Drugs that can cause respiratory depression with concomitant use of opioids

B.D. Sigmarsdottir[a], Th.K. Gudmundsdottir[b], S. Zoëga[c,d,*], P.S. Gunnarsson[a,b]

[a] *Univeristy of Iceland, Faculty of Pharmaceutical Sciences, Reykjavík, Iceland*
[b] *Landspítali – The National University Hospital of Iceland, Pharmacy, Reykjavík, Iceland*
[c] *Landspítali – The National University Hospital of Iceland, Surgical Services, Reykjavík, Iceland*
[d] *Univeristy of Iceland, Faculty of Nursing, Reykjavík, Iceland*
E-mail address: bds5@hi.is (B.D. Sigmarsdottir).

Aims: Respiratory depression is a serious life threatening condition and a known adverse event of opioids. Little is known about the use of the opioid antidote naloxon in Iceland, and the additive effects of other potentially respiratory depressive drugs administered with opioids. The aim of the study was to review the literature on drugs that may cause respiratory depression and to assess medication use in patients receiving parenteral naloxone in Landspítali University Hospital.

Methods: A review and analysis of drugs that can cause respiratory depression based on information from the scientific literature, medicine databases and clinical guidelines. A retrospective study was performed using data collected from the electronic medical records system of Landspítali University Hospital for all patients, 18 years and older that had parenteral naloxon administered in the years 2010–2014. Information about the type of opioid and other respiratory depressive drugs was collected and the data was further investigated in regards to age, gender, and type of service.

Results: The most potential drugs and drug classes that can cause respiratory depression when used concomitantly with opioids are benzodiazepines and other anxiolytics, hypnotics and sedatives, antipsychotics, antiepileptics, antihistamins and anesthetics. When use was examined ($N = 138$) morphine was the most frequent opioid given (49%). Concomitant use of opioids and other respiratory depressive drugs was seen in 63% of cases, and benzodiazepines were the most frequent drugs given with opioids (33%).

Conclusions: The concomitant use of benzodiazepines and other sedative drugs with opioids is frequent, despite the known risk of additive respiratory depression as described in the literature. Other patient risk factors such as medical condition, general health and consciousness should be considered in context with drugs used.

http://dx.doi.org/10.1016/j.sjpain.2017.04.060

The potential use of a serious game to help patients learn about post-operative pain management – An evaluation study

B. Ingadóttir[a,b,c], S. Zoëga[b,c,*], K. Blöndal[b,c], D. Thue[d], I. Thylen[a], T. Jaarsma[a]

[a] *Linköping University, Linköping, Sweden*
[b] *Landspítali – The National University Hospital of Iceland, Reykjavík, Iceland*
[c] *University of Iceland, Reykjavík, Iceland*
[d] *Reykjavík University, Reykjavík, Iceland*
E-mail address: szoega@landspitali.is (S. Zoëga).

Aims: To describe the evaluation of a serious computer game designed for patients to learn about post-operative pain management.

Methods: This was a usability and evaluation study. The sample consisted of 20 people, recruited from the public. The computer game was developed by an interdisciplinary team. In the game, the player controls the actions of a virtual human character who has been discharged home after surgery. The player needs to make decisions about the character's daily activities, such as common household tasks and self-care, including pain management. The player observes how his decisions influence the character's recovery. The usability and efficacy of the game were evaluated in one session with semi-structured interviews and questionnaires on knowledge acquisition and usability. The playing session was video recorded to assess if technical problems arose and how often the player needed assistance.

Results: The mean age of participants was 48 years (SD = 14), 11 were women. Participants described the usability of the game as high (range 3–5 on a 0–5 scale) and expressed satisfaction with this novel method of learning, despite some technological challenges. Ease of use was confirmed by observation. Knowledge of pain medications and pain management strategies improved after playing the game. The number of correct answers increased from 54%, before playing, to 71% after playing the game ($p = 0.001$).

