Validation of the capsaicin 1% ethanolic solution model for use in early-phase clinical drug studies

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Introduction

Topical application of capsaicin is used to induce nociceptive sensitization by activating nociceptive afferent fibers via the Transient Receptor Potential cation channel subfamily V member 1 (TRPV1) receptor. Previous work of us using a capsaicin 1% cream formulation, showed only peripheral sensitization was induced (i.e. decreased heat pain thresholds on the application area), but not central sensitization (using laser stimuli and von Frey filaments on the site surrounding treated area). A different formulation may induce central sensitization (Schaffler et al., 2017; van der Schueren et al., 2007), due to superior skin penetration. We aimed to validate the use of a topical capsaicin 1% ethanolic solution formulation, to assess primary and secondary allodynia, as an extension to CHDR's evoked pain test battery (PainCart).

Methods

Two-period, open-label study in 10 healthy males. 7-day washout between periods. Each period lasted one full day. Application of capsaicin 1% on 3x3 cm dominant volar forearm for 30 min. Contralateral area served as control. The following tests were performed several times throughout the day:

- Capsaicin-induced pain (verbal NRS)
- LEP and von Frey tests to assess area of secondary allodynia
- PainCart (cold pressor-, pressure-, and electrical pain tests)
- Dermatological assessments (LSCI, MSCI, OCT thermography)

Contrasts were calculated using a mixed effects model and estimated with 95% confidence.

Results

Parameter	ED	p-value
Secondary mechanical allodynia vs 0	NA	0.0486
LEP: NRS, primary area vs control	0.76	<0.0001
LEP: NRS secondary area vs control	0.57	<0.0002
Capsaicin-induced vs normal heat PDT	-10%	<0.0001
MSCI: haemoglobin level, primary area vs control	0.11 AU	<0.0001
LSCI: basal flow, primary area vs control	44.02 AU	<0.0001
LSCI: area of redness, primary area vs control	211.26 AU	<0.0001
OCT: blood flow, primary area vs control	18.9%	0.0013

- Secondary allodynia was significantly induced in both periods
  No significant difference between periods (p=0.27, responder subset)
  4 non-responding subjects (area of secondary allodynia in both periods = 0mm2)
- No notable effect on EEG-related LEP endpoints
- No significant effect on cold pressor-, pressure- and electrical PDT or PTT
- Max perceived pain from capsaicin application: NRS of 4/10

Conclusions

Capsaicin 1% ethanolic formulation induced both primary and secondary allodynia, as well as redness of the skin. The pain induced by the capsaicin application was tolerable, without evidently interfering with other PainCart measurements, Area of secondary allodynia was on average smaller in the second period, but did not significantly differ from the first.

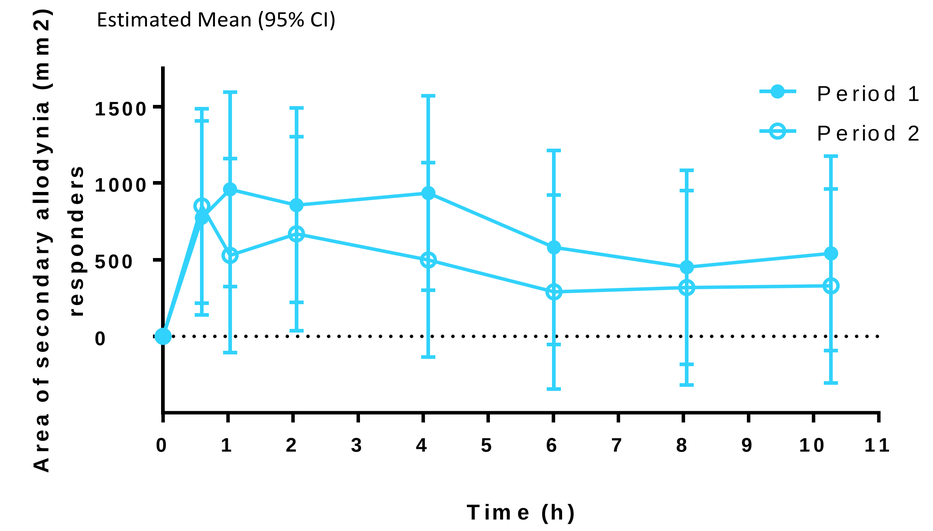

Fig. 1: Area of secondary allodynia (mm2) in responder population (secondary allodynic area > 0mm2)

