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THE CENTRALLY ACTING ION CHANNEL MODULATOR FLUPIRTINE IMPROVES BLADDER FUNCTION IN ANIMAL MODELS AND PATIENTS WITH OVERACTIVE BLADDER SYNDROME

Hypothesis / aims of study

Flupirtine is a centrally acting ion channel modulator, mainly opening KCNQ potassium channels (1), which is clinically used in several countries for the treatment of pain (2). Based upon the role of central nervous processing in the control of bladder function, we have tested the concept that central ion channel modulation may be useful for the treatment of the overactive bladder syndrome (OAB).

Study design, materials and methods

In vivo animal studies were performed in urethane-anesthetized rats using two standard models, i.e. volume-induced bladder contraction (VIBC) and acetic acid-induced bladder irritation (AAIBI). Additional in vitro experiments were performed with isolated rat bladder strips.

A multi-national, placebo-controlled, randomized, doubled-blind, actively controlled clinical proof of concept study was performed in OAB patients. Patients randomized for a planned 12 weeks treatment with placebo, flupirtine (400 mg/d week 1-8, escalated to 600 mg/d for week 9-12) or tolterodine ER 4 mg (2:2:1 randomization) using reductions in mean number of micturitions per 24 h as compared to placebo as the primary efficacy parameter. Statistical analysis was by ANCOVA. The study had 80% power to detect a reduction in frequency by 0.7 episodes per 24 h relative to placebo based upon a 3-day micturition diary.

Results

In the VIBC model, flupirtine (0.1-10 mg/kg) dose-dependently reduced the frequency of bladder contractions with maximum reductions of about 60%. This was not accompanied by significant alterations of contraction amplitude. Oxybutynin and duloxetine (0.1-10 mg/kg) reduced frequency at up to 1 mg/kg but not at higher doses, and oxybutynin additionally depressed contraction amplitude. In the AAIBI model, flupirtine also dose-dependently reduced the frequency of bladder contractions with the highest dose reducing them by >80%. Duloxetine doses up to 1 mg/kg reduced contraction frequency by up to 40%. While flupirtine also reduced KCl-induced contractions of isolated rat bladder strips, the required concentrations (EC_{50} 7.5 µM) markedly exceeded plasma concentrations achieved by any of the above in vivo doses, indicating that its effects on bladder function are not peripherally mediated.

The clinical study was prematurely terminated due to unexpected hepatotoxicity in several patients (asymptomatic increase in liver enzymes, particularly alanine aminotransferase). At that time 207 patients had been recruited into the study, 189 (74, 76 and 39 on placebo, flupirtine and tolterodine, respectively) had at least one efficacy assessment during treatment (FAS population), and only 88 (38, 32 and 18) had reached the 8 week assessment point without major protocol violations (PP population). The difference between patients in the FAS and the PP populations were largely due to the premature study termination. In the FAS population changes from baseline in micturition frequency were -0.79 for placebo, -1.29 for flupirtine and -2.12 per 24 h for tolterodine (8 week assessment or last observation carried forward; p = 0.074 for flupirtine vs. placebo). In the PP population after 8 weeks of treatment corresponding changes were -1.27, -2.22 and -3.14, respectively (p = 0.0296 for flupirtine vs. placebo). Due to the premature study termination, secondary efficacy parameters were not analyzed.

Interpretation of results

Flupirtine dose-dependently reduces contraction frequency in two rat models of bladder dysfunction, the magnitude of reduction being at least as large as with oxybutynin or duloxetine. A low potency for inhibition of bladder contraction in vitro indicates that the in vivo effects of flupirtine, similar to its analgesic effects, are centrally mediated.

Due to safety-related premature study termination, the clinical efficacy data are difficult to interpret with small patient numbers leading to poor statistical power. Nevertheless, in patients a statistically significant effect of flupirtine relative to placebo was observed in the PP population with a similar trend in the FAS population.

Concluding message

The central ion channel modulator flupirtine improves bladder function in animal models and possibly also in patients. While the risk of hepatotoxicity prevents the further testing or use of flupirtine in OAB patients, this adverse effect appears compound-specific rather than related to its mechanism of action. Therefore, we propose that central ion channel modulation is a novel and promising principle to treat bladder dysfunction.

References

1. Curr Med Chem (2005) 12; 453-460
2. Drugs (1993) 45, 548-569

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**EudraCT 2006-004854-26**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Ethikkomission Landesärztekammer Hessen (Frankfurt, Germany). The animal part of our studies had been approved by the Committee on Animal Care and Use of the Federal State of Saxony and carried out following the German Law on the Protection of Animals.**
Was the Declaration of Helsinki followed?	**Yes**

Was informed consent obtained from the patients?	**Yes**