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Relationship among serum concentrations, doses and clinical responses of quetiapine fumarate in patients with schizophrenia

GUO Rui-Chen, FU Chong-Ming[1]

Department of Clinical Pharmacology, Qilu Hospital, Shandong University, Jinan 250012, Shandong, China;
[1]Pharmacy of Shandong Mental Health Center, Jinan 250014, Shandong, China

ABSTRACT **AIM:** To establish a method for determination of serum concentrations of quetiapine fumarate in patients with schizophrenia of different doses and to study its relationship with clinical response. **METHODS:** A HPLC method was used to determine serum concentrations of quetiapine fumarate in 76 patients with schizophrenia before or after 2, 4, 6-week treatment and its therapeutic efficacies were measured by BPRS. **RESULTS:** The standard curve was linear within the concentration range of 0.05—0.5 mg·L^{-1} of quetiapine fumarate in serum (r =0.9850). The serum concentrations of quetiapine fumarate were proportionally increased with the daily dose of 50—450 mg, but there was no significant correlation with age and sex. The optimal range estimated was 0.126—0.350 mg·L^{-1}. **CONCLUSION:** The assay is simple, precise and suitable for therapeutic monitoring of quetiapine fumarate and the optimal concentration window is 0.126—0.350 mg·L^{-1} in treatment of patients with schizophrenia.

KEY WORDS pharmacodynamics; quetiapine fumarate; serum drug concentration; schizophrenia; chromatography; HPLC

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Schizophrenia represents a group of ill-defined, chronic idiopathic, psychotic disorders characterized primarily by distinctive damages in reasoning. Symptoms typically become evident during adolescence or early adulthood. The pharmacological treatment of schizophrenia is indicated when symptoms result in significant disorder of the patients' ability to perform important daily routine at work or at home. Quetiapine fumarate is a relatively new antipsychotic drug of the dibenzothiagepine with properties of minimal extrapyramidal side effects, absence of tardy dyskinesia and minimal elevation of serum prolactin level[1].

Although the safety and effectiveness of quetiapine fumarate as a standard and atypical antipsychotic agent have been well studied in adult population, few relative studies have focused on the therapeutic and adverse effects, serum concentrations, doses and clinical responses of the agent in population of children or adolescents, males or females with psychotic disorders. Quetiapine is extensively metabolized in human, with less than 1% of the administered dose excreted unchanged in the urine and feces, primarily by cytochrome P4503A4 to its major inactive sulfoxide metabolite, and to a much lesser extent, by cytochrome P4502D6 to its demethyl metabolites[2].

The aim of this study is mainly to establish a simple, specific and sensitive method for the determination of serum concentrations of quetiapine to individualize dosage regimen for different groups of human population and to evaluate the relationship of serum concentrations of quediapine, dosage, sex and age of patients with clinical responses in purposes of routine therapeutic drug monitoring and pharmacokinetic researches.

1 METERIALS AND METHODS

1.1 Patient population A total of 76 male or female patients were enrolled in this study. These patients had to

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GUO Rui-Cheng, correspondence author, male, professor, tutor of master, engaged in pharmacokinetics and clinical pharmacology.
Tel: 0531-6109975 E-mail: Guo-rc@16900.net

have a chronic or intermittent psychosis with a documented clinical diagnosis of schizophrenia in accordance with CCMD-3. Their mean age was 39 ±15 yr, body weight was 55 ±7 kg and disease course was 23 ±19 mon. The process and purpose of this study were fully explained to every patient involved and oral informed consent was conducted. The data from patients who met the trial inclusion criteria, completed the study in compliance with the protocol were valuable.

1.2 Dosage regimen All patients enrolled in this study were grouped on age (group A and group B) to distinguish any pharmacokinetic differences based on age. Ongoing treatment with antipsychotics other than quetiapine was discontinued 3 days before quetiapine medication. Quetiapine fumarate tablets were administered starting from 50—100 mg labeled daily dose, escalated to 300 mg within 7—14 days.

1.3 Blood sampling and clinical effects assessing Blood samples were obtained in heperinized tubes and the clinical effects assessment, including BPRS measurement, was carried out before and after 2, 4, 6-week treatment of quetiapine fumarate. Serum samples were inverted immediately, centrifuged at a speed of 3000 rounds per minute for 10 minutes and frozen under −20 ℃ until analysis.

1.4 Determination of the serum concentration of quetiapine fumarate Concentrations of quetiaping fumarate in serum were determined by modified high performance liquid chromatographic method and extraction procedures. The standard curve was linear within the range of 0.05—0.5 mg·L^{-1} of quetiapine fumarate in serum. Quetaipine was eluted by HPLC Beckman System Gold with a Hypersil ODS-C_{18} column (250× 4.5 ID, 5 μm) and a mobile phase of methanol and water (73 ∶27, v/v). The ultraviolet detector was set to a wavelength of 254 nm.

