569

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THE EFFECT OF PROPIVERINE ON CARDIAC SAFETY IN HEALTHY FEMALE SUBJECTS (A) AND IN PATIENTS SUFFERING FROM ISCHAEMIC HEART DISEASE (B)

Hypothesis / aims of study

The influence of propiverine hydrochloride (p-HCL, Mictonorm®, Detrunorm®, Propinorm®, BUP-4®) on cardiac safety is currently under evaluation as latest in vitro results indicate a potential $Ca2^{+}$-and K^{+}-channel inhibitory property of p-HCL which may prolong myocardial re-polarisation (MR).

The aim of the **study A** was to assess potential effects of p-HCL on MR using QTc-interval, QT-dispersion and shape of T-wave as surrogate parameters in healthy female subjects, aged between 45-60 years.
As an increasing number of non-cardiac active compounds, associated with life-threatening cardiac arrhythmia of the torsade de points type is currently concerning health authorities, the cardiac safety of p-HCl was assessed in patients with ischemic heart disease (IHD), too (**study B**). These patients were considered to have an increased risk in the development of life-threatening cardiac arrhythmia.

Study design, materials and methods

Study A

24 healthy female subjects were enrolled and treated with p-HCL and placebo during two treatment periods of six days each (cross-over), separated by a washout period of at least 14 days. ECGs were recorded under strictly controlled resting conditions at predose, 1, 2, 4, 6, 8, 12 and 24 hrs post dose on days 1 and 6 and 7 days after the last intake of study medication, at corresponding time points, in each treatment period. Safety was assessed by investigation of ECGs, vital signs, clinical laboratory, adverse event monitoring (AEs), and physical examination (PE).

Study B

24 male patients with various degrees of IHD were included. They received 30 mg p-HCl/placebo on days 1 and 14 and 15 mg p-HCl/placebo t.i.d. on days 2-13 in a double blind, randomised manner with two weeks wash-out between periods 1 and 2 (cross-over). 12-lead rest- and exercise-ECGs were recorded at predose, and up to 24 hrs post dose on days 1, 14 and 21 in both periods. Statistical analysis of the differences in maximum increase in QTc, maximum QTc, mean $QTc_{(0\text{-}12h)}$, $AUC_{(0\text{-}12h)}$ of the QTc-interval and QTc at maximum load after p-HCl and placebo administration was performed. The shape of T-wave was investigated descriptively.

Results

Study A
Exploratory statistical analysis revealed no effect of p-HCL on myocardial re-polarisation in healthy women in comparison to placebo. There was no difference between p-HCL and placebo in QTc maximum increase, post-dose maximum of QTc, average QTc (over post-dose assessments up to 12 hours), rating of maximum QTc interval, rating of maximum increase of QTc interval, shape of T-wave, maximum increase of QT-dispersion and maximum decrease of QT-dispersion ($P<.05$).
P-HCL was well tolerated with respect to vital sings, clinical laboratory, AEs and PE.

Study B
Although the administered dose of p-HCl was at the upper clinical dose range, statistically significant difference in all investigated parameters between p-HCl and placebo treatment nor under resting as well as under physical stress conditions has been detected. No clinically relevant difference in the shape of T-wave between the treatments were observed. P-HCL was well tolerated with respect to vital sings, clinical laboratory, AEs and PE.

Interpretation of results

The present data revealed no effect of p-HCL on myocardial re-polarisation in healthy female subjects as well as in patients suffering from ischaemic heart disease.

Concluding message

It may therefore be concluded, that p-HCL does not raise concerns on cardiac safety in healthy subjects as well as in patients with ichaemic heart disease. P-HCL was well tolerated with respect to vital sings, clinical laboratory, AEs and PE.