Letters to the Editors

Limited adherence to safety instructions in drug leaflets

Drug effects are not solely determined by the pharmacological properties of the active substance, but also depend heavily on the way it is used in practice by health professionals and patients. Non-adherence to instructions for use seems to have contributed to the withdrawal of drugs such as troglitazon, mibefradil, and most recently cerivastatin [1–3]. Hepatotoxicity and myopathy are two rare but serious side-effects of statins. Myopathy can lead to a life threatening rhabdomyolysis. Product labelling of statins advises to monitor hepatic function and creatinine kinase (CK) concentrations (especially in patients who are experiencing muscle pain), because this may prevent progress of these drug-induced complications. The objective of the present study was to estimate the incidence of CK and hepatic function measurements in a cohort of patients starting with a statin, and to evaluate whether this was influenced by the withdrawal of cerivastatin.

From eight community pharmacies located in Tilburg, the Netherlands and surroundings, patients starting with a statin during the period December 2000–April 2001 (period 1), or during the period August 8, 2001–October 2001 (period 2) were selected. Period 2 was chosen after the withdrawal of cerivastatin. Date of filling the prescription was the index date. Age, gender, statin, prescribed dosage, and relevant concomitant drug use were obtained for all patients. From the regional clinical chemistry laboratory, which performs measurements for in- as well as outpatients, the number of hepatic function and CK measurements was determined during a 3 month follow-up period after the index date.

Five hundred and thirty patients were included. Any clinical chemistry measurement during follow-up was performed in 54.2% (287) of all patients; CK levels were checked in 13.0% (69) of the patients while hepatic function tests were performed in 22.3% (118) of all patients. There was no difference in these frequencies before, and after the withdrawal of cerivastatin (Table 1).

Gender, age, standardized dosage, interacting concomitant drug use, and CK-inducing concomitant drug use did not cause significant deviations of these outcomes. Only 5.3% (1) of the patients starting with cerivastatin was checked for CK compared with 13.3% (68) of the patients using other statins (RR 0.40 (95% CI 0.06, 2.70)). In contrast, any clinical chemistry measurement and hepatic function were determined more frequently in cerivastatin starters compared with other statin starters: RR 1.48 (95% CI 1.16, 1.90) respectively RR 3.04 (95% CI 2.08, 4.47).

This study shows that, in daily medical practice, adherence to drug prescribing guidelines to perform clinical chemistry measurements is limited. The withdrawal of cerivastatin has not led to an increase in hepatic function- and CK measurements. Cerivastatin was taken off the market because available evidence (mainly case reports) suggested a higher frequency of serious side-effects in comparison with other statins [4]. It is remarkable that CK was less frequently checked in patients using cerivastatin while hepatic function was more frequently measured in this study. It is important to recognize that the population was limited to 530 patients with only 19 starters of cerivastatin. The strength of this study was the conductance in daily practice. The risk of losing patients during follow-up was minimized because in The Netherlands outpatients usually visit the same pharmacy [5], and all clinical chemistry testing was concentrated in one laboratory.

Overall it is important to realize that a drug is not a chemical entity alone but comes along with instructions for patients and prescribers in order to optimize the benefit-harm balance. Strategies for adherence to such instructions should be developed and implemented.

Table 1 Incidence of CK, hepatic function or any clinical chemistry measurement during 3 months of follow-up

Variables	*CK measurement (%)*	*RR (95% CI)*	*Hepatic function measurement (%)*	*RR (95% CI)*	*Any clinical chemistry (%)*	*RR (95% CI)*
All statins ($n = 530$)	13.0		22.3		54.2	
Other statins ($n = 511$)	13.3	1.00	20.7	1.00	53.2	1.00
Cerivastatin ($n = 19$)	5.3	0.40 (0.06, 2.70)	63.2	3.04 (2.08, 4.47)	78.9	1.48 (1.16, 1.90)
Before withdrawal ($n = 369$)	13.3	1.00	23.6	1.00	53.4	1.00
After withdrawal ($n = 161$)	12.4	0.94 (0.58, 1.52)	19.3	0.82 (0.57, 1.18)	55.9	1.05 (0.89, 1.24)

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Received 23 May 2002, accepted 28 May 2002

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The effect of diltiazem, a calcium channel blocker, in asthmatic patients

In their recent article, Twiss *et al.* clearly indicate that calcium channel blockers are not clinically effective as maintenance therapy for persistent asthma [1]. Their hypothesis was that the results of broncoprovocation studies could be used to predict whether two calcium channel blockers, nifedipine and diltiazem, or which of them would be clinical effective to suppress the signs and symptoms of persistent asthma. Previous studies demonstrated nifedipine efficacy in broncoprovocation studies [2, 3] while diltiazem was consistently ineffective [4], so that the authors were not surprised by the results for diltiazem.

