Etablierung von effizienten Schmerzbehandlungsmethoden für die Labormaus

Dr. Paulin Jirkof & Dr. Margarete Arras, Forschung Chirurgie, UniversitätsSpital Zürich

Key words
Pain, Analgesia, Refinement, Mouse

Goal
Assessing pain is a crucial prerequisite to treat and minimize pain, stress and suffering in animal experimentation. Considering the difficulties that still remain in the routine assessment of well-being in laboratory mice scientific validated analgesia protocols are still scarce for this widely used species. Goal of this project was to validate pain treatment protocols using non-invasive pain indicators.

Material and methods
Changes in species-typical home cage behaviors like nest building, burrowing, social interaction, general activity and circadian rhythm were observed in adult females of the commonly used strain C57BL/6J after surgery/laparotomy, in a model of bone cancer and induced colitis and under different housing conditions. Additionally aberrant pain behaviors, clinical observations and the Mouse Grimace Scale were used in several studies. With the diverse indicators of pain we were able to analyze the efficacy of several pain treatment regimens (NSAID: Carprofen, s.c.; Opioid: Buprenorphine, s.c. depot formulation, application via drinking water or combinations). To determine duration of action and therapeutically effective serum concentrations classical analgesiometric tests and blood sampling were performed.

Results and significance
Due to the lack of scientific proof for the efficacy of widely used analgesia protocols there is concern that at least part of the mice used in pain evoking experiments may not be treated sufficiently. Regarding the approximately 100‘000 mice (severity degree 2 and 3, source: BLV), that undergo painful experiments in Switzerland every year knowledge leading to improved pain therapy has a high significance.
The used indicators of pain have been developed partly in our laboratory and have been proved to be indicative of pain (and analgesic action of the analyzed NSAIDs and opioids) in surgical, oncological and inflammatory models. We experience high interest for our methods in the laboratory animal science community and several well-known research groups adapted our approach for the assessment of severity grades.
In our last project we compared a depot formulation of buprenorphine (SB, 2.2 mg/kg) with a standard protocol of three injections of buprenorphine (Temgesic, 0.1 mg/kg/8 h) in mice. Serum concentrations and thermal sensitivity tests indicated duration of action of at least 4 h (but less than 8 h) with the Temgesic protocol, and 24–48 h with SB. Behavioural and clinical parameters indicated at least partial pain relief after surgery for both protocols. Observed side-effects of buprenorphine independent of the protocol were increased activity, disturbed circadian rhythm and several abnormal behaviours. A tendency for decreased food and water intake as well as body weight reduction was also seen. Body weight decreased significantly in animals that received three injections of Temgesic, regardless of whether surgery was performed or not, hinting at a stress response towards this repeated intervention. In conclusion, an application interval of 8 h (Temgesic) appears too long and might lead to repeated periods with insufficient analgesia in animals undergoing lasting and/or substantial pain after surgery. In comparison to the standard protocol, SB provided a long-lasting, assured analgesia without possible stressful repeated injections in a standard surgical model, with only limited and acceptable behavioural side-effects.
At the moment we are analyzing the administration of buprenorphine via drinking water +/- the combination with repeated buprenorphine injections (project ongoing). This project aims to deliver an evidence based recommendation for the treatment of mice in group housing (see also guideline „Merkblatt Buprenorphin“).
The guideline generated in our group is widely used in Switzerland i.e. in the Swiss Animal welfare officer network and is adapted by us regularly with the latest insights. Additionally all project results have been or will be published in established journals and have been presented on symposia and training courses. Therefore these and other project results have immediate impact on the implementation of pain treatment in mice in Switzerland and internationally.

Publications
See attached publication list.

Project *2.12.01 Etablierung von effizienten Schmerzbehandlungsmethoden für die Labormaus*

Project duration *01.07.12-30.06.15*