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Poster presentation

Pharmacological characterization of the novel phosphodiesterase type 5 (PDE5) inhibitor lodenafil carbonate on human and rabbit corpus cavernosum

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Background

Nitrergic nerves and endothelial cells release nitric oxide (NO) in the corpus cavernosum (CC), a key mediator that stimulates soluble guanylyl cyclase to increase cGMP levels and cause penile erection. Phosphodiesterase 5 (PDE5) inhibitors, such as sildenafil, prolong NO effects by inhibiting cGMP breakdown.

Purpose

We aimed to investigate the effects of the novel PDE5 inhibitor lodenafil carbonate (Fig. 1a) on *in vitro* cavernosal relaxation, mean arterial pressure, activity of crude PDE extracts from human platelets as well as to evaluate its pharmacokinetic properties.

Methods

In functional studies, cavernosal strips were mounted in organ baths for isometric force recording, coupled to a PowerLab 8/SP™ data acquisition system. Rats were surgically manipulated and telemetry transmitters were implanted in the abdominal aorta for measurements of systolic, diastolic and mean arterial blood pressure. For determination of PDE activity by LC-MS/MS analysis, lodenafilc arbonate (0.005–1 μM) was preincubated in the enzymatic mixture for 5 min at room temperature. Reaction was initiated by the addition of the substrate cGMP (5 μM) at 35°C for 30 min. Pharmacokinetics was studied by tandem mass spectrometry (LC-MS/MS) with positive ion electrospray ionization using multiple reactions monitoring (NMR) method. Blood samples were collected at 0.02 to 24 h after drug administration by intravenous (1 mg/kg) and oral (10 mg) routes. The hydrolysis of lodenafil carbonate (final concentration 10 μM) was also studied in human, dog and rat plasma as well as in acid solution (100 mM hydrochloric acid).

Results

The cumulative addition (0.001–100 μM) lodenafil carbonate to the bathing medium produced concentration-dependent relaxations in phenylephrine-precontracted CC with pEC_{50} values of 6.55 ± 0.02 and 5.97 ± 0.07 in rabbit and human tissues, respectively (Fig. 1b). The addition of lodenafil carbonate (0.1 μM) caused significant leftward shifts in the concentration-response curves to acetylcholine (0.01–100 μM) in rabbit and human corpus cavernosum, along with and enhancement of maximal responses. The addition of lodenafil carbonate significantly potentiated both the magnitude and the duration of electrically-evoked relaxant responses (1–20 Hz) in human and rabbit penile tissue. Treatment with lodenafil carbonate (1–10 mg/kg) caused neither dose- nor time-dependent changes in the mean arterial blood pressure (123 ± 6 mmHg to 132 ± 7 among the different doses and times selected for measurements). Lodenafil carbonate