Herein we present experimental evidence that might explain the results obtained in clinical studies. We have published that diltiazem, *in vitro*, affects the maturation of monocyte-derived dendritic cells by reducing their interleukin(IL)-12 production and, consequently, by preventing T helper(Th)1 polarization [5]. More recently, we extended our study by analysing Th2 cytokine production. Figure 1 shows that human naïve T lymphocytes, after incubation with dendritic cells pretreated with a high dose of diltiazem (10^{-4}M), produce a lower amount of interferon-γ (produced by Th1 lymphocytes), and, very interestingly, a higher level of IL-5. No change of the level of IL-4 and IL-10 was observed. IL-5 is produced by T cells that belong to the Th2 but not the Th1 subset. By virtue of the pattern of cytokines that they synthesize, Th2 cells are thought to control the growth and effector function of those cell types that are involved in allergic inflammatory responses [6]. In fact, IL-5 is responsible for the maturation of eosinophils in

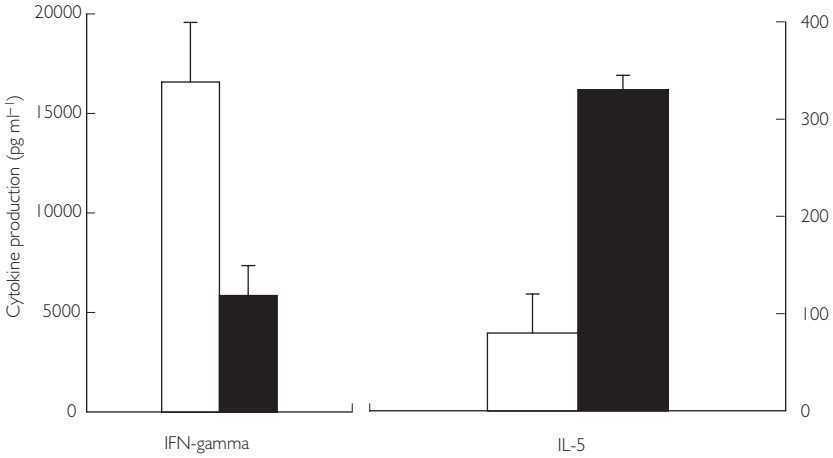

Figure 1 Effect of diltiazem on cytokine production by naive T cells. Control dendritic cells (DC, □) or DC treated with diltiazem (dil-DC, ■) at 10^{-4}m, were matured by CD-40 l-J558 and used to stimulate naïve allogeneic T cells. On day 5 of culture, T cells were expanded with IL-2 for 2 weeks. Cells were then harvested, washed and stimulated with PMA (10^{-7}m) and anti-CD3 (10 μg ml^{-1}) overnight. Supernatants were collected and tested for cytokine measurement by ELISA. Results shown represent the mean ± s.d. of four independent experiments; $P < 0.05$.

the bone marrow and for their release into the blood. It may also be important for the recruitment of eosinophils from blood vessels into tissues. In humans, IL-5 is a very selected cytokine as a result of the restricted expression of its receptor on eosinophils and basophils. Several allergic diseases, first of all asthma, have prominent inflammatory components that are characterized by pronounced eosinophilic infiltration. Eosinophils are therefore an ideal target for selectively inhibiting the tissue damage that characterizes allergic disease.

Several studies demonstrated a correlation among the activation of T lymphocytes, increased concentration of IL-5 in serum and broncoalveolar lavage (BAL) fluid, and increased severity of the asthmatic response [7, 8]. In particular, Robinson *et al.* [7] found a strong correlation among the number of BAL cells that expressed mRNA for IL-5, the magnitude of baseline airflow obstruction and brochoconstrictor reactivity to methacholine. For this reason, humanized antibodies against IL-5 are now tested in clinical studies in asthmatic patients [6].

From the above observation, our evidence that diltiazem is able to up-regulate IL-5 production by T cells may substantiate the clinical effect observed by Twiss *et al.* Therefore, our results might contribute to discourage the clinical use of diltiazem in attenuating airway responsiveness in asthmatic patients.

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Received 17 May 2002, accepted 20 May 2002

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Treatment functional GI disease: the complex pharmacology of serotonergic drugs

We have read the recent review [1] on the use of serotonergic drugs in functional gut disorders with great interest and would like to comment on two aspects that may confuse the readers involved in drug development in this difficult area.

