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Letter to the Editors

The role of concentration–effect relationships in the QT_c interval prolongation: case sotalol

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We read with interest the review 'The role of concentration' effect relationships in the assessment of QT_c interval prolongation' by France & Della Pasqua [1]. The authors discuss the advantages and disadvantages of population pharmacokinetic–pharmacodynamic modelling and simulations and present several examples of their application used to predict QT interval prolongation. We agree with these views. However, we would like to underline a careful exploration of data from acute drug intoxications and cardiac arrhythmias in real-life patients for the detection of previously unrecognized QT prolongations. To this end the case sotalol serves as an example.

In early clinical trials the β-adrenoceptor blocking agent sotalol (d,l-sotalol) was given to humans in huge doses, up to 60 mg kg^{-1} or 4.0 g day^{-1}, without recognition and reporting of its cardiotoxic effects [2], and doses up to 1200 mg daily have been used therapeutically [3]. In many countries, like in Finland, sotalol was in clinical use for several years in doses up to 480 mg day^{-1} for the treatment of, for example, hypertension, angina pectoris and cardiac arrhythmias. The prolongation of the QT interval was not mentioned in the sotalol product label before 1979, when we reported the first cases [4, 5], and then six other cases [6] of the concentration-dependent QT prolongation and severe tachyarrhythmias in the patients who had taken sotalol in overdoses. There was a good correlation between plasma concentrations of sotalol, prolongation of the QT interval, up 200% of normal, and severe cardiac arrhythmias. Furthermore, in the 29 patients who used sotalol therapeutically in doses of 160 to 640 mg daily, a strong concentration-dependent prolongation of the QT_c interval was seen, for example, by 70 ± 9 (SEM) ms in 21 patients with the sotalol concentration ranging from 3.1 to 6.7 μg ml^{-1}. Prolongation of the QT_c interval did not correlate with the QT_c interval measured before the use of sotalol [7]. One of these patients had within 6 months on sotalol use two episodes of sudden unconsciousness. These episodes, obviously caused by torsades de pointes ventricular tachycardia, were first mis-diagnosed as epileptic attacks until the prolongation of his QT interval was noted and connected to sotalol and shown to be independent of its β-adrenoceptor blocking effect [7, 8].

The potential of sotalol to cause QT prolongation and many factors changing its concentration–effect relationships are nowadays well known. However, there may still be unknown individual factors caused by, for example, pharmacogenetics, diseases, age, gender or drug interactions, which may render certain patients exceptionally sensitive to the QT prolonging and torsadogenic effect of some drugs [9, 10]. Therefore, while we agree with the views presented in the review of France & Della Pasqua [1], we would like to underline the careful analysis of the data in clinical intoxications and potential adverse effects. The consideration of plasma drug and electrolyte concentrations, ECG and relevant clinical information may uncover previously unrecognized concentration-dependent effects of drugs on the QT interval.

A drug (sotalol) may have been in a wide clinical use for a decade, without recognition of its potentially hazardous adverse effect (QT prolongation), until careful examination of acute intoxications uncovers its concentration-dependent effect and helps to recognize risks associated with its use, even after therapeutic doses in certain patients.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available

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REFERENCES

1 France NP, Della Pasqua O. The role of concentration–effect relationships in the assessment of QT_c interval prolongation. Br J Clin Pharmacol 2015; 79: 117–31. doi: 10.1111/bcp.12443.

2 Frankl WS, Soloff LA. Sotalol: a new, safe beta adrenergic receptor blocking agent. Am J Cardiol 1968; 22: 266–72.

3 Verniory A, Staroukine M, Telerman M, Delwiche F. Effect of sotalol on arterial blood pressure and renin-angiotensin system in hypertensive patients. In: Advances in Beta-Adrenergic Blocking Therapy, Vol. 3: Sotalol. Proceedings of International Symposium, Rome, Italy, May 1974, ed. Snart AG. Amsterdam: Excerpta Medica, 1974; 36–49.

4 Neuvonen PJ, Elonen E, Tarssanen L. Sotalol intoxication, two patients with concentration-effect relationships. Acta Pharmacol Toxicol 1979; 45: 52–7.

5 Elonen E, Neuvonen PJ, Tarssanen L, Kala R. Sotalol intoxication with prolonged Q-T interval and severe tachyarrhythmias. Br Med J 1979; 1: 1184–6.

6 Neuvonen PJ, Elonen E, Vuorenmaa T, Laakso M. Prolonged Q-T interval and severe tachyarrhythmias, common features of sotalol intoxication. Eur J Clin Pharmacol 1981; 20: 85–9.

7 Neuvonen PJ, Elonen E, Tanskanen A, Tuomilehto J. Sotalol prolongation of the Q-T interval in hypertensive patients. Clin Pharmacol Ther 1982; 32: 25–32.

8 Laakso M, Pentikäinen PJ, Pyörälä K, Neuvonen PJ. Prolongation of the Q-T interval caused by sotalol – possible association with ventricular tachyarrhythmias. Eur Heart J 1981; 2: 353–358.

9 Ritter JM. Editors's view: drug-induced long QT syndrome and drug development. Br J Clin Pharmacol 2008; 66: 341–4.

10 Ritter JM. Editors'view: cardiac safety, drug-induced QT prolongation and torsade de pointes (Tdp). Br J Clin Pharmacol 2012; 73: 331–4.

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