MP25

Experimental evidence that a combination of sGC stimulator BAY 60-4552 and PDE5 inhibitor vardenafil might salvage patients with insufficient response to PDE5 inhibitors after cavernous nerve injury

PELVIPHARM

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OBJECTIVES

- Promoting cGMP accumulation via **PDE5 inhibitors** constitutes currently the first-line therapy and the **gold standard treatment of erectile dysfunction** (ED).
- In several pathological conditions, including post-radical prostatectomy (RP)-associated ED, the NO release is impaired. It results in **insufficient response to PDE5 inhibitors** since their effectiveness needs at least a minimal NO drive.
- A valuable approach to bypass the need for a sufficient NO drive would be the **activation of cGMP production by sGC in a NO—independent manner by the use of a sGC stimulator.**

Therefore the aims of the present study were:

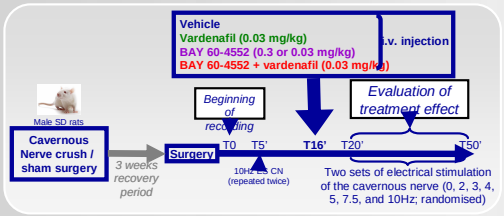
1/ to test the effects of a new therapeutic strategy: the use of a NO-independent heme-dependent sGC stimulator, BAY 60-4552, and to compare them to the effects of a PDE5 inhibitor, vardenafil, and

3/ to evaluate the possible additional benefits offered by a combined treatment with BAY 60-4552 and vardenafil on the erectile responses to electrical stimulation of the cavernous nerve (ES CN) in anesthetized rats with bilateral CN crush injury.

METHODS

Research design

Male Sprague-Dawley rats underwent laparotomy (sham, n=10) or bilateral CN crush injury (n=57). After 3 weeks of recovery, erectile function was evaluated in urethane-anesthetized rats following electrical stimulation of the cavernous nerve (ES CN) at different frequencies. The effects of intravenous (iv) injection of vehicle, vardenafil 0.03 mg/kg, BAY 60-4552 0.03 mg/kg or 0.3 mg/kg, or a combination of BAY 60-4552 0.03 mg/kg + vardenafil 0.03 mg/kg were evaluated in CN crushed rats.



Bilateral cavernous nerve crush injury

Rats were anesthetized with isoflurane (1-1.2 %, CSP, France), the CN was isolated and crushed with a micro serrefine (100g jaw pressure, FST), applied for 120 seconds, removed for 30 seconds, and then reapplied for a further 120 seconds.

Erectile function evaluation : electrical stimulation of the cavernous nerve (ES CN)

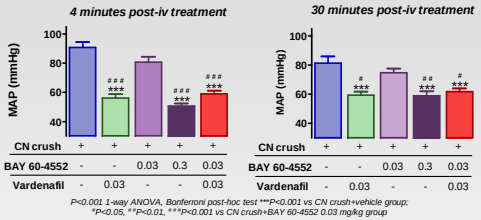
* Erectile function was evaluated 3 weeks after surgery. The rats were anesthetized (urethane 1.2 g/kg), tracheotomized, and, the carotid artery and the jugular vein were catheterized to respectively record mean arterial pressure (MAP) and perform iv injections. A needle connected to a catheter was inserted in one of the corpora cavernosa to record intracavernous pressure (ICP). One of the CN was exposed and mounted on a bipolar platinum electrode connected to an electrical stimulator (AMS 2100, Phymep, France).

* After a 5 minute-period of simultaneous computerized measure of MAP and ICP recording, two consecutive ES CN (6V, 10Hz, 1 ms for 45 s) were performed to evaluate the baseline erectile response. Then, acute iv treatment (1 ml/kg) was administered exactly 4 minutes before the beginning of the ES CN for frequency-response curves. The CN was thereafter stimulated at different frequencies (0, 2, 3, 4, 5, 7.5, and 10 Hz) at 2-minute intervals in a randomized manner and repeated twice in order to assess the erectile responses.

* Erectile responses to ES CN were expressed as a ratio of ΔICP (mmHg) / MAP (mmHg) x 100, with ΔICP being the difference between ICP in the flaccid state and ICP during the plateau phase of the erectile response. ΔICP was normalized with MAP to account for the close influence of the systemic blood pressure in the amplitude of ICP increase during the plateau phase of the erectile response.