Conclusions: Playing an educational computer came has the potential to improve knowledge regarding post-operative pain management. The game was well received by participants. Serious computer games can be a useful tool in enhancing patient education. The game needs to be tested with surgical patients.

http://dx.doi.org/10.1016/j.sjpain.2017.04.061

Modelling activity-dependent changes of velocity in C-fibers

J. Tigerholm[a,*], M.E. Petersson[b], O. Obreja[c], A. Lampert[d,e], R. Carr[c], M. Schmelz[c], E. Fransén[b]

[a] *Center for Neuroplasticity and Pain (CNAP), SMI®, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark*
[b] *Department of Computational Biology, School of Computer Science and Communication, KTH Royal Institute of Technology, Stockholm, Sweden; Stockholm Brain Institute, KTH Royal Institute of Technology, Stockholm, Sweden*
[c] *Anaesthesiology, Universitaetsmedizin Mannheim, University of Heidelberg, Mannheim, Germany*
[d] *Institute of Physiology and Pathophysiology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany*
[e] *Institute of Physiology, RWTH Aachen University, Aachen, Germany*
E-mail address: jvt@hst.aau.dk (J. Tigerholm).

Aims: When C-nociceptors are activated repeatedly using electrical stimulation at relatively low frequencies (0.125–2 Hz), their propagation velocity will decrease. This is referred to as activity-dependent slowing (ADS). The main reason why activity-dependent changes in velocity are of interest is that they can be recorded directly, using invasive methods (microneurography), in patients with chronic pain. Interestingly, in certain patients with neuropathic pain, reduced activity-dependent slowing of conduction has been observed, indicating that these axons have an increased excitability. Through a computational model, it is possible to link such velocity alterations with changes in active conductances, opening for an understanding the underlying excitability changes occurring in these patients.

Methods: We have developed a detailed multicompartment model of a C-nociceptor fiber. This model incorporates a wide range of voltage-gated ion channels ($Na_v1.7$, $Na_v1.8$, $Na_v1.9$, K_{dr}, K_A, K_M,

K_{Na} and h) which were implemented across a detailed and realistic axon morphology.

Results: The model predicts that the small diameter of the axon can accumulate intracellular sodium when it is repeatedly activated in a similar fashion as during single fiber microneurography. This increase of intracellular sodium concentration can shift the balance between ion channel currents, shift the membrane potential and membrane input resistance, and thereby generate activity-dependent changes of velocity, such as ADS as well as recovery cycle supernormality.

Conclusions: Our results thus provide insight into how activity-dependent excitability changes can be generated in C-fibers. By identifying which ion channels are contributing to activity-dependent changes of velocity this could provide insight into ion channel alterations in neuropathic pain patients.

http://dx.doi.org/10.1016/j.sjpain.2017.04.062

Choice of rat strain in pre-clinical pain-research – Does it make a difference for translation from animal model to human condition?

S. Hestehave[a,b,*], G. Munro[a,c], T. Brønnum-Pedersen[d], A.M. Heegaard[e], K.S.P. Abelson[b]

[a] *Department of In Vivo Neurodegeneration, H. Lundbeck A/S, Valby, Denmark*
[b] *Department of Experimental Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark*
[c] *Department of Neurology, Danish Headache Center, Glostrup Research Institute, Glostrup, Denmark*
[d] *Department of Non-Clinical Safety Research, H. Lundbeck A/S, Valby, Denmark*
[e] *Department Drug Design and Pharmacology, Faculty of Health and Medical Sciences, Copenhagen, Denmark*
E-mail address: sara.kristensen@sund.ku.dk (S. Hestehave).

