PAIN PERCEPTION AND PROCESSING IN A MEDICATED STATE: A PILOT STUDY IN AN ELDERLY COHORT

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Background

Although pain is experienced at all ages, older adults (60 years or more) are at double the risk of experiencing pain in comparison to their younger counterparts [1].

Current research suggests that there is a reduced sensitivity to mild pain in the elderly that is likely responsible for the under-reporting of mild pain symptoms with consequent under-diagnoses of disease or injury [see (2) for a review]. On the other hand, the elderly show a decreased tolerance to more severe pain that increases their vulnerability to the negative impacts of persistent and chronic pain [see (2) for a review].

Acetaminophen (APAP) is a simple analgesic commonly prescribed to elderly patients for management of mild to moderate acute and persistent pain

A lack of understanding surrounding the age-dependence of the acetaminophen pharmacokinetic-pharmacodynamic correlation has led to dose guidance that is independent of age > 12 years

Study Purpose

Assess acetaminophen analgesic efficacy in an elderly (> 65 years) cohort and compare with a historical young adult cohort

Methods

DESIGN:
The pilot-study was conducted in a randomized, double-blind, single-dose, placebo-controlled, intra-individual crossover mode.

Trial population was 6 elderly participants > 65 yrs (mean 67 yrs; M:F 3:3)

A. Screening: sign ICL, MedCheck, pain threshold and Minimal Erythema UV_B Dose (MED) assessment
B. Medication Session: placebo
C. Medication Session: single 1000 mg APAP dose

ENDPOINTS:
Objective: CO_2-Laser (radiant-heat) induced somatosensory evoked potentials (LEPs) from Vertex-EEG on untreated and UV_B-irradiated (hyperalgesic) skin. LEP amplitudes of the (N2)Peak-to-(P2)Peak component (**Figure 1**) (primary target variable) will be examined for both untreated and UV_B skin.

Subjective: Impressions of pain ("Post Laser Pain") will be recorded based on a Visual Analogue Scale (100mm VAS).

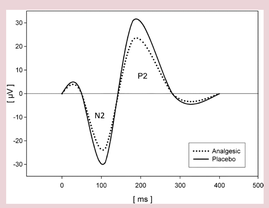

Figure 1. Effect of analgesics on N2 and P2 components using laser stimulation in human pain models.

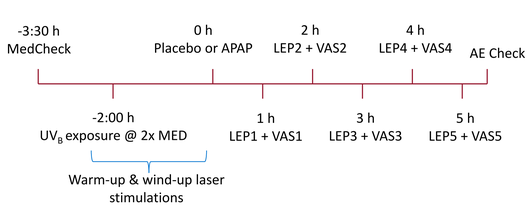

Figure 2. Intradiurnal timeline for 1 representative participant. A MedCheck was completed in each of session B and C. UV exposure two hours prior to dose administration allowed enough time to start erythema development. A number of wind-up laser stimulations on the UV treated skin ensured onset and incline of hyperalgesia. Each hour post-administration, a series of 13 laser shots was applied to the appropriate skin area and LEP and VAS scores were collected.

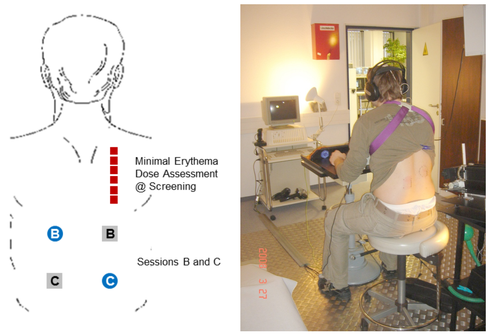

Figure 3. Positioning of MED assessment at screening and of untreated (circles) and UV_B exposed (2x MED; squares) skin in sessions B and C (left figure). UV_B area is approximately 5x5 cm to ensure adequate space for repeated measures (6-7 rows of 13 laser shots) (right photo).

ASSESSMENT & EVALUATION:
The timeline for each assessment day is presented in **Figure 2**. The positioning of untreated and UV_B treated skin for sessions B and C are presented in **Figure 3**.

Time-course LEPs and VAS pain scores were compared to a previously assessed young adult (<50 yrs) cohort [3] under the same protocol (n=24).

