Predictive Value of Laser Evoked Potentials & VAS

PW285

Exploring Anti-Nociceptive/Anti-Hyperalgesic Activity: Effects of Different Compound Classes on Normal, UVB and Capsaicin Irritated Skin in Healthy Human Volunteers

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INTRODUCTION

Translational human pain models have been proposed to assess the analgesic potency of drugs in early clinical development (ECD) and to support go-/no-go decisions, before entering intense phase II/III patient studies. The EEG Laser Evoked Potential (LEP) paradigm is one promising method – combined with visual analog scale scoring (VAS-Pain) – to assess the anti-nociceptive and anti-hyperalgesic properties of analgesic compounds on normal and sensitized skin (UVB, capsaicin). Compounds approved for treatments of different pain states and with different Modes of Actions (MoAs):

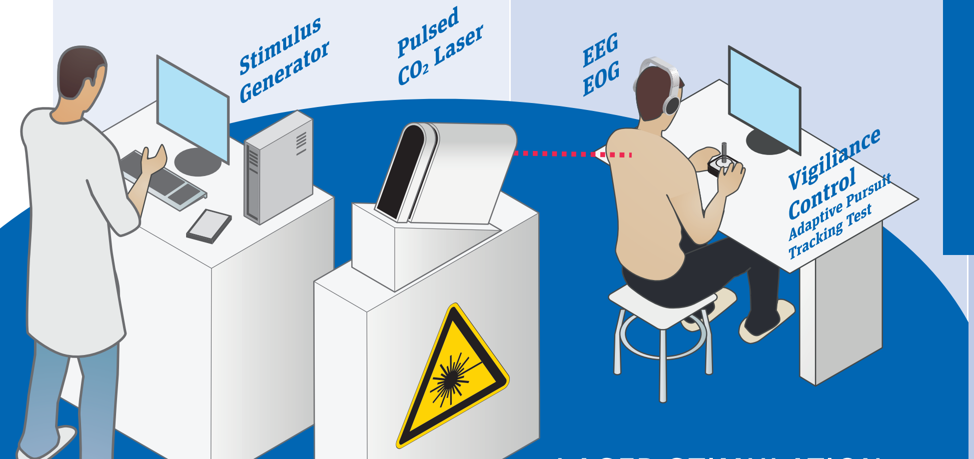
Celecoxib/ C, Duloxetine/ D, Lacosamide/ L, Pregabalin/ P, were tested in this paradigm to further assess the model's predictivity, sensitivity, and validity after single dose (SD) administrations.

Keywords:
Laser-EP/LEP, VAS, UV, capsaicin, anti-nociception, anti-hyperalgesia, PoC

Competing Interests:
This (validation) study was sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG – the employer of T. Brand, A. Borta, L. Nicolas, J. Scholpp – and K. Schaffler was the Principal Investigator to run this study at HPR Munich. There was no conflict of interests.

METHODS

These latter issues were investigated in a single center, single-blind, randomized, SD, placebo-controlled, 5-way crossover trial (EC and CA approved) by assessing the efficacy of C, D, L, and P vs. placebo in 25 healthy Caucasian volunteers (f9/m16), age 20-52 years inclusive. Eligible subjects were randomized to 1 of 10 treatment sequences (Williams Design) and received SDs of C/200mg, D/60mg, L/100mg, P/150mg & placebo. There were 5 separate study visits with a minimum 1-week washout period between each treatment visit. Subjects underwent multiple (infra-red) CO_2-Laser-EP & VAS sessions in turn on normal, UVB- and capsaicin-irritated skin at 0, 1, 2, 3, 4, 5, and 6h post administration (p.a.). Subjects separately received UVB irradiation (311nm narrow band, 2-fold minimal erythema dose/MED to different skin areas of 5x5cm each) and diverse occlusive topical (30min) capsaicin applications (1% alcoholic extract at -2h pre-dose, 5.5cm in diameter on the back).
Statistics (SAS 9.2) of LEP variables and VAS were based on a linear mixed effects model for crossover designs.



LASER STIMULATION AND EVALUATION UNIT

RESULTS

The primary endpoint (attenuation of LEP Peak to Peak (PtP) amplitude) ***Fig. 8***, showed the following effects in the 3 different skin types:

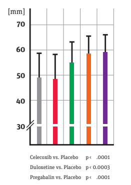
NORMAL SKIN *FIG. 1/2*

Compared to placebo the averaged 6h p.a. PtP amplitudes of LEPs (***Fig. 2***) were significantly reduced by D (-1.7 µV; P<0.0215) and P (-2.68 µV; P<0.0004) – starting between 1 & 2h p.a. and being maintained up to >6h post dose (***Fig. 1***). LEP was unaffected by C. No consistent effect was seen for L, although lower PtP amplitudes were measured 5 & 6h p.a.
D & L failed to significantly reduce the 6h p.a. VAS scores vs. placebo, but significance was achieved with SDs of P (-9.1 mm; P<.0001) and C (-2.94 mm; P<0.0111).

UVB SKIN *FIG. 3/4/5*

Compared to placebo the averaged 6h p.a. PtP amplitudes (***Fig. 4***) were significantly reduced by C (-6.20 µV; P<.0001), D (-4.54 µV; P<.0001) & P (-3.72 µV; P<.0001) – starting at 1h p.a., but not by L.
VAS scores (***Fig. 5***) in the 6h p.a. period were significantly decreased by P(-8.71mm; P<.0001), C(-8.08mm; P<.0001) and D (-4.19 mm; P<0.0003), whereas L had no effect.