Aims: Translating preclinical drug-efficacy of analgesics from animal models to humans has proven challenging with many failures. Reasons are likely multifaceted, but lack of sufficiently rigorous study design, and phenotypical relevant animal models may be part of the explanation. Chronic pain is often associated with substantial comorbid burden, consisting of changes in affective state and cognitive impairment amongst other behavioral disturbances. Accordingly, many preclinical pain research activities have started to include assessment of comorbidity as a possible experimental outcome measure, but surprisingly, little consideration has been paid to the influence of animal-related factors to pain models. To address this essential issue, we have embarked on several comparative experiments in different pain-models, comparing Sprague Dawley's (SD) from two different vendors with different inbred rat strains (Lewis (LEW), Fisher (F344) and Wistar Kyoto (WKY)) selected based on reported stress, depression, inflammatory and pain phenotypes.

Methods: Male rats were characterized in acute (hot-plate), inflammatory (Complete Freund's Adjuvant (CFA)) and neuropathic (Spared Nerve Injury (SNI)) pain models, with dose-response to morphine (0.3–6.0 mg/kg) in hot-plate, CFA-induced hyperalgesia, and a locomotor motility-assay (LMA).

Results: F344 and SD's were sensitive to morphine in hot-plate and CFA (Minimum Effective Dose (MED) = 3.0 mg/kg). WKY rats developed a less robust mechanical hypersensitivity after CFA injection, and were less sensitive to morphine in both pain-tests (MED = 6.0 mg/kg). LEW rats were completely insensitive to morphine in the hot plate, in contrast to reversal of CFA-induced hyperalgesia (MED = 3.0 mg/kg). Additionally, neuropathic sensitivity developed with a later onset and less robustly in this strain after SNI. All strains tested in LMA exhibited sedative effects at 3.0 mg/kg.

Conclusions: Sensory phenotyping in response to acute, inflammatory and neuropathic pain, and sensitivity to morphine in these strains indicates that different pathophysiological mechanisms are engaged after injury. This could have profound implications for translating preclinical drug discovery efforts into pain-patients.

http://dx.doi.org/10.1016/j.sjpain.2017.04.063

Omics as a potential tool to identify biomarkers and to clarify the mechanism of chronic pain development

M.C. Gerra*, C. Dagostino, S. D'Agnelli, L. Boggiani, V. Rizza, M. Marchesini, M. Allegri, G. Fanelli

Anesthesia Intensive Care and Pain Unit, Surgical Sciences Division, Department of Medicine and Surgery, University of Parma, Italy
E-mail address: mariacarla.gerra@studenti.unipr.it (M.C. Gerra).

Aims: The present study aims to identify the underlying mechanisms in the acute to chronic pain transition. Acute pain is a physiological response to an experience of noxious stimuli that can progress to chronic, becoming a disease. The negative consequences as personal suffering, reduction in physical function, maladaptive behaviours, reduction of productivity, make this condition a central and common problem affecting individuals and the society. After an acute damage, pain in some cases persists, being the process attributed to different causes, in particular persistent tissue and neuronal damages, central neuroplastic changes, psychosocial factors.

Methods: The techniques actually used to investigate acute and chronic pain offer only a partial explanation of the process and in addition, the obtained results are often far away from the possibility to lead some benefits in the clinical practice. Omics technologies could be the right way to detect biomarkers explaining these mechanisms. Our previous study examined epigenetic and pharmacogenetic aspects of acute and chronic pain in a large group of patients. Other omic approaches, such as metabolomics and glycomics, could help to (1) better identify metabolites that can serve as chronic pain development or side effects therapy biomarkers and to (2) better understand new insights involved into the pathophysiological mechanism that drives from acute to chronic pain. SNPs, DNA methylation, miRNA analyses, expression and protein assays on the identified pathway would than clarify the causative molecular mechanisms. In addition, linking these results to clinical evaluation of the central sensitization processes through algometry in nociceptive and neuropathic pain patients may reveal crucial clinical and pharmacological implications.

Conclusions: Our project will be implemented by omic technologies in different chronic pain patient cohorts (acute low back pain vs chronic low back pain patients and chronic postsurgical pain patients) in order to evaluate new possible pathophysiological mechanism with special focus in central sensitization.

http://dx.doi.org/10.1016/j.sjpain.2017.04.064