RESULTS

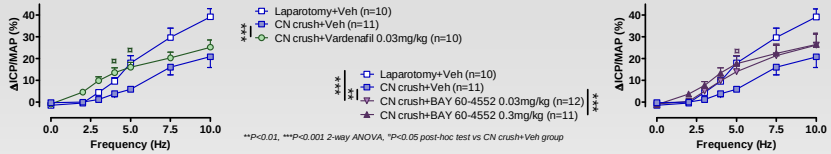
Effects of iv treatments on mean arterial pressure



*P<0.001 1-way ANOVA, Bonferroni post-hoc test ***P<0.001 vs CN crush+vehicle group; #P<0.05, ##P<0.01, ###P<0.001 vs CN crush+BAY 60-4552 0.03 mg/kg group*

- In CN crushed anesthetized rats, while iv BAY 60-4552 0.03mg/kg did not change MAP, BAY 60-4552 0.3mg/kg significantly lowered MAP.
- **Intravenous BAY 60-4552 (0.03 mg/kg) / vardenafil (0.03 mg/kg) combination decreased MAP similarly to iv vardenafil alone.**

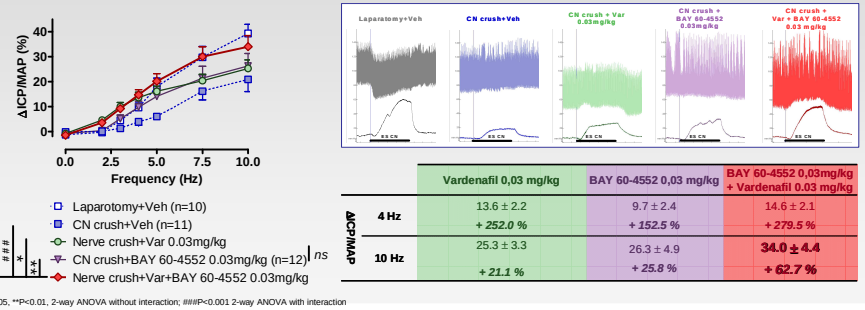
Effects of iv treatments on erectile responses to ES CN in rats with CN crush injury



**P<0.01, ***P<0.001 2-way ANOVA, *P<0.05 post-hoc test vs CN crush+Veh group*

- **Bilateral CN crush injury** followed by a 3-week recovery period **decreased erectile responses** to ES-CN by about 50%.
- In CN crushed rats, both **iv vardenafil** 0.03 mg/kg and **BAY 60-4552** 0.03 or 0.3 mg/kg **increased erectile responses** to ES-CN to the same extent.
- Normal erectile function was not totally restored by vardenafil, which supports the relevance of the CN crushed injured rat as an experimental model of insufficient response to PDE5 inhibitors mimicking the clinical setting observed in men with RP-associated ED.
- The absence of a dose-effect relationship following BAY 60-4552 suggests that only a low dose is needed to produce its maximal effects on erectile function, limiting thus its potential side effects on blood pressure-lowering.

Effects of intravenous vardenafil/BAY 60-4552 combined treatment on erectile responses to ES CN in rats with CN crush injury



ΔICP/MAP	Vardenafil 0,03 mg/kg	BAY 60-4552 0,03 mg/kg	BAY 60-4552 0,03mg/kg + Vardenafil 0.03 mg/kg
4 Hz	13.6 ± 2.2 *+ 252.0 %*	9.7 ± 2.4 *+ 152.5 %*	14.6 ± 2.1 *+ 279.5 %*
10 Hz	25.3 ± 3.3 *+ 21.1 %*	26.3 ± 4.9 *+ 25.8 %*	**34.0 ± 4.4** **+ 62.7 %**

*P<0.05, **P<0.01, 2-way ANOVA without interaction; ###P<0.001 2-way ANOVA with interaction

- Neither the acute vardenafil 0.03 mg/kg iv treatment nor the acute iv BAY 60-4552 0.03 mg/kg treatment were able to fully restore a normal erectile function when administered alone.
- However, **the combined administration of both vardenafil 0.03 mg/kg and BAY 60-4552 0.03 mg/kg exerted additive effects** in the present model of CN crush injury and **restored a normal erectile response to ES CN in the anesthetized rat with CN crush injury.**
- This suggests that by increasing cGMP production using a sGC stimulator, BAY 60-4552, while inhibiting its degradation using a PDE5 inhibitor, vardenafil, erectile responses following ES CN are better potentiated probably by bypassing the need for a preserved NO pathway.

CONCLUSIONS

To conclude, the present study supports the hypothesis that:

*** stimulation of sGC by BAY 60-4552 could ameliorate ED following CN injury,**

*** a combined administration of the sGC stimulator BAY 60-4552 and the PDE5 inhibitor vardenafil constitutes a valuable approach in treating ED in situations in which PDE5 inhibitors alone are not fully efficacious, and in which NO release is impaired as it is the case in men post-RP.**

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