Topical allyl isothiocyanate as a model of TRPA-1 mediated vasodilation in humans

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Background & Aims

- The transient receptor potential cation channel A1 (TRPA1) could be a target for the development of pharmaceuticals, since it is involved in the pathophysiology of many disorders, including lung fibrosis, neuropathic pain and inflammatory bowel disease.
- Previous research observed a temporary increase in dermal blood flow (DBF) through TRPA1-activation after topical dermal administration of allyl isothiocyanate (AITC) [Andersen et al, 2017; Joseph et al, 2021].

This study aimed to validate the AITC skin challenge as a model to quantify pharmacodynamic activity of drugs targeting TRPA1 and to evaluate its tolerability and safety for humans.

Methods

- Open-label interventional study.
- Topical application of 25µL of 15% AITC in mineral oil within an O-ring on the forearm of healthy volunteers (*Figure 1*).
- Pre-AITC application baseline DBF and post-AITC maximal DBF were measured in arbitrary units (AU) using laser speckle contrast imaging (LSCI) *(Figure 1).*
- Subjects with ≤ 20% increase in DBF were classified as non-responders and excluded from statistical analysis conform prior research [Joseph et al, 2021].
- The full flare area was defined as the largest response area observed in all measurements.
- Intensity of application site reactions was measured using an 11-point numeric rating scale (NRS).
- Data are presented as mean ± standard deviation, unless stated otherwise.

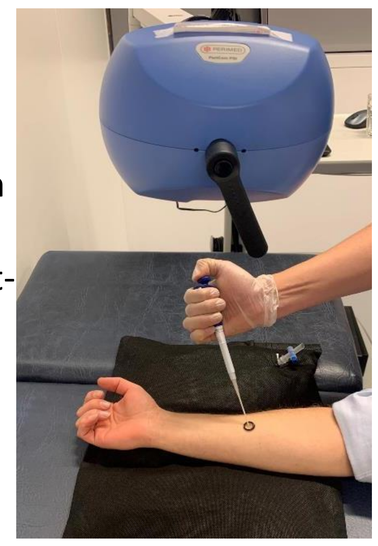

Figure 1 – Set-up of AITC application & LSCI

Results

Baseline characteristics

- 12 healthy white male subjects (age 33.6 ± 16.2 years) were included.

Dermal blood flow (Table 1)

- 9 participants were qualified as responders to AITC (75%).
- The dermal blood flow increased after AITC-application *(Figure 2)*.
- In the full flare area and within the O-ring the basal DBF was 28.8 ± 2.9 AU and 32.3 ± 3.0 AU respectively. Maximal DBF was 52.1 ± 11.0 AU and 111.9 ± 29.2 AU respectively (*Figure 3*).

Safety and tolerability

- Temporary local adverse reactions consisted of pain and pruritis at the AITC-application site (*Table 2*).
- No systemic adverse reactions were observed (n = 12).

Conclusions

1. AITC induces an increase in DBF.
2. AITC was tolerable and safe, without systemic side effects.
3. Our data affirm that the AITC skin challenge can be used as a pharmacological challenge model to evaluate the pharmacodynamic activity of TRPA1 antagonists in healthy subjects.

Figure 2 – Example of the basal DBF (A) and maximal DBF (B) in the full flare area (1) and within the O-ring (2) measured by LSCI.

The color-legend represents AU from 0-300.

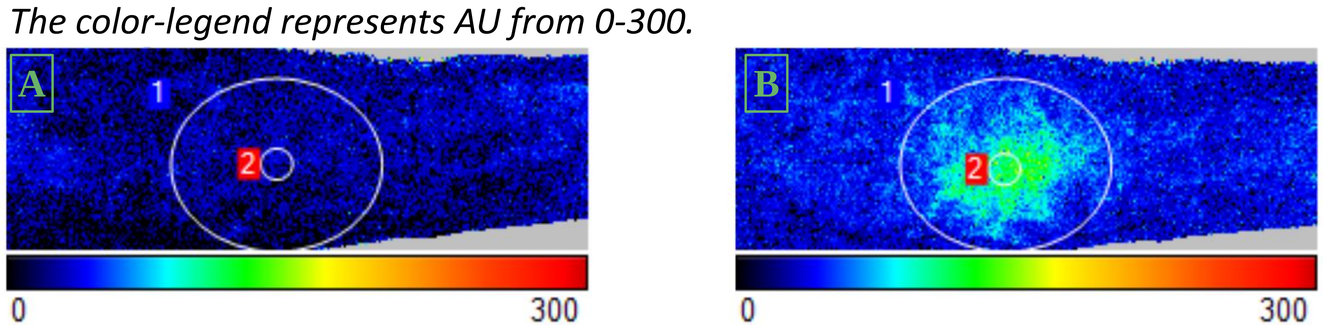

Table 1 – Measurements of DBF using LSCI

	Full flare area	*Within O-ring*
Basal flow (AU)	28.8 ± 2.9	32.3 ± 3.0
Maximal flow (AU)	52.1 ± 11.0	111.9 ± 29.2
Change from baseline (%)	80.7	246.6
Flare area (mm^2)	1411.1 ± 554.1	N/A

