MOVING TOWARDS PRECISION DOSING OF IVABRADINE IN PEDIATRIC ARRHYTHMIAS: A PHARMACOMETRICS APPROACH

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Objective: Ivabradine is a heart rate lowering drug, approved for the treatment of heart failure, but is increasingly used as an off-label drug for automatic tachyarrhythmias like atrial ectopic tachycardia (AET), both congenital and post-surgical junctional ectopic tachycardia (JET) in children. In contrast to most antiarrhythmic drugs, ivabradine has no negative inotropic or vasoactive effects, which makes it an attractive anti-arrhythmic agent in patients with low cardiac output state, either due to incessant tachycardia or following cardiac surgery.

However, there is no rationale for ivabradine dosing regimens in pediatric arrhythmias. Current dosing is based on extrapolation of adult data and studies in pediatric heart failure patients. Ivabradine is available as an oral substrate only. It is absorbed enterally and primarily metabolized by CyP3A4. Both enteral dysfunction as well as decreased CyP3A4 metabolism due to younger age and critical illness will likely alter the pharmacokinetics of ivabradine.

We describe serum levels of ivabradine in pediatric arrhythmia patients in relation to the administered dose and effect on heart rate.

Methods: We retrospectively collected a cohort of children, from all four Dutch pediatric cardio-surgical centers, treated with ivabradine for arrhythmias. In a subset of post-surgical JET patients, we measured ivabradine (and its N-demethyl metabolite) serum levels.

Results: We collected cases of 25 children treated with ivabradine (17 Post-Surgical JET, 4 Cong-JET and 4 AET).

Analysis revealed that serum levels of ivabradine after enteral administration were unpredictable. In consecutive measurements after the first dose, patients showed high inter individual variability with respect to maximum concentration from 36 µg/L to undetectable concentrations. Large inter individual variability was also observed with respect to time to maximum concentration ranging from <2 hours to >11 hours. Due to this high variability a prediction model with an acceptable fit could not be constructed.

Using mixed models a significant negative association between heart rate and ivabradine serum levels was found. This result persisted after correction for other important factors that influence heart rate such as body temperature, amiodarone and clonidine use.

Conclusion: We describe, for the first time, serum levels of ivabradine in the treatment of pediatric arrhythmias. The strong association between serum levels and a decrease in heart rate suggests that ivabradine might have a beneficial effect on post-surgical JET. However the unpredictable serum levels after enteral use of ivabradine in these patients is a point of concern. Intravenous administration of ivabradine might be a solution for this problem.