1.5 Statistical analysis All data were presented as mean ±s. Serum concentration data were analyzed by a nonlinear mixed effects modeling program, and the response relationship of quetiapine fumarate versus time, dose and sex were evaluated with t-test and χ^2-test.

2 RESULTS

2.1 Precision and recoveries The intra and inter-day precisions were performed by analyzing three concentrations of quatiapine 5 times each. The precisions and recoveries were as shown in Tab 1. Linear range was 0.05—0.5 mg·L^{-1}. The LOQ was 0.005 μg.

Tab 1 Precision and recoveries of quetiapine fumarate (n= 5)

Concentration of standard /μg·ml^{-1}	Determined concentration /ng·ml^{-1}	Recovery /%	Intra-day RSD /%	Inter-day RSD /%
0.1	100.1±0.7	101.2±7.1	5.28	6.71
0.2	200.2±1.2	100.8±4.0	4.23	6.05
0.4	400.6±3.8	99.3±6.3	6.20	5.29

2.2 Chromatographic behavior The HPLC profiles of quetiapine standard (A), spiked blank serum (B) and patient serum (C) were shown as Fig1. Under above chromatographic conditions, the retention time of quetiapine was 6.1 minute at flow rate of 1.0 ml·min^{-1} and ambient temperature.

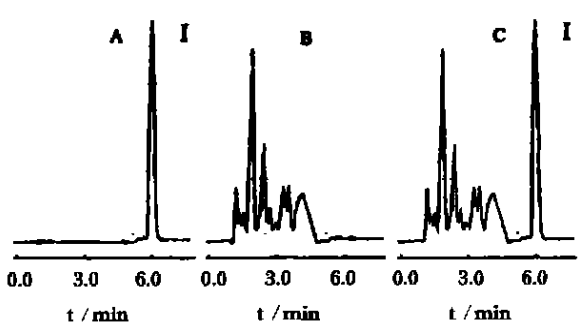

Fig 1 Chromatograms of quetiapine in standard solution (A), spiked blank serum (B) and patient serum(C)

2.3 Serum concentrations versus age and sex Tab2 illustrated the response relationship of serum concentration of quetiapine fumarate versus age and sex. Neither age nor sex was related to serum concentration with statistic significance, but the big variances between male and female patients with same doses were existed.

Tab 2 Relationship between serum concentrations of quetiapine fumarate and age or sex ($\bar{x}\pm s$)

Group	n	2nd week	4th week	6th week
A	30	98±32	249±70	291±83
B	46	85±36	253±59	276±69
Male	42	85±30	223±78	280±79
Female	34	100±38	256±82	302±88

There is no significance between group A and B, group Male and Female (P > 0.05).

2.4 Clinical improvements in BPRS The improve-

ment in BPRS positive symptoms to dose and serum levels of quetiapine fumarate in 76 patients were illustrated in Fig2 and 3 respectively. Responders had a significant shorter duration of illness and less chronic course, and the percentage improvement in BPRS positive symptoms was correlated among the nonresponders, as shown in Tab3.

Tab 3 Relationship between serum concentrations of quetiapine and clinical effects

Concentration /mg·L^{-1}	Cases with effects	Cases without effects
< 0.126	6	24
≥ 0.126	26	20