First, Dr Spiller states that prolongation of the QT interval by cisapride is due to an action on cardiac 5-HT_4 receptors. However, there is now consensus that the occurrence of QT prolongation and ventricular tachyarrhythmias such as *torsades de pointes* by cisapride is due to blockade of human ether-a-go-go-related gene K^+ channels [2–5]. Cisapride may indeed trigger tachycardia and supraventricular arrhythmia through stimulation of atrial 5-HT_4 receptors [6]. However, the incidence of the atrial arrhythmia is very low [7], probably because cisapride behaves as a partial agonist on the human atrium and because the density of 5-HT_4 receptors in the atrium is low [8]. The lack of involvement of 5-HT_4 receptors in generating QT prolongation is also supported by the failure of the selective 5-HT_4 receptor antagonist GR113808 [9] to modify cisapride-induced action potential prolongation in guinea-pig isolated papillary muscles.

Thus, we may conclude that QT prolongation is not a class effect necessarily shared by all 5-HT_4 receptor agonists and that it is possible to develop selective 5-HT_4 receptor agonists with no effect on the QT interval: tegaserod may be an example [10]. In addition, it should be noticed that all 5-HT_4 receptor agonists so far devel-

oped (including cisapride, prucalopride and tegaserod) are partial agonists, but only tegaserod is presented as such in Table 1 of Dr Spiller's paper.

Secondly, we would like to point out that buspirone and sumatriptan are both defined as 5-HT_{1P} receptor agonists throughout the review, whereas buspirone is a 5-HT_{1A} receptor agonist (and also a dopamine D_2 receptor antagonist) [11] and sumatriptan is the prototype 5-$HT_{1B/D}$ receptor agonist [12]. Sumatriptan has been extensively investigated by Dr Tack's group [13, 14] and was found to have important effects on gastric tone and perception of gastric distension [14], but the receptors involved in mediating its effects are still a matter of debate. Therefore, the fact that 5-HT_{1P} receptors are presented as potential therapeutic targets in functional gut disorders is misleading, all the more so because 5-HT_{1P} receptors are not included in the official IUPHAR classification of serotonin receptors [12]. We are aware that the presence of 5-HT_{1P} receptors is reported in enteric neurones [15], but the hypothesis that sumatriptan determines its gastric motor effects *in vivo* through these receptors still awaits confirmation by pharmacological studies with selective antagonists. It is noteworthy, however, that a preliminary report by our group [16] showed that the gastric motor effect of sumatriptan was blocked *in vivo* by GR127935, a selective 5-$HT_{1B/D}$ receptor antagonist.

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Treatment of functional GI disease: the complex pharmacology of serotonergic drugs. Reply from author

I thank Drs De Ponti & Crema [1] for their interest and for their valuable comments, which help to clarify some evolving concepts. I would entirely agree that while cisapride can induce atrial tachycardia acting via cardiac 5-HT_4 receptors, this is not the main cause of cardiotoxicity which is the delayed repolarization of cardiac muscle as shown by prolongation of the QT interval. As they have pointed out, several recent publications have confirmed that the mechanism responsible is likely to be cisapride's action on the human *ether-a-go-go*-related gene (HERG) product, the rapidly activating delayed-rectifier K^+ current in cardiac muscle. Mutations in this gene have

been associated with long QT [2] and susceptibility to cisapride induced arrthymias [3]. The HERG channel cavity is lined with aromatic residues, a feature which distinguishes it from other K^+ channels. This feature appears to render it particularly susceptible to drug interaction [4]. Drs De Ponti and Crema make a very important point that this is not directly related to 5-HT_4 receptor agonist properties, as some (tegaserod, mozapride) appear to be free from this effect [5].

I would also like to thank them for correcting the unintentional description of buspirone as a 5-HT_{1p} receptor agonist. I am further grateful to them for drawing our attention to their recent work, which suggests that the fundal relaxing effect of sumatripan may be mediated via 5-$HT_{1b/d}$ receptors. This is encouraging since there are numerous 5-$HT_{1b/d}$ agonists now in development for the migraine market and they may well be of value to gastroenterologists.

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Effects of supratherapeutic doses of ebastine and terfenadine on the QT interval

Sir,

Drs Gillen *et al.* recently reported [1] that at supratherapeutic doses, ebastine caused increase in heart rate and that, dependent on the method used for heart rate correction of QT interval, it led either to small but statistically significant, or minute and nonsignificant prolongation of the QTc interval.