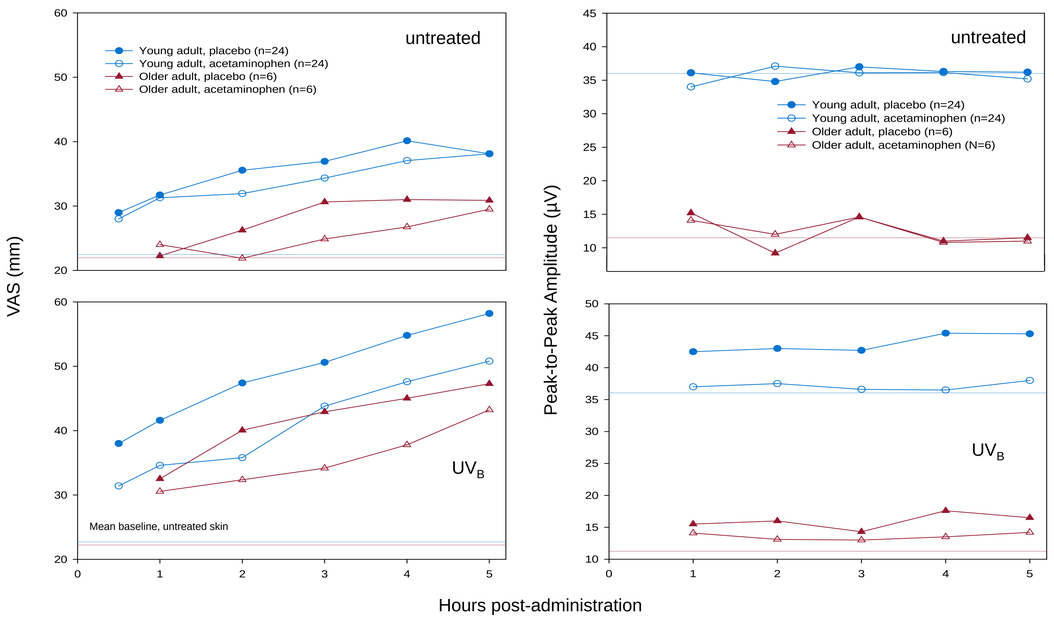

Figure 4. Visual Analog Scale (VAS) pain scores and Peak-to-Peak amplitude (µV) following laser stimulation 1-5 hours post administration of placebo or 1000 mg acetaminophen in untreated and UV_B treated skin in a young and older adult cohort. Faint dashed lines are mean baseline amplitudes (measured pre-dose) on untreated skin.

Results

- Baseline LEP amplitudes are greater in the young adult cohort as compared to the elderly cohort without a baseline change in pain rating (**Figure 4**); a result similar to Gibson et al [4].
- Therapeutic efficacy (e.g. analgesia/anti-hyperalgesia) based on 'subjective' VAS score (**Figure 4**) appears to be similar between the cohorts; the average difference across time between placebo and acetaminophen treatment is similar.
- Therapeutic efficacy based on 'objective' LEP amplitudes (**Figure 4**) showed that the average effect difference across time between placebo and acetaminophen treatment in the older cohort experiencing hyperalgesia (e.g. UV_B treatment) is only 36% that of the younger cohort.

Preliminary Conclusions

Decreased therapeutic efficacy in elderly cohort due to either:

1. **a reduction in drug concentration-normalized analgesia**
2. **an increase in placebo analgesia**

Future Research

A randomized, pharmacokinetic-pharmacodynamic, double-blind, placebo-controlled intra-individual crossover design with three age cohorts (18-30, 35-55, >65 yrs)

A: Screening
B: Natural History: no medication administration (compared to C for placebo analgesia assessment)
C: Placebo (compared to D through F for therapeutic efficacy)
D-F: 325, 650, 1000 mg APAP

Expected Outcome:
Development of a PK-PD algorithm that will output the APAP dose required in elderly adults to achieve the same therapeutic efficacy as in young adults.

[1] Cook AKR, Niven CA, Downs MG. Assessing the pain of people with cognitive impairment. International Journal of Geriatric Psychiatry 1999; 14(6):421-425.
[2] Gibson SJ. Pain and aging: the pain experience over the adult life span. In Proceddings of the 10th World Congress on Pain, Progress in Pain Research and Management, V24. Dostrovsky JO, Carr DB, Koltzenburg M (eds). IASP Press, Seattle, WA, USA. 2003: pgs 767-790.
[3] Chizh BA, Priestley T, Rowbotham M, Schaffler K. Predicting therapeutic efficacy - experimental pain in human subjects. Brain Res Rev 2009; 60(1):243-254.
[4] Gibson SJ, Gorman MM, Helme RD. Assessment of pain in the elderly using event-related cerebral potentials In Proceedings of the VIth World Congress on Pain Research and Clinical Management V4. Bond MR, Charlton J, Edmond, Woolf CJ (eds). Elsevier Science Publishers; 1991: pgs 527-533.