Figure 3 – Basal flow before AITC-application and maximal flow after AITC-application in the full flare area (mean ± standard deviation)

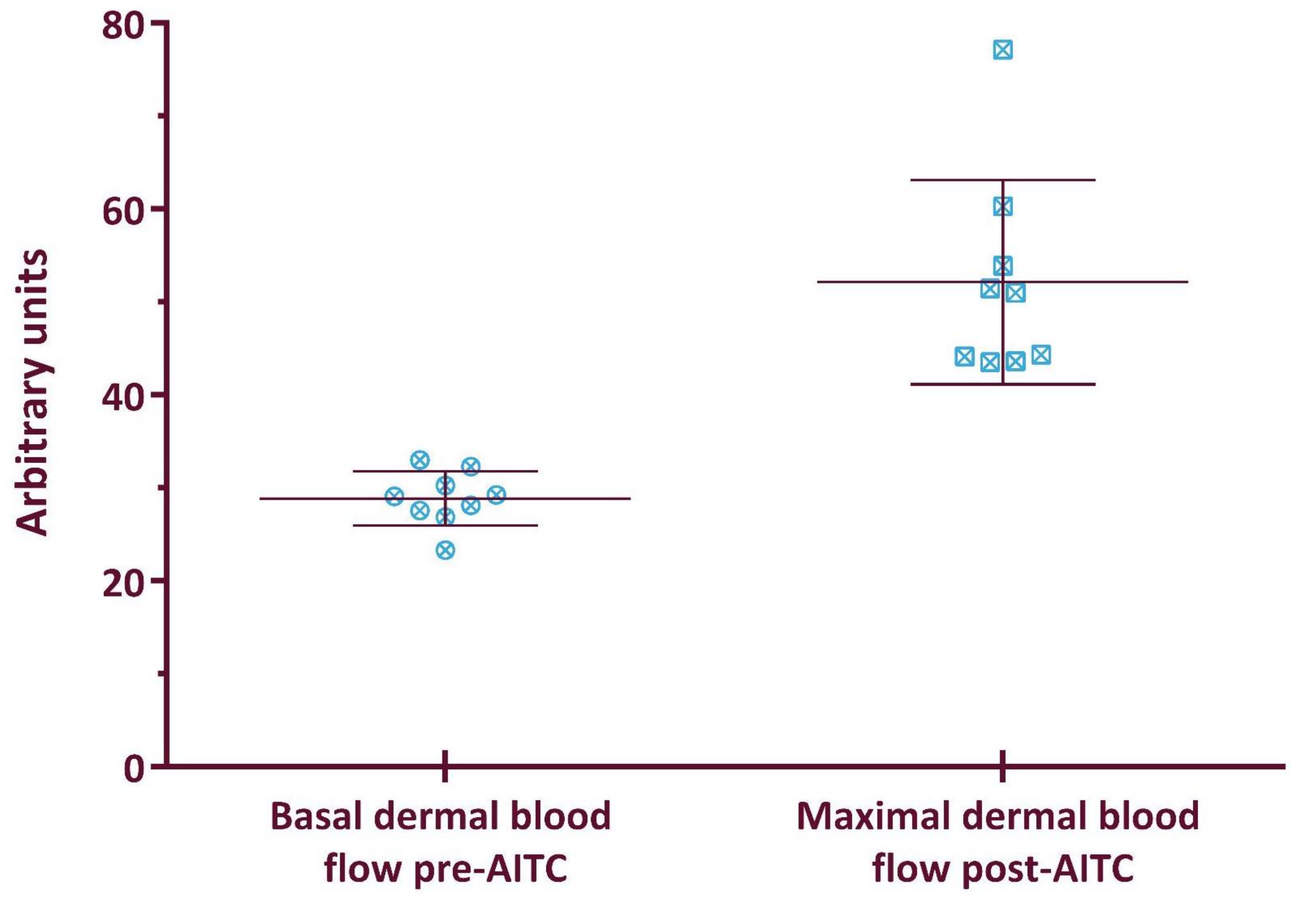

Table 2 – Characteristics of adverse events

Adverse event	*Absolute number of occurrences (%)*	*Range peak NRS (median)*	*Duration in minutes (median)*
Application site pain	8 (66.7)	1-7 (4)	16-64 (27.5)
Application site pruritus	2 (16.7)	1-1 (N/A)	3-69 (N/A)

References: Andersen H, et al. Pain. 2017 Sep;158(9):1723-1732. Joseph V, et al. Br J Clin Pharmacol. 2021 Jan;87(1):129-139.

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