Scandinavian Journal of Pain 3 (2012) 149–150

Contents lists available at SciVerse ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

Pharmacological modulation of chronic pain after whiplash injury

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Chronic pain after whiplash injury is a largely unresolved medical and social problem. By definition, symptoms follow a trauma, which is in most cases a motorvehicle accident. The majority of patients recover, but for those who have persisting complaints an odyssey begins. Imaging techniques rarely reveal changes that explain the magnitude of symptoms [1]. As a result, patients are frequently told that they have nothing serious. Nevertheless, pain persists and is frequently associated with disability and depression. Many sufferers stop working. Some patients experience progressive spread of pain to body regions that are distant from the site of injury [2], which additionally complicates the understanding of the disease. Not uncommonly, the lack of understanding of the cause of pain leads to mistrust and questions as to whether the symptoms are real, or rather some sort of gain is behind the complaints. The resulting sense of perceived injustice is an additional factor for disability [3], further worsening the overall clinical picture.

The general perception of clinicians, lawyers, judges and insurances is that the nature of whiplash-associated disorders is unknown. However, an evaluation of the available literature reveals that many aspects of the pathophysiology of this condition have become clear. Basic research in animal models, kinematics, kinetics and biomechanics support the concept that lesions occur after a whiplash injury and these lesions can produce nociception [4]. Clinical research has provided strong evidence that the zygapophysial (facet) joints are sources of pain in whiplash patients [5,6], which is concordant with extensive data from animal and bioengineer research [7,8]. Unfortunately, these lesions are not visible by imaging techniques. A recent investigation with magnetic resonance imaging has shown that patients in the acute phase of a whiplash injury have more pathological findings than matched healthy controls, but reliability, sensitivity and specificity of the findings is poor [1]. Positron Emission Tomography has revealed signs of inflammation in whiplash patients, but the clinical significance needs to be investigated by further studies [9]. On average, patients with pain after whiplash injury display facilitation of central pain processes [2,10,11], which may explain exaggerated pain in the presence of limited tissue damage. Psychosocial factors are associated with central hypersensitivity [12] and have been shown to affect the outcome of whiplash injuries [13]. Thus, important progresses have been made in our understanding of the pathophysiology of whiplash. Because the importance of different mechanisms is likely to vary across patients, the clinical challenge is to identify which factors play a role in the determination of symptoms in individual patients. To date, a comprehensive assessment of the different potential contributors is essential to formulate a working hypothesis for an individualized treatment.

Whenever the cause of pain cannot be identified or removed, drug treatment is an option. Oddly, research on the efficacy of analgesics in whiplash-associated disorders is extremely sparse [14]. The paper by Persson et al. in this issue of the *Scandinavial Journal of Pain* [15] analyzes the response of patients with chronic pain after whiplash injury to intravenous infusions of morphine, ketamine and an active placebo (midazolam). The drugs were administered as single doses. A variety of assessments of the psychosocial status and quality of life were made. Responses were categorized as positive or negative based on the cutoff of 50% pain relief. The study was completed in 94 patients, which is a considerable number in the frame of whiplash clinical research. Among patients who did not respond to placebo, 47% were morphine responders, 41% ketamine responders, 25% responded to both drugs and 37% to neither drug.

Because of the extreme paucity of data on the efficacy of drugs in chronic pain after whiplash injury, this study is important. It suggests that this pain condition might be modulated by opioids and NMDA-antagonists in part of patients. Although links between this finding and mechanistic aspects should be made with caution, the data support the view that whiplash injury is associated with changes in central modulatory processes. The interindividual response was variable, and some patients did not respond to any drug. In the field of chronic pain, this is not a unique feature of whiplash. Several factors may account for lack of analgesic effect, such as individual dose–response relationship or pharmacogenetic polymorphisms [16]. Interestingly, the group of patients who did not respond to morphine or ketamine displayed a trend for a worse performance in some of the psychometric tests, supporting clinical observations that psychic disorders may represent obstacles to the efficacy of treatments. Clearly, this finding needs to be confirmed by studies that are designed and powered to address this question.

The study has limitations. Responses to single drug doses do not necessarily imply long-term efficacy. On the other hand, lack of effect after a single administration does not rule out efficacy with long term treatment, since central modulating effects might become clinically detectable after days or weeks of drug exposure. The study did not test the combination of the two drugs. In

DOI of refers to article: 10.1016/j.sjpain.2012.01.003.
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1877-8860/$ – see front matter
doi:10.1016/j.sjpain.2012.02.008

a study on patients with post herpes zoster pain, a chronic central and peripheral neuropathic pain, morphine and ketamine had a more pronounced analgesic effect when both drugs were given together, compared with single drug administrations [17]. The use of midazolam as active placebo may be questioned, due to the anti-hyperalgesic and hypoalgesic effects of $GABA_A$-agonists in a large amount of animal studies [18], confirmed by some clinical investigations [19]. Thus, an undetermined proportion of the placebo responders might actually be responders to $GABA_A$-agonists.

In summary, the study by Persson et al. shed some additional light on the pathophysiology and management of whiplash-associated disorders. Most patients do respond to drug treatment, at least in the short term. The hope is that most of these patients would respond also on the long term, a hypothesis that needs to be tested by further clinical trials. Furthermore, the finding does not support the view that pain after whiplash injury has nothing to do with nociceptive processes. Hopefully, the study will motivate researchers to perform pharmacological trials on the middle- and long-term efficacy of drugs in whiplash-associated disorders.

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