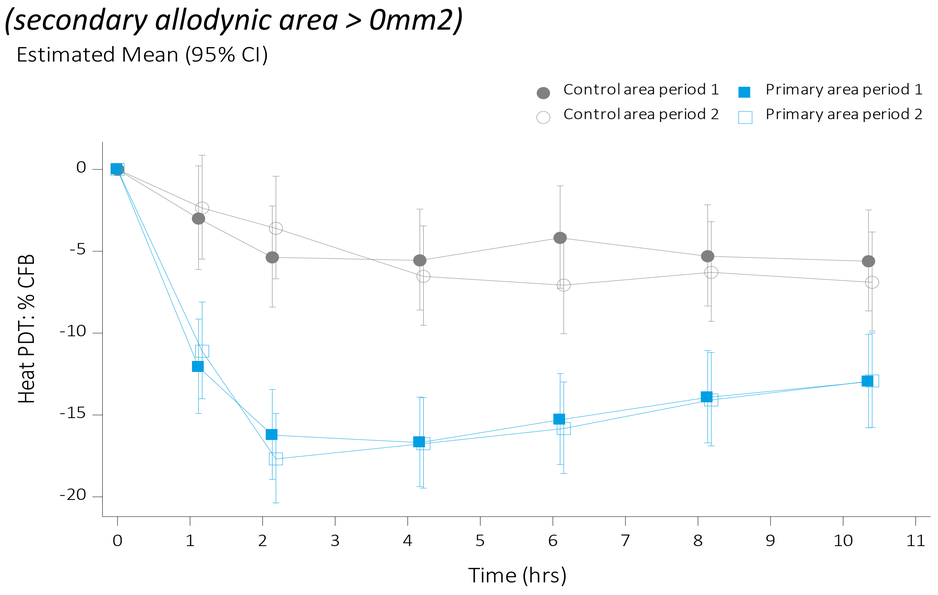

Fig. 2. heat PDT on capsaicin-treated and untreated skin (°C), change from baseline

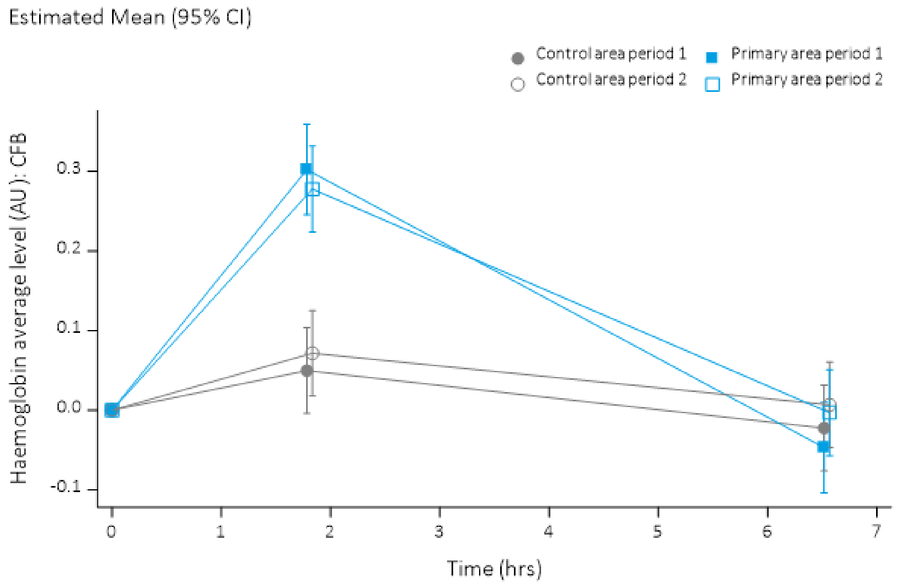

Fig. 3. haemoglobin average level (AU), change from baseline

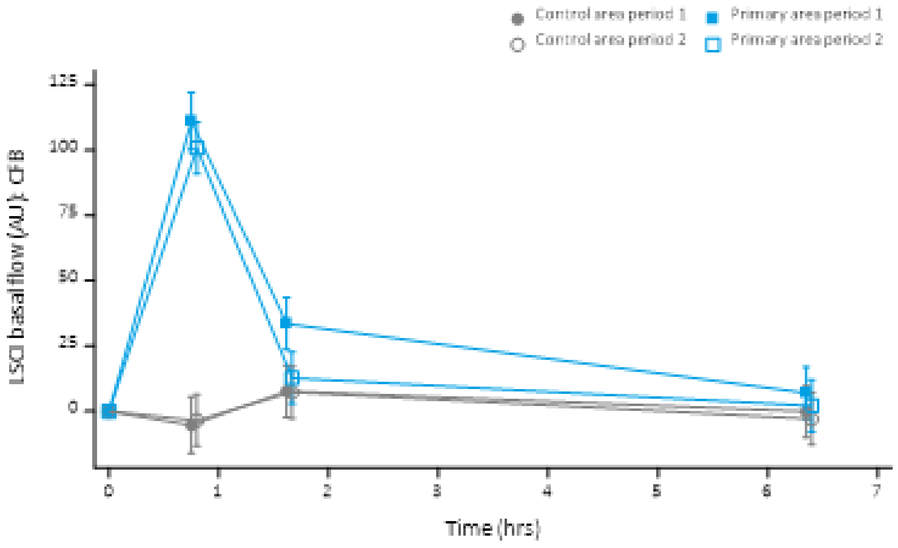

Fig. 4 LSCI basal flow (AU), change from baseline

References:

Shaffler et al., 2017: https://doi.org/10.1111/bcp.13247

Van der Schueren et al., 2017: doi:10.1111/j.1365-2125.2007.02939.x

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Abbreviations: AU: Arbitrary Units ED: Estimate of Difference; h: hours; LEP: laser-evoked potential; LSCI: laser speckle contrast imaging, MSCI: multispectral contrast imaging; mm: millimeter NA: Not Applicable; NRS: numeric rating scale; OCT: optical coherence tomography; PDT/PTT: pain detection/tolerance threshold