Transient receptor potential channels as possible targets for paracetamol and metamizole: Translation from bench to bedside

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Despite their ubiquitous clinical use, exact mechanisms underlying the analgesic and antipyretic effects of paracetamol and metamizole remain undetermined. Recent preclinical evidence points in the direction of transient receptor potential vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) pathways as potential targets, yet in human evidence is lacking (1–5).

This study aims to unravel the clinical relevance of these results using human target engagement biomarkers for TRPV1 and TRPA1. By topically applying selective agonists, capsaicin (CAPS) for TRPV1 and cinnamaldehyde (CA) for TRPA1, a local vasodilatory response was evoked. Measuring this increase in dermal blood flow (DBF) provided a non-invasive approach to assess TRPV1 and TRPA1 interaction in vivo, in human (6,7).

Part I involved a randomized, double-blind, two-way cross-over study to address the acute effect of single oral doses of paracetamol (1 g) and metamizole (500 mg) in 16 healthy male volunteers. DBF was measured at baseline and 10, 20, 30, 40 and 60 minutes following application of CAPS (1000 µg/20 µL), CA (2 µL/20 µL) and vehicle solutions. Data was expressed as area under the curve over the 60 minutes period (AUC_{0-60}) and analyzed using one-way repeated measures ANOVA with post-hoc Bonferroni adjustment.

The CA-induced DBF response was not influenced by paracetamol as there was no difference compared to no drug intake ($p > 0.999$ for AUC_{0-60}). Metamizole tended to reduce the CA-induced DBF with a trend towards statistical significance ($p = 0.051$ for AUC_{0-60}). The CAPS-induced DBF response was not affected by either paracetamol ($p > 0.999$ for AUC_{0-60}) or metamizole ($p = 0.702$ for AUC_{0-60}) compared to no drug intake (Figure 1). To further investigate these effects, Part II has been set up to examine the influence of steady

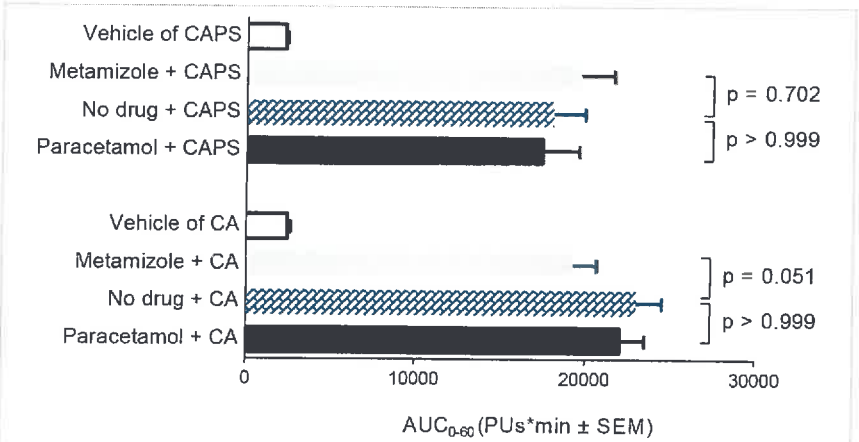

FIGURE 1: Influence of a single oral dose of paracetamol (1 g) and metamizole (500 mg) on the CAPS- and CA-induced DBF response (AUC_{0-60}) in 16 healthy male subjects (one-way ANOVA with post-hoc Bonferroni).

state concentrations of paracetamol (4 x 1g) and metamizole (4 x 500 mg) on TRPV1 and TRPA1. Recruitment is ongoing, but preliminary results suggest a significant inhibition of the CA-induced DBF after metamizole intake compared to no drug intake.

Keywords: transient receptor; channel; paracetamol; metamizole

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