The use of Bazett and/or Fridericia formulae for QT interval correction is well placed in clinical practice because the relative magnitude of the errors due to under- or over-correction of the QT interval is unlikely to lead to incorrect clinical decision. However, in order to investigate drug related QTc interval changes in the presence of drug-induced heart rate change, the appropriateness and precision of the method used for correcting the QT interval for heart rate is essential. If the QTc interval is under- or over-corrected, the heart rate changes are projected into the QTc interval data and the analysis of the study becomes potentially meaningless with the possibility of both false positive and false negative findings.

There are ways of judging the success of heart rate correction. Perhaps the simplest test is to investigate the correlation coefficient between the RR and QTc interval in the electrocardiograms obtained in drug-free stage. While a correlation coefficient of 0 does not guarantee that the QTc and RR interval data are truly independent, a value different from 0 shows that the heart rate correction formula used to obtain the QTc values has not been successful in removing the dependency of QT interval on heart rate.

Drs Gillen *et al.* rightly say that a large number of heart rate correction formulae have previously been proposed. However, as their multiplicity implies, none of these formulae has found truly universal acceptance. The reasons for such a lack of a universally acceptable heart rate correction have become understood only recently. It has been observed that the QT/RR interval relationship is both different in different subjects and stable in the same individual over time [2, 3]. The intersubject variability of the QT/RR relationship means that a heart rate correction formula that correctly works in one individual, that is, provides QTc values that are independent of heart rate, will not necessarily be the optimum in another individual. Thus, to obtain truly heart rate-

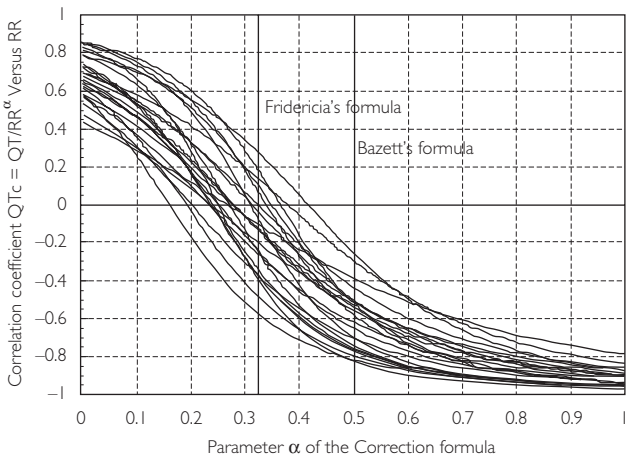

Figure 1 The drug-free RR/QT interval data of each subject of the study reported by Drs Gillen *et al.* [1] were used to calculate heart rate corrected QTc intervals using the formula $QTc = QT/RR^{\alpha}$, ranging the values of α from 0 to 1. For each value of α and for each individual subject, the correlation coefficient was calculated between the QTc and RR interval values. Individual lines in the graph correspond to the results obtained in the individual subjects of the study and show that the values of α for which the correlation coefficient between QTc and RR was 0 were very different between different individuals (ranging from 0.161 to 0.417). Note that while the Fridericia formula is within the range of individual α values, Bazett's formula falls way outside the individual values. (See the previous publication [5] for more details.)

independent QTc values, individual characteristics of the QT/RR relationship need to be taken into account. This effectively means that the individual QT/RR pattern needs to be translated into an individual heart rate correction formula [4].

It is not for the first time that the study reported by Drs Gillen *et al.* has been analysed and published. I had the possibility of analysing the very same data set of this study and I have previously published the results obtained when using the technology of individual heart rate corrections [5]. Briefly, in the drug-free data of the study published by Dr Gillen *et al.*, the heart rate correction formula $QTc = QT/RR^{\alpha}$ has been optimized for each study participant, obtaining different values of the coefficient α for each individual. In these analyses, I have observed that while the coefficient of Fridericia's formula $\alpha = 0.33$ was within the range of individually optimized coefficients (it was still significantly overcorrecting for some and under-correcting for other subjects), the coefficient of Bazett's formula $\alpha = 0.5$ was well outside this range (Figure 1).

The analyses based on the individually optimized heart rate corrections showed that in the study reported by Dr Gillen *et al.* ebastine did not in fact cause any QTc interval prolongation. The changes of the QTc interval on placebo, ebastine 60 mg daily ebastine 100 mg daily, and terfenadine 360 mg daily were -2.76 ± 5.51 ms, -3.15 ± 9.17 ms, -2.61 ± 9.55 ms, and 12.43 ± 15.25 ms, respectively [5].

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Accepted 9 January 2002

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