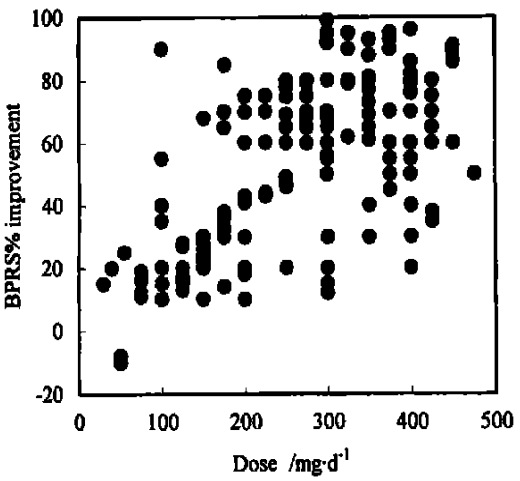

Fig 2 Relationship of percent improvement in BPRS to daily dose of 76 patients

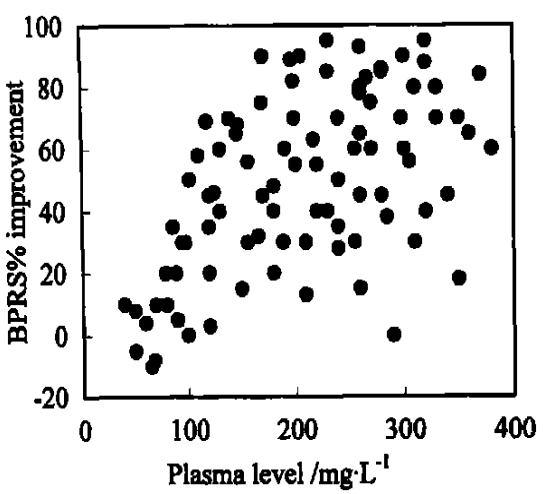

Fig 3 Relationship of percent improvement in BPRS to serum level of 76 patients

2.5 Serum levels and daily doses Serum levels were 0.126—0.35 mg·L^{-1} and daily doses were 150—450 mg when percentage of BPRS were 30% or higher. If 0.126 mg·L^{-1} of quetiapine fumarate was selected as an effective cutoff, the analyzed results of effective or un-effective cases show no statistical significant.

3 DISCUSSION

The assay of serum quetiapine fumarate was fast, specific, simple and had an excellent linearity in the range of 0.05—0.5 μg·mL^{-1} and can be used to monitor serum concentrations of quetiapine fumarate at purpose of modifying, adjusting and designing individual quetiapine dosage regimen.

Quetiapine fumarate is absorbed easily after oral administration, reaching peak concentration in about 2 hours. Its biovalability is not affected by food. Quetiapine fumarate was metabolized in liver to inactive metabolites, indicating that the antishchizophrenic effects are related to parent compound, not metabolites[3].

The receptor pharmacology of quetiapine differs from traditional antipsychotic agents, which have high affinity mainly for dopamine D_2 receptors in the brain, with less effect on α-adrenergic receptors and muscarinic receptors. Atypical antipsychotic agents exhibit an affinity for serotonergic, especially 5-HT_{2A} receptors, which is higher than that for dopaminergic D_2 receptors. This contributes to reduce extrapyramidal symptoms and treat "negative" symptoms. The absence of extrapyramidal effects is related to D_2 binding prominence of orthostatic hypotention and tachycardia from α-adrenergic blockers and somnolence from histamine blockade. Quetiapine binds to a wide varieties of neurotransmitter sites, including dopamine-1 (D_1) and D_2 and serotonin-A (5-HT_{2A}) and 5-HT_{1A}, but with a greater affinity for 5-HT_{1A}. This contributes its antipsychotic properties and low EPS liability[4].

The age and sex of involved patients do not interfere the effects of quetiapine fumarate in accordance with the published results previously[5]. But the significant individual varieties of patients with same doses indicate that other possible factors as metabolic polymorphism in population are existed. The involved subjects might be fast or slow metabolizers.

Serum concentrations of quetiapine fumarate are related to clinical responses and therapeutic effects. Quetiapine monitoring can be carried out to modify, adjust and design individual dosage regimen. In this report, the minimum effective concentration of quetiapine is 0.126 mg·L^{-1}, and maximum 0.35 mg·L^{-1} in most quetiapine treated patients. Thus, the range of 0.126 — 0.35

mg·L^{-1} might be considered as the ideal therapeutic range. More rational therapies are based on plasma quetiapine levels, and in someway, on the frequency and degree of adverse reactions, the pharmacoeconomics and therapeutic effects of quetiapine fumarate treatment. Further studies in this area are necessary and, practically, with much more clinical importance.

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精神分裂症患者富马酸喹硫平血浓度测定及血浓度疗效关系

郭瑞臣, 傅崇铭[1]
山东大学齐鲁医院临床药理研究所, 济南 250012, 山东; [1]山东省精神卫生中心, 济南 250014, 山东

摘要　目的: 建立反相高效液相色谱法测定精神分裂症患者富马酸喹硫平血浓度的方法学, 探讨其血浓度与患者年龄、性别、服药剂量及临床疗效的关系。方法: 采用高效液相色谱法测定76例单一服用富马酸喹硫平的精神分裂症住院患者治疗前及治疗后第2、4、6 wk 肘静脉血浓度, 并进行 BPRS 量表评定及相关性分析。结果: 富马酸喹硫平血浓度在0.05～0.5 mg·L^{-1} 范围内有良好线性关系 (r = 0.9850)。日剂量50～450 mg 时血浓度随剂量增大而升高, 但与服药患者年龄、性别无显著相关性。血浓度在0.126～0.350 mg·L^{-1} 范围内临床效果较好。结论: 测定方法简便、准确、专一性强, 可用于富马酸喹硫平治疗药物监测。治疗窗浓度为0.126～0.350 mg·L^{-1}。

关键词　药效学; 富马酸喹硫平; 血药浓度; 高效液相色谱法; 精神分裂症