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Editorial comment

Finally a promising analgesic signal in a long-awaited new class of drugs: TRPV1 antagonist mavatrep in patients with osteoarthritis (OA)

Rolf Karlsten*

Multidisciplinary Pain Center, Dept of Surgical Sciences/Anaesthesiology, Uppsala University Hospital, Uppsala, Sweden

In this issue of *Scandinavian Journal of Pain*, Mayorga et al. report positive efficacy data of mavatrep, a transient receptor potential vanilloid subtype 1 (TRPV1) antagonist, in OA pain [1]. A positive signal of efficacy has been reported previously in dental extraction pain [2], but this is the first report of a signal of efficacy with a TRPV1 antagonist in a chronic pain condition.

1. What is transient receptor potential vanilloid subtype 1 (TRPV1)?

TRPV1 is a cation channel located on peripheral nociceptive fibres, but also in areas involved in nociception in the central nervous system [3,4]. The receptor is activated by heat, capsaicin and low pH and the activity is regulated by inflammatory regulators [5]. The TRPV1 receptor acts as a polymodal signal detector and may be influenced by several simultaneous stimuli, e.g. the thermal activation curve for the TRPV1 receptor is shifted to the left by capsaicin [6].

2. Difficulties in developing this class of analgesic drugs – the TRPV1-anatagonists

Based on these properties, indicating a pivotal role for TRPV1 in nociception, many TRPV1 antagonists have been developed displaying efficacy in animal models of a variety of pain conditions, like inflammatory, osteoarthritis, and neuropathic pain models [5,7]. The clinical development of this class of compounds has so far been challenging, mainly due side effects. The first is an increase in core body temperature, usually mild but sometimes exceeding 39 °C. The other problem has been that subjects experience increased detection thresholds for warmth and pain thresholds for heat pain [7]. The implication of the deficit to sense noxious heat is the possibility for burns in real life situations e.g. when drinking hot beverage or taking a hot shower.

3. Previous aborted attempts to develop TRPV1-anatagonist-analgesic drugs

In a previous study in OA with a TRPV1 antagonist (AZD1386), no signal of efficacy was seen and the study was halted due to elevated liver enzymes in a subset of patients [8]. In that 4-week phase IIA/B study (combined proof of concept and dose-finding), patients were included that had failed treatment with paracetamol and/or NSAIDs. The reason behind the patient selection was a combination of scientific and commercial aspects, potentially positioning the drug as an alternative for patients failing first line treatments of OA pain. The primary variable was the WOMAC pain subscale with 48 h recall, change from baseline to mean of week 2 and 4 [8]. This is an unreliable analgesic effect measurement: Patients are not good at remembering "average" pain.

4. A smart design for developing the TRPV1-antagoist mavatrep

The study by Mayorga et al. [1] is interesting in several aspects, applying measures to reduce variability and thereby increase the possibility to show a potential signal of efficacy. In this case by means of selecting the study population, choosing the primary variable and a 3-way cross-over design.

- In the study only patients that had responded to previous treatment with non-opioid analgesics are included. They were also tested for their ability to report pain in a consistent manner using the focused analgesia selection test (FAST), recently published [9]. Subjects defined as "poor pain reporters" (17/63 screened), were excluded.
- The primary variable in OA-studies has historically mainly been based on recall of mean pain during a period 12–24 h or a combination of items as in the WOMAC pain subscale (walking, using stairs, in bed, sitting/lying and standing). In the present study the primary variable is based on evoked pain, the sum of pain intensity difference (4-h post-dose) following stair-climbing, using an 11-point (0–10) numeric rating score. Only patients experiencing an increase of pain (PGIC) and with a minimum pain post-stair-climbing ≥4 were included in the study.

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* Corresponding author at: Pain Center, Akademisk Sjukhuset, 751 85 Uppsala, Sweden.
E-mail address: rolf.karlsten@anestesi.uu.se

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- Cross-over designs are often used in order to reduce variability [10]. In this case the patients were randomly assigned to 1 of 6 treatment sequences, representing all possible combinations of placebo, naproxen (500 mg bid) and mavatrep (50 mg single dose, due to long half-life). Each sequence was 1 week of treatment followed by one week of wash-out.

To prevent burns, the patients were well informed and were also quizzed to ensure the understanding of the burn prevention measures. Also, patients that were routinely exposed to situations in which they had a risk of sustaining burns were excluded.

5. Mavatrep is superior to the traditional NSAID naproxen (and placebo)

The results shows that mavatrep significantly reduced pain after stair climbing 4 h post-dose ($p = 0.005$), while no significant effect was seen on naproxen ($p = 0.229$). The analgesic efficacy was further supported by secondary variables, WOMAC (24 h recall) pain, function and stiffness at 2 and 7 days. For this variable also naproxen was effective. Notably, no effect could be seen on pain at rest (4-h SPID) or mean average current pain (NRS-scores, 7 day mean) with mavatrep or naproxen.

6. Mechanism-based, expected adverse effects of mavatrep

Although measures had been taken to reduce burns, 3/33 patients reported mild burns. All patients receiving mavatrep reported adverse events. 79% feeling cold, 61% thermohypoesthesia, 58% dysgeusia (=distortion of the sense of taste), 36% paresthesia, and 15% feeling warm, all related to the mechanism of action. One patient had a body temperature of 38 °C 2-h post-dosing, that returned to normal within 4 h.

7. Finally a hope for this class of analgesic drugs

The study by Mayorga et al. [1] shows that TRPV1 antagonists may have a role in reducing pain in OA. The study was designed for signal detection and must be seen as such. The study population was highly selected and the high number of target related adverse events might have had impact, as it could un-mask the drug. Even if further studies will prove the efficacy in OA patients, there will still be a substantial challenge to manage the potential for burns in real life situations, when larger numbers of patients will be treated.

There might be a way forward for TRPV1 antagonists if it would be possible to modulate the effects on thermoregulation and the risk for burns associated with the impaired detection of warmth and heat pain. Not only would it reduce those specific side effects, but possibly allow higher exposure and increase the possibility for analgesic efficacy in the clinical setting. In later years a new set of substances, second generation compounds, have been developed that are designed to be modality specific molecules, acting on the capsaicin site, but with or without effects on acid induced TRPV1 activation. The compounds that block acid induced TRPV1 activation elicit profound hyperthermia in rats (for review see [7]). In a recently published study, NEO6860 a TRPV1 antagonist inhibiting capsaicin activation but with little or no effect against heat or acid activation, was studied in healthy subjects. The authors report minor effects on heat pain thresholds and an effect on capsaicin evoked pain and hyperalgesia [11]. Further studies are needed to explore the potential analgesic efficacy in chronic pain patients as well as the safety profile of these types of compounds.

Conflict of interest

None declared.

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