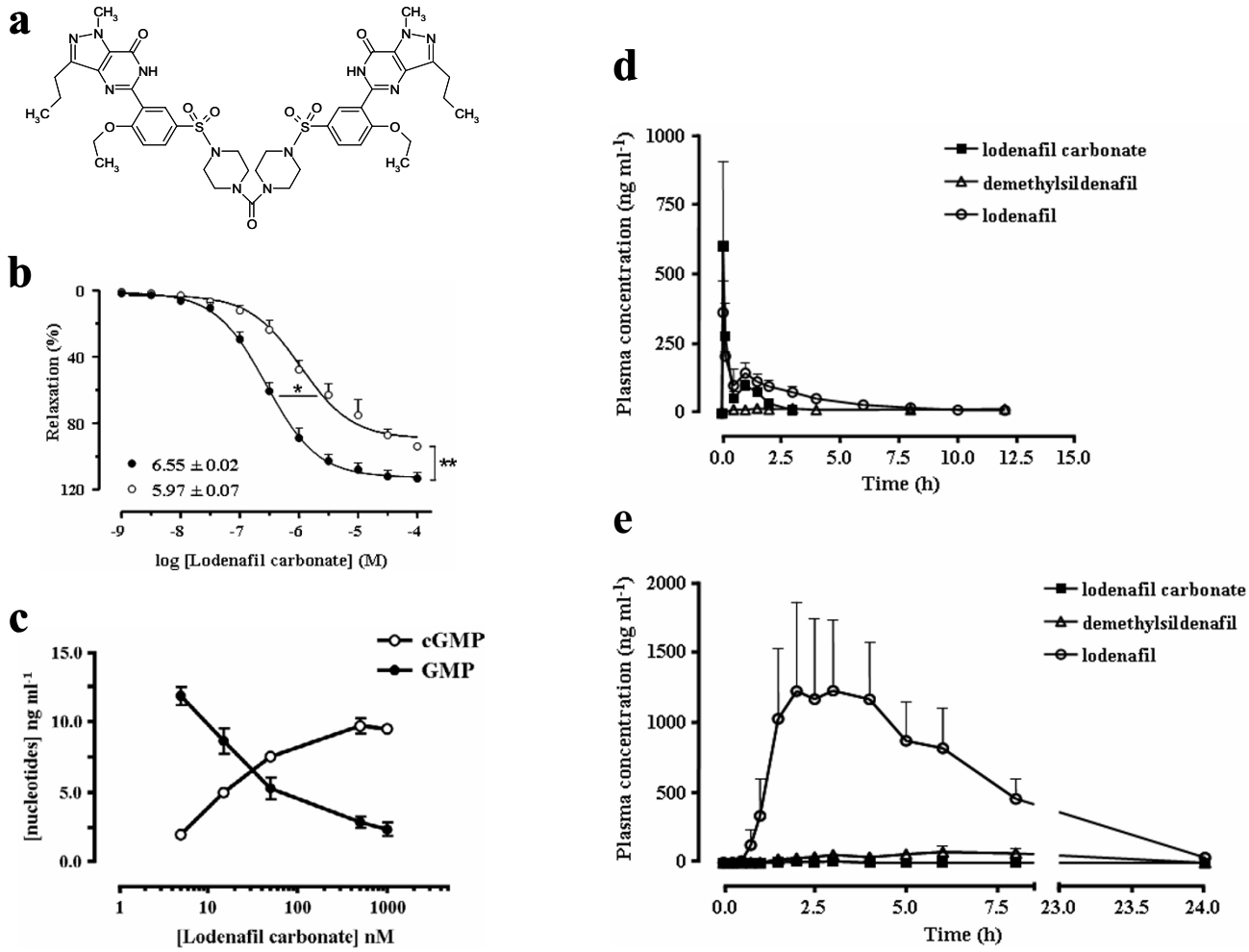

Figure 1

(a) Structure of lodenafil carbonate; **(b)** Concentration-response curves to lodenafil carbonate (0.001–100 μM) in rabbit (closed circles) and human (open circles) CC; **(c)** Effect of lodenafil carbonate on cyclic GMP hydrolysis; **(d, e)** Mean plasma concentrations of lodenafil carbonate, lodenafil and demethylsildenafil in Beagle dogs after single intravenous (1 mg/kg; top) and oral (10 mg; bottom) doses of lodenafil carbonate.

reduced cGMP hydrolytic activity as a function of increasing inhibitor concentration, with IC_{50} value approximately 2-fold lower than sildenafil at the substrate concentration used (5 μM) (Fig. 1c). Following a single i.v. dose of lodenafil carbonate (1 mg/kg) to male Beagle dogs, the compound exhibited C_{max} of 599 ng/ml and high plasma clearance of 3.24 l/h/kg with a volume of distribution of 2.73 l/kg. This volume of distribution resulted in the elimination half-life value of 0.57 h (Fig. 1d). Plasma concentrations of lodenafil carbonate after a single oral dose (10 mg) achieved a C_{max} of 11 ng/ml (Fig. 1e). However, the C_{max} for lodenafil was 1357 ng/ml and T_{max} was approximately 2 h, reflecting the occurrence of systemic metabolism. The half-life of lodenafil carbonate after p.o. administration (2.11 h) was slightly longer than the equivalent value after i.v. dosing, suggesting that the rate of absorption limited the overall rate of elimination. In the study of the stability of lodenafil carbonate (1 μM) in acid solution, the employment of HPLC and mass spectral analysis of the 2 h incubations revealed the presence of lodenafil and lodenafil carbonate as the major components detected. The retention times obtained for sildenafil, lodenafil, lodenafil carbonate and demethylsildenafil were 4.00, 2.51, 7.43 and 2.04 min, respectively. In human and dog plasma, a similar qualitatively pattern was observed, with lodenafil carbonate being detected in higher levels than lodenafil. No trace of demethylsildenafil was detected in both acid and plasma stability assays.

Conclusion

Lodenafil carbonate compound, which concentration-dependently inhibits cGMP-dependent PDE hydrolytic

activity, relaxes human and rabbit cavernosal tissue and enhance endogenous NO-induced responses. Advances in treatment of erectile dysfunction seem likely in the immediate future and lodenafil carbonate represents an attractive agent in that regard, based on the findings provided in the present investigation.