

## **Refinement of animal models of pain: Establishment of strategies to alleviate avoidable pain in rat models for pain and inflammation**

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To develop functioning treatments against the chronic inflammatory pain conditions, the use of laboratory animals is inevitable at the moment. Using animals in pain research is an ethical problem, since the animals often are subjected to various degrees of pain, which in some cases are long lasting and can't be avoided by the animals. These animals are rarely treated with any pain medication, since there is a risk of interference with the experimental data. This is indeed true in many cases, for instance when pain behavior is studied. But in some cases, where the pathological development of the pain and inflammation is of interest, pain medication may be withheld merely as a precaution based on a suspicion rather than based on scientific data. We hypothesized that it would be possible to treat the animal pain models against pain without disturbing the relevant parameters, provided that the correct pain treatment is chosen. This would increase the welfare of the animals used, as well as the quality of the research.

We studied male Sprague-Dawley rats that were injected with complete Freund's adjuvant (CFA) in the tibio-tarsal joint, which initiated an inflammatory response in the joint and surrounding tissue. After 10-14 days, the rats were expected to have fully developed clinical signs and pathological changes in the joint, resembling the manifestations of rheumatoid arthritis and/or osteoarthritis. The rats were thus monitored during about a week before the experiment started, and then during 21 days after CFA injection. Parameters monitored for assessing the pathological development of the arthritis were joint stiffness, joint circumference, stance, mobility and lameness, as well as post-mortem histological changes in the joint. Parameters monitored to assess the pain, stress and the wellbeing were body weight changes, hyperalgesic sensitivity in the electronic von Frey test, facial expression according to the Rat Grimace Scale, fecal corticosterone as well as a general welfare score. During days 0-11, starting prior to CFA injection, rats were either not treated with analgesia (control animals), or treated with buprenorphine or carprofen, and the effects on the above mentioned parameters were compared between the treatment groups

The overall finding was that the analgesic treatments had only minor impact on the clinical and pathological development on the arthritis parameters. The anti-inflammatory compound carprofen appeared to have a more pronounced effect on the joint stiffness and joint swelling than the opioid buprenorphine, which was as expected. The differences between groups on pain, stress and wellbeing parameters were only subtle, where the most notable finding was a decreased hyperalgesia in one of the buprenorphine groups.

In conclusion, the findings in the present study indicate that there is no immediate justification to withhold buprenorphine analgesia to rats subjected to the applied monoarthritis model, in the present setup. However, more studies are needed, to further improve the wellbeing of the animals. There is also room for improvement of the actual model in itself, in order to focus the inflammation to the joint and avoid infiltration into surrounding tissue.