Letter to the Editors

Effect of lamotrigine on the PR interval in healthy subjects

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In a thorough QT/QTc study of lamotrigine [1], healthy subjects received a single oral dose of moxifloxacin (400 mg) or placebo in crossover design, followed by a dose-escalating regimen of lamotrigine ($n = 76$) over a 77 day period, or matched placebo ($n = 76$). Digital 12-lead electrocardiograms (ECGs) were recorded and ECG intervals measured manually by a central reader. In a *post hoc* analysis, PR interval data were analysed using repeated-measures analysis of covariance (ANCOVA) separately for day 42 (lamotrigine 50 mg twice daily), day 63 (lamotrigine 150 mg twice daily) and day 77 (lamotrigine 200 mg twice daily) as previously described [1]. Point estimates and corresponding 90% confidence intervals (CIs) were calculated for the difference between each dose of lamotrigine and the corresponding placebo at each time point. The same type of analysis was used to determine the difference between moxifloxacin and placebo, taking into account the crossover design. The normal range for PR interval is 120–200 ms.

Small decreases in mean PR interval were observed after moxifloxacin compared with placebo. The maximal adjusted mean difference from placebo was -1.1 ms (90% CI $-1.99, -0.22$) at 6 h postdose. Small increases in mean PR interval were observed on lamotrigine compared with placebo (Figure 1). The largest mean differences from placebo at each dose level were 2.76 ms (90% CI 0.41, 5.12) 1 h postdose at the 50 mg twice daily dose level, 4.49 ms (90% CI 1.99, 6.99) 15 min postdose at the 150 mg twice daily dose level, and 5.11 ms (90% CI 2.48, 7.74) 15 min postdose at the 200 mg twice daily dose level. The median, steady-state, maximal plasma concentration occurred at around 1.0–1.5 h postdose across the three dose levels.

A mean increase in PR interval of 5 ms on lamotrigine compared with placebo is consistent with the paper by Matsuo *et al.* [2], which describes a placebo-controlled study in which the efficacy of lamotrigine was evaluated when added on to existing anti-epileptic medications in patients with refractory partial seizures. Whilst the lamotrigine doses used were similar (300 and 500 mg day⁻¹), mean trough plasma concentrations were lower than in

our study, 3.6 µg ml⁻¹ at 500 mg day⁻¹, compared with approximately 2, 5 and 7 µg ml⁻¹ at the 50, 150 and 200 mg twice daily dose levels, respectively. However, in our study, even though plasma concentrations were dose proportional, the degree of PR interval prolongation was similar at the mid- and high-dose levels, suggesting that a maximal effect is achieved at these doses.

In a more recent paper by Saetre *et al.* [3], the mean change from baseline in PQ interval after 40 weeks of treatment with lamotrigine ($n = 29$, mean dose of 111 mg) was an increase of 8.8 ms, although the median change from baseline was zero. The mean plasma lamotrigine concentration was 2.64 µg ml⁻¹. In the carbamazepine comparator group, the mean change from baseline was larger (14.1 ms) than on lamotrigine. Comparison of our data with that of the paper by Saetre *et al.* [3] is limited by the absence of placebo in their study. Furthermore, the population has some important differences compared with the young healthy volunteer population in our study, being comprised of elderly subjects with epilepsy, some of whom had significant cardiovascular co-morbidities and frequent concomitant medications.

A recent review of aggregate data in GlaxoSmithKline's safety database, which is comprised of all postmarketing spontaneous adverse event reports and all serious adverse events from clinical trials, for events including and relating to PR prolongation in patients on lamotrigine did not identify a safety concern.

In conclusion, a rigorous study of the effects of lamotrigine on ECG intervals in a healthy volunteer population indicates that the PR interval may be slightly prolonged, especially at high doses of lamotrigine. However, postmarketing safety surveillance has not revealed this to be a clinically relevant adverse effect.

Competing Interests

The authors are employees of GlaxoSmithKline and holders of GSK shares.

Figure 1

Difference in adjusted mean PR interval compared with placebo over 12 h postdose at lamotrigine dose levels of 50, 150 and 200 mg twice daily (bd). Lamotrigine 50 mg bd vs placebo (—♦—); Lamotrigine 150 mg bd vs placebo (—■—); Lamotrigine 200 mg bd vs placebo (—▲—); moxifloxacin SD vs placebo SD (—×—)

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