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ACUTE DAPOXETINE DELAYS PUDENDAL MOTONEURON REFLEX DISCHARGES IN ANESTHETIZED RATS

François Giuliano[1,3*], Jacques Bernabé[1], Peter Gengo[2], Miguel Laurin[1], Pierre Clément[1]

[1] PELVIPHARM Laboratories, Gif-sur-Yvette, France. [2] ALZA Corporation, Mountain View, California, USA. [3]Neuro-Urology unit, Department of Neurological Rehabilitation, Raymond Poincaré Hospital, Garches, France. * e-mail address: giuliano@cyber-sante.org

ABSTRACT

Introduction and objective: Premature ejaculation (PE) is under-recognized and under-treated whereas currently available data on the epidemiology of PE indicate this disorder as frequent and widespread. The efficacy of on-demand treatment of PE with serotonin selective re-uptake inhibitors (SSRIs) is still a matter of controversy. In the present study we aimed at investigating the effect of acute i.v. delivery of dapoxetine, a short-acting SSRI, in an experimental model of ejaculatory reflex in rats: the pudendal motoneuron reflex discharges (PMRD) elicited by stimulation of the dorsal nerve of the penis (DNP).

Methods: Male Wistar rats were equipped with bipolar electrodes for bilateral stimulation of DNP and for recording reflex electrical discharges in the motor branch of the pudendal nerve. PMRD was measured in anesthetized rats before and 1 hour after i.v. injection of vehicle or one of the three doses (1, 3 or 10 mg/kg) of dapoxetine tested (10 rats per group). Latency and duration of PMRD in response to DNP electrical stimulation were determined 1 hour after injection of each treatment and compared to those obtained before treatment.

Results: At the three dapoxetine i.v. doses tested, the latency for PMRD to occur in response to DNP stimulation was significantly increased in comparison with pre-treatment values. This effect was maximal with dapoxetine 1 mg/kg (pre- vs post-treatment mean±sem: 10.28±0.12 vs 12.42±0.54 ms; paired t-test, $p<0.01$). The duration of PMRD resulting from bilateral DNP stimulation was significantly decreased after i.v. delivery of dapoxetine, whatever the dose tested, in comparison with pre-treatment values. This effect was maximal with 10 mg/kg dapoxetine (pre- vs post-treatment mean±sem: 13.31±0.25 vs 10.85±0.33 ms; paired t-test, $p<0.01$).

Conclusion: The present data demonstrate that acute i.v. administration of dapoxetine is capable to modulate the ejaculatory reflex in delaying PMRD and in reducing its duration measured in response to DNP stimulation even at a dose of 1 mg/kg. These results provide pre-clinical evidence supporting the use of dapoxetine for the on-demand treatment of PE.

INTRODUCTION & OBJECTIVE

➢The efficacy of chronic treatment with serotonin selective re-uptake inhibitors (SSRIs) in delaying ejaculation is well documented although their ability to delay ejaculation after acute administration is still a matter of debate (McMahon and Touma, 1999; Waldinger et al., 2004).

➢Sensory stimuli from the genitourinary area is transmitted to perineal muscle reflex circuits in the spinal cord. Electrical stimulation of the dorsal nerves of the penis (DNP), which convey sensory inputs from the penile glans, has been shown to induce pudendal motoneuron reflex discharges (PMRD) measured in the motor branch of the pudendal nerve, which drives motor outputs to bulbspongiosus muscle (Johnson and Hubscher, 1998).

➢The goal of the study is to investigate the effects of acute i.v. delivery of dapoxetine on PMRD elicited by stimulation of DNP.

METHODS

Surgical preparation

All animal experiments were carried out in accordance with European Communities Council Directives on the use of laboratory animals.

Adult male Wistar rats weighing 250-300 g were anesthetized with urethane (1.2 g/kg, i.p.), tracheotomized, and the carotid artery catheterized for blood pressure measurement.

Bipolar platinum stimulating electrodes connected to an electrical stimulator (AMS 2100, Phymep, Paris, France) were placed bilaterally on the dorsal nerves of the penis (DNP). Electrical stimulation consisted of 0.1 ms duration pulses which intensity was set between 50 and 175 µA.