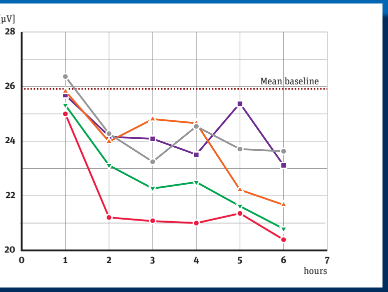
VAS "POST LASER PAIN" + CI (95%) UVB SKIN *FIG. 5*



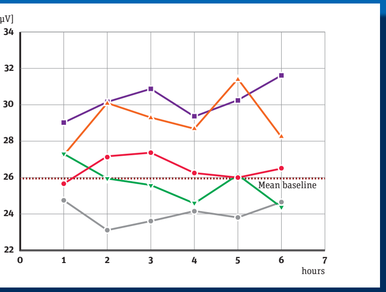
CAPSAICIN SKIN *FIG. 6/7*

Compared to placebo the averaged 6h p.a. PtP amplitudes (***Fig. 7***) were significantly reduced by P (-3.78 µV; P<.0001) and D (-2.32 µV; P<0.0025) – starting at 1-2h (***Fig. 6***), but not by C & L.
VAS scores in the 6h p.a. period were significantly reduced by P (-7.61 mm; P<.0001) and to a lesser extent by L (-3.74 mm; P<0.004) and D (-2.98 mm; P<0.0156). C reduced VAS score, but failed to achieve significance.

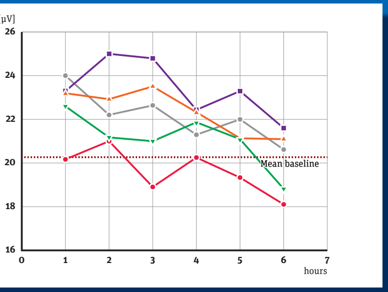
LEP PTP-AMPLITUDE NORMAL SKIN *FIG. 1*



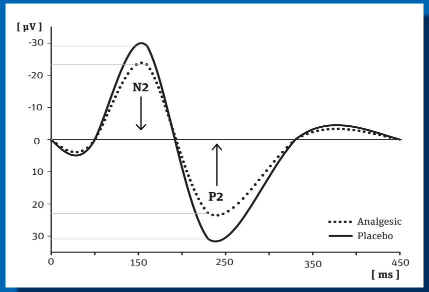
LEP PTP-AMPLITUDE UVB SKIN *FIG. 3*



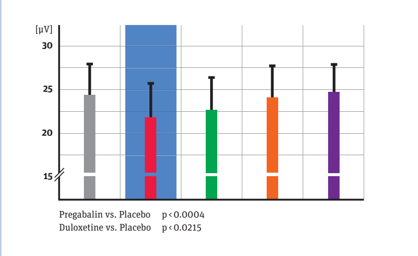
LEP PTP-AMPLITUDE CAPSAICIN SKIN *FIG. 6*



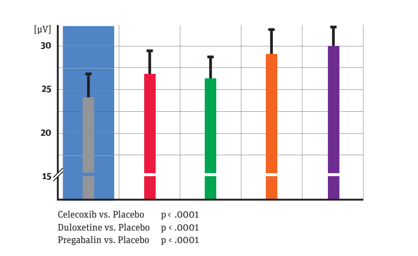
LEP PRINCIPLE & ANALGETIC EFFECT *FIG. 8*



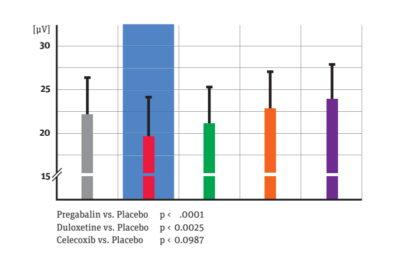
LEP PTP-AMPLITUDE + CI (95%) NORMAL SKIN *FIG. 2*



LEP PTP-AMPLITUDE + CI (95%) UVB SKIN *FIG. 4*



LEP PTP-AMPLITUDE + CI (95%) CAPSAICIN SKIN *FIG. 7*



LEGEND

- **Celecoxib** 200mg
- **Pregabalin** 150mg
- **Duloxetine** 60mg
- **Lacosamide** 100mg
- **Placebo**
- **Mean baseline**

CONCLUSIONS

As expected from MoA – LEPs generated from inflamed UVB skin – were most effectively attenuated by a SD of the selective COX-2 inhibitor **Celecoxib**. For all other skin conditions **Pregabalin** (a GABA analogue, working on resting voltage-gated Ca-channels) showed in LEPs as well as in VAS the most prominent effects. The effects were largest for LEPs on capsaicin pretreated skin, followed by UVB skin and normal skin.
Duloxetine, with its descending noradrenergic inhibition, was generally ranking second in efficacy for all skin types in LEPs.
Lacosamide, enhancing slow inactivation of sodium channels, was not effective in these LEP/VAS paradigms.

Overall the LEP paradigm – as a "human algesimetric model" – seems to have value when implemented in early analgesic drug development programs; however its predictive value for compounds with other or novel MoAs remains to be established.

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