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IMPACT OF OROS® CONTROLLED-RELEASE DELIVERY ON PHARMACOKINETICS OF OXYBUTYNIN AT DIFFERENT DOSAGES: SEVERITY-DEPENDENT TREATMENT OF OVERACTIVE BLADDER

Hypothesis / aims of study

To assess the pharmacokinetics of OROS® controlled-release oxybutynin (OROS®-Oxy) at different dosages compared with immediate-release oxybutynin (IR-Oxy), and to determine the pharmacodynamic properties with regard to severity-dependent reduction of urge urinary incontinence (U-UI).

Study design, materials and methods

A total of 105 patients were enrolled in this multicenter, randomized, double-blind study. Individual dose titration was performed to assess the minimum effective (MED), maximum tolerated (MTD) or maximum allowed dose (MAD) of either OROS®-Oxy or IR-Oxy. Blood samples were collected during maintenance therapy with frequent sampling to analyze for R-oxybutynin and R-desethyloxybutynin concentrations. Predose plasma levels were obtained as the minimum concentrations achieved at steady state during the dosing regimen. In parallel, U-UI episodes were assessed at baseline and during maintenance therapy at the final dose level.

Results

For both IR-Oxy and OROS®-Oxy, predose R-oxybutynin plasma concentrations increased in a dose-dependent fashion. For comparable dosages predose plasma levels were higher for OROS®-Oxy as compared with IR-Oxy. Following a single dose of IR-Oxy, plasma concentrations peaked about 27-fold after 1 hour and decreased to baseline levels within 4 to 8 hours. In contrast, plasma concentrations of R-oxybutynin remained constant for up to 24 hours following administration of OROS®-Oxy at either dose. The overall percent reduction in weekly U-UI episodes was 84% (to 4.8 episodes) and 88% (to 3.1 episodes) for OROS®-Oxy and IR-Oxy, respectively ($p<0.05$). Patients who titrated to final dose levels of 10, 15, and 20 mg OROS®-Oxy differed regarding their weekly U-UI episodes at baseline ($14.5<30.3<42.0$). Due to individual dose titration, U-UI-episodes/week were profoundly reduced at all applied doses (1.9-2.0 episodes/week, respectively). Fewer patients reported moderate to severe dry mouth with OROS®-Oxy as compared with IR-Oxy (25 versus 46%, $p<0.05$).

Interpretation of results

The pharmacokinetic parameters of OROS® controlled-release oxybutynin are dose proportional with minimized fluctuations between peak and trough concentrations associated with immediate-release (IR) oxybutynin.

Concluding message

In clinical practice OROS® controlled-release oxybutynin may thus facilitate highly efficacious, severity-dependent treatment of U-UI with flexible dose adaptations based on the patients' needs.

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