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LETTER TO THE EDITORS

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QTc interval lengthening and debrisoquine metabolic ratio in psychiatric patients treated with oral haloperidol monotherapy

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The increased prevalence of the potentially life-threatening torsade de pointes type of arrhythmias and sudden cardiac death in psychiatric patients receiving antipsychotic drugs has become a public concern [1, 2]. The prolonged heart-rate-corrected QT interval (QTc) in the electrocardiogram (ECG) is a warning sign of this potentially fatal side effect [2]. Prolonged QTc interval may be a genetically inherited trait or the effect of drug treatment [1]. Several antipsychotic drugs has been associated with QTc lengthening and sudden cardiac death, such as thioridazine, droperidol, pimozide, or sulpiride [3]. Haloperidol is a butyrophenon-type antipsychotic drug which is widely used in the treatment of different psychiatric disorders and also in surgery and anesthesia. Haloperidol seems also to have an effect on the QTc interval and may increase the risk of torsade de pointes arrhythmia after intravenous [4] and oral doses [5].

Around 7% of Caucasian individuals have decreased capacity to metabolize debrisoquine by the polymorphic drug-metabolizing enzyme cytochrome P_{450} (CYP)2D6 [6]. The relationship between CYP2D6 activity and haloperidol plasma concentration has been shown in healthy volunteers [7] and also in patients [8]. Thus, enzyme activity may be associated with a tendency to cardiac arrhythmias in patients during treatment. The present study aimed to determine the effect of CYP2D6 enzyme activity, haloperidol dose, and plasma concentrations on the QTc interval among patients receiving oral haloperidol monotherapy.

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Twenty-seven Spanish, Caucasian psychiatric patients without any relevant organic disease were studied. The patients were receiving oral haloperidol (Haloperidol, Syntex Latino, Barcelona, Spain) monotherapy for at least 14 days. The dose range was 1.5–30 mg/day, and the average dose was 7 ± 5 mg/day (mean ± SD). The mean age of the patients was 47 ± 15 years (range: 23–77 years), and 22 (81%) were males. All patients were phenotyped using debrisoquine during antipsychotic drug treatment. After an overnight fast the subjects took a single oral dose of 10 mg debrisoquine sulfate (Declinax, Hoffman-La Roche, Switzerland), and all urine was collected over 8 h. Urine concentrations of debrisoquine and 4-hydroxy-debrisoquine were measured using gas chromatography [9]. Debrisoquine metabolic ratio (MR) was calculated as the ratio of the molar concentration of the parent drug to that of 4-hydroxy-debrisoquine in the 0-h to 8-h urine. Plasma concentrations of haloperidol were measured using high-performance liquid chromatography according to a previously published method [7, 8]. Cardiologic examination was performed with a routine, clinically used ECG apparatus, which calculated automatically the QTc intervals.

The mean QTc interval of the patients was 418.1 ± 48.0 ms. Three patients of 27 (11.1%) could be identified to have a QTc interval longer than 456 ms (481, 549, and 565 ms), which may be considered as the cut-off value for limit of risk of cardiac arrhythmia [10, 11] (Fig. 1). Reilly et al. [10] reported that 13.9% of patients receiving haloperidol treatment had lengthened QTc intervals and found an almost significantly increased odds ratio for QTc lengthening by haloperidol. The proportion of patients with QTc interval over 456 ms in the present study was similar to that (11.1%) thus supporting the effect of haloperidol treatment on QTc interval at clinically used oral doses.

There was a great interindividual variability in haloperidol plasma levels. The steady-state dose-corrected plasma concentrations of haloperidol showed approximately eightfold interindividual variation (from 0.12 μg/l/mg to 0.92 μg/l/mg). The dose and plasma

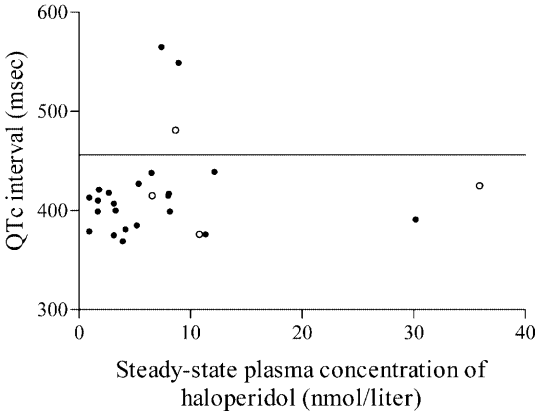

Fig. 1. Relationship between the steady-state plasma concentration of haloperidol (nmol/liter) and QTc interval (ms) in patients ($n = 27$). Four patients (15%) had debrisoquine metabolic ratio (MR) greater than 12.6 (*open circles*). The cut-off value for limit of risk of arrhythmia was set at 456 ms (*solid line*) [10, 11]

concentrations of haloperidol correlated significantly (Spearman's non-parametric *t*-test, $r = 0.84$, $P < 0.001$). No correlation was found between QTc interval and the dose, plasma concentrations of haloperidol, or with the debrisoquine MR (Fig. 1). The present results suggest that the CYP2D6 activity and haloperidol plasma concentration seem not to be determinant factors in the tendency to QTc interval lengthening among patients receiving haloperidol monotherapy at clinically used doses. However, prolonged QTc intervals in psychiatric patients due to genetic factors or cardiac disorders [1] and the reported cases of prolonged QTc intervals during haloperidol treatment, as seen also in the present study, may suggest caution and ECG control in patients with elevated risk for developing potentially fatal cardiac arrhythmias and sudden death.

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