The recording electrode was placed on the motor branch of the left pudendal nerve. Electrical signals were amplified (DP-301, Warner Instrument Corp., Phymep; gain, 10000; Low pass, 10 KHz; High pass, 300 Hz) before being digitized.

Experimental procedure

Sixty successive single-shock stimuli were bilaterally delivered to DNP and the average evoked responses recorded in the motor branch of the left pudendal nerve were generated.

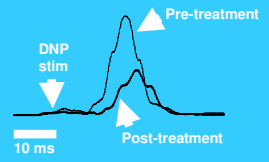
Pudendal motoneuron reflex discharges (PMRD) recordings were performed 5 minutes prior to and 60 minutes after i.v injection of saline or dapoxetine (volume 1ml/kg).

Each rat was injected with one of the three tested doses of dapoxetine (1, 3 or 10 mg/kg, i.v.).

Latency and duration of PMRD elicited by stimulation of DNP were determined.

Study sponsored by Johnson & Johnson Health Care Companies

RESULTS



Treatment: Dapoxetine 3 mg/kg i.v.

Figure 1: Example of pudendal motoneuron reflex discharges (PMRD) elicited by bilateral stimulation of the dorsal nerves of the penis (DNP) measured 5 min before and 60 min after i.v. delivery of dapoxetine 3 mg/kg.
The signal was rectified for analysis purpose and traces correspond to 60 averaged integrated trials. Following dapoxetine treatment, PMRD latency was increased and PMRD duration as well as amplitude were decreased.

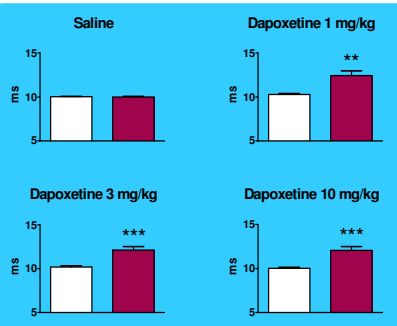


Figure 2: Effect of acute i.v. injection of dapoxetine on latency of PMRD elicited by stimulation of DNP. The latency of PMRD was increased after dapoxetine treatment in comparison with pre-treatment at the three doses of dapoxetine tested.

Values represent the means±sem of 9-10 rats. Statistics. Asterisks (two symbols, $p<0.01$; three symbols, $p<0.001$): paired t-test.

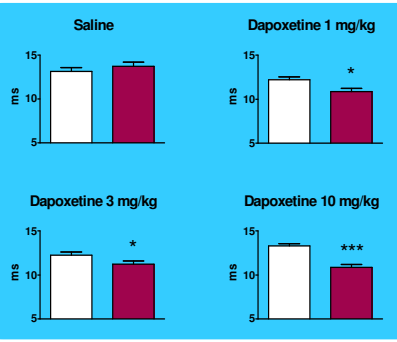


Figure 3: Effect of acute i.v. injection of dapoxetine on duration of PMRD elicited by stimulation of DNP. The latency of PMRD was increased after dapoxetine treatment in comparison with pre-treatment at the three doses of dapoxetine tested.

Values represent the means±sem of 9-10 rats. Statistics. Asterisks (one symbol, $p<0.05$; three symbols, $p<0.001$): paired t-test.

CONCLUSION

➢Acute i.v. delivery of dapoxetine increases PMRD latency and reduces PMRD duration at a dose of 1 mg/kg.

➢Acute i.v. dapoxetine is capable of modulating the ejaculatory reflex loop in anesthetized rats.

References

➢McMahon C.G. and Touma K. (1999) Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. J. Urol. 161: 1826-1830.

➢Waldinger M.D., Zwinderman A.H. and Olivier B. (2004) On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. Eur. Urol. 46: 510-516.

➢Johnson R.D. and Hubscher C.H. (1998) Brainstem microstimulation differentially inhibits pudendal motoneuron reflex inputs. Neuroreport 9: 341-345.