic parameters following QTP treatments with or without SB whether patients using clozapine or not. Furthermore, according to their day-1 fasting plasma glucose (FPG), patients were subgrouped into non-hyperglycemic group or hyperglycemics (FPG≧100 mg/dL). In non-hyperglycemic schizophrenic group, there were four patients whose AST or ALT increased more than 10% at day 15, but there was no one had increased AST or ALT more than 10% at day 22. Average peak QTP concentration (Cmax) of hyperglycemic patients were lower than the non-hyperglycemic patients (p=0.04). However, when patients co-treated QTP and SB, the average Cmax became similar between two groups. Moreover, at day 22, total cholesterol levels were statistical significantly

higher (p=0.04), but still within normal ranges, than that of samples collected on day 15 in hyperglycemic patients. Mean volume of distribution of the non-hyperglycemic patients was significantly lower (p=0.03) at day 22 than that of samples collected on day 15. The results suggest that: (1) Number of schizophrenic patients with liver function abnormality observed after QTP treatment may be reduced when SB was co-administered for one week, especially in non-hyperglycemic patients. (2) There was no need to adjust QTP therapeutic dosage in non-hyperglycemic schizophrenic patients when the duration of their combination treatment of QTP (300 mg/day) with SB (70 mg/day) was no longer than one week. But TDM for QTP is suggested in schizophrenic patients with hyperglycemia.