Monitoring of cardiac electrophysiology after injection of gadobenate dimeglumine: intra-individual comparison with placebo in healthy volunteers and patients with cardiovascular disease

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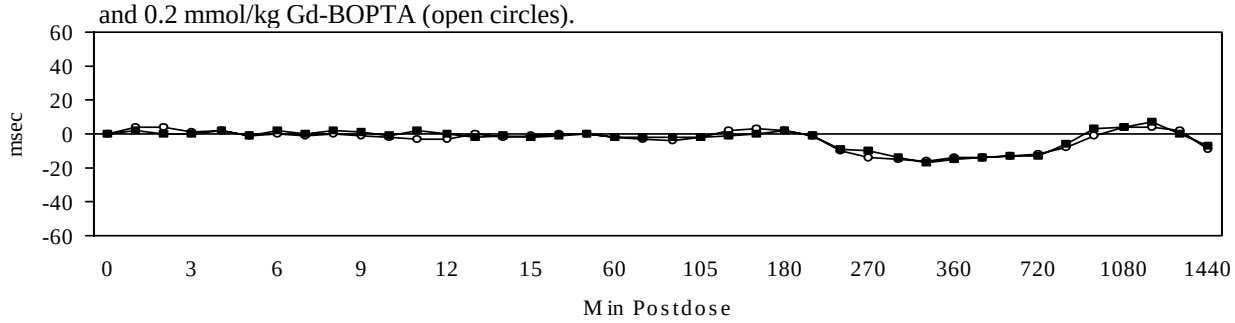
Synopsis: 24 healthy volunteers and 23 patients with coronary artery disease received by single intravenous injection in randomized crossover fashion 0.2 mmol/kg Gd-BOPTA and saline, separated by ~72 hours. Twelve-lead ECG monitoring was performed from 3h pre-dose until 24h post-dose with acquisition of continuous 10-second ECGs. Evaluation by automated read and single, blinded cardiologist revealed no significant differences between placebo and Gd-BOPTA concerning effects on the QTc interval or other ECG parameters. Correction for heart rate was best achieved on an individualized basis rather than by means of Bazett's formula. 0.2 mmol/kg Gd-BOPTA has no detrimental effect on cardiac electrophysiology in healthy volunteers or patients with CAD.

Background/Purpose: The clinical development of all new therapeutic and diagnostic agents now requires a detailed evaluation of the possible effects on cardiac electrophysiology. Principal among the ECG parameters to evaluate is the QTc interval since abnormal QTc interval prolongation is recognized as a major surrogate marker of potential proarrhythmic activity (1). Generally, prolongations of the QTc interval of >60 msec are considered to be of potential clinical importance. Gadolinium contrast agents are not among the list of compounds that are known to have proarrhythmic activity. However, detailed assessments of the possible effects of gadolinium agents on cardiac electrophysiology in general, and the QTc interval in particular, have not yet been reported: most evaluations of the effects of agents on cardiac electrophysiology have considered only intermittent electrocardiogram (ECG) recordings, and few studies have evaluated the potential effects in patients with known cardiovascular disease. The present study was designed to evaluate in as detailed a manner as possible the potential effects of gadobenate dimeglumine (Gd-BOPTA, MultiHance®; Bracco Imaging SpA, Milan, Italy) on cardiac electrophysiology, with emphasis on the potential for QTc interval prolongation. The study was performed in both healthy volunteers and patients with known coronary artery disease (CAD) and was conducted using an intra-individual crossover approach with placebo (saline).

Methods and Materials: 24 healthy volunteers and 23 patients with CAD received by single intravenous injection in randomized fashion 0.2 mmol/kg BW Gd-BOPTA and saline, separated by approximately 72 hours. Twelve-lead Ambulatory (Holter) ECG monitoring was performed from 3 hours pre-dose until 24 hours post-dose. Data were continuously collected as individual 10-second ECGs. Quantitative (heart rate, QT, PR, and QRS, intervals) and qualitative (abnormal QT dispersion, U-wave presence, T-wave morphology, and arrhythmias) evaluation was performed at predetermined time-points using automated, algorithmic interpretations (quantitative data) and blinded single cardiologist assessment (quantitative and qualitative data). Determination of possible QT interval prolongation was performed after correction for heart rate on an individualized basis and by means of Bazett's formula.

Results: The overall profiles for the QTc interval were similar over the course of the 24-hour monitoring period following injection of placebo and 0.2 mmol/kg Gd-BOPTA (Fig. 1). A non-significant difference between Gd-BOPTA and placebo of 3.1 msec (95% C.I.: -1.8, 8.0) after individualized correction was noted by automated read for the mean increase from baseline for the QTc interval. Overcorrection for heart rate was noted with Bazett's formula (mean difference: 5.6 msec; 95% C.I.: -2.2, 13.5). The results of the cardiologist were consistent with those of the automated readings. Overall, QTc interval prolongations of potential clinical importance (>60 msec) during the 24-hour monitoring period were observed on two occasions following placebo but on just one occasion following Gd-BOPTA when individualized correction was employed. Similar findings were noted for healthy volunteers and patients with CAD. No consistent differences between treatments were noted for evaluations of other quantitative or qualitative parameters although more frequent effects were noted in patients with CAD.

Fig. 1. QTc interval changes during 24-hour monitoring period after injection of placebo (closed squares) and 0.2 mmol/kg Gd-BOPTA (open circles).



Conclusion: Gd-BOPTA at a dose of 0.2 mmol/kg bodyweight has no detrimental effect on cardiac electrophysiology in healthy volunteers or patients with CAD.

1. European Agency for the Evaluation of Medicinal Products (EMEA): Committee for Proprietary Medicinal Products (CPMP) December 1997. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products.