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Letter to the Editor

On the role of concentration–effect relationships in safety pharmacology: only the dose makes a drug not to be poison!

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In our review on the role of concentration–effect relationships in the assessment of QT_c interval prolongation we have highlighted the importance of characterising the potential for pro-arrhythmic effects in a strict quantitative manner [1]. Neuvonen & Elonen [2] appear to agree with the approach, but suggest the need to explore carefully data from acute drug intoxications and cardiac arrhythmias in real-life patients for the detection of previously unrecognised QT prolongation. They refer to *d,l*-sotalol as a drug whose cardiotoxic effects have been overlooked even after the use of high doses in clinical trials.

The authors forget to mention, however, that *d,l*-sotalol was approved before the introduction of regulatory guidance on the evaluation of pro-arrhythmic effects, i.e. when concentration–effect relationships were not systematically explored during drug safety evaluation. In fact, for a long time pharmacokinetic–pharmacodynamic (PKPD) modelling has remained underutilised in safety pharmacology and toxicology. Such an analysis was finally performed for *d,l*-sotalol at the time of its approval for the treatment of supraventricular and ventricular arrhythmias in children. The data clearly show the effects across the therapeutic exposure range and beyond [3].

Intoxications can be a traumatic experience for patients, prescribers and regulators, especially when they are not self-inflicted. Whilst information arising from such an event should not be ignored and lessons could be learnt in order to prevent further casualties, we believe that the understanding of a compound's safety pharmacology profile should not be based on toxic doses. Toxicology is not where one should start, if the intent is to develop a medicine. This concept is not new. In 1538, Theophrastus of Hohenheim (Paracelsus) wisely stated that 'all things are poison and nothing is without poison. Only the dose makes a thing not to be poison' [4]. Neuvonen & Elonen's suggestion has therefore important conceptual limitations [2]. Extrapolations from toxic levels are not accurate without further understanding of the concentration–effect curve. In addition, intoxications are often poorly supported by information on dose and time of drug intake relative to the onset of clinical symptoms and signs.

Neuvonen & Elonen also allude to the fact that concentration–effect relationships may be altered by numerous factors or confounders [2]. We share their concern and have raised questions about the clinical validity of considering the thorough QT study a worst case scenario. On the other hand, it should be noted that there are no examples of drugs that have been associated with the development of torsades de pointes, for which no concentration–effect relationship has been identified (i.e. negative TQT study).

Undoubtedly, new approaches are required that take into account not only the toxic effects. Understanding of the overall benefit risk balance is essential to decide on the suitability of a drug or dose for a given population. We have shown that not-in-trial simulations can be used to predict the impact of different sources of variability on the overall safety profile of a compound in real-life conditions [5]. Our findings for *d,l*-sotalol illustrate how co-morbidities and drug–drug interactions can be evaluated prospectively, allowing for the characterisation of the differences in overall risk in vulnerable or high risk populations. Clearly, it is time that drug developers, prescribers and regulators start understanding overdose in virtual patients. Let's ensure that real patients receive the right dose and if the medicine is contra-indicated, identify an alternative option.

Clinical pharmacology is evolving as one of the few medical disciplines which promotes synthetical skills, enabling the prediction of drug effects across species, disease conditions and populations. We anticipate that careful evaluation of concentration–effect relationships by modelling and simulation techniques using data from pre-clinical species and phase 1 dose escalation studies will become pivotal for the characterisation of pro-arrhythmic risk. Clinically relevant factors such as drug interactions and co-morbidities can be incorporated into the analysis to ensure drug effects are quantified taking into account real-life conditions. These advancements are irreversible, but at present modelling and

simulation remain accessible to very few. Our endeavour is to make it within reach for those involved in the evaluation of the benefits and risks of a medicine. Prescribers and regulators should not rely on the fate of intoxicated patients to learn about drug effects that can be predicted and prevented.

Competing Interests

The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares OPD is Chair of Clinical Pharmacology & Therapeutics at UCL and Senior Director of Clinical Pharmacology at GlaxoSmithKline. There are no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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