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Whiplash Associated Disorders (WAD): Responses to pharmacological challenges and psychometric tests

Mats Persson[a,b,*], Jan Sörensen[b,c], Björn Gerdle[b,c]

[a] Clinical Department of Operation and Intensive Care, Pain Unit, County Hospital Ryhov, SE-551 85 Jönköping, Sweden
[b] Rehabilitation Medicine, Faculty of Health Sciences, SE-581 85 Linköping, Sweden
[c] Pain and Rehabilitation Centre, University Hospital, SE-58185 Linköping, Sweden

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ABSTRACT

Objectives: The present study challenges chronic Whiplash Associated Disorders (WAD)-subjects to a pharmacological intravenous (i.v.) test with morphine, ketamine, and active placebo (midazolam). The aim was to describe the short-term responses to drugs and the assumed heterogeneity in the patterns of responses. We related the different responder groups to the results from psychometric tests.
Methods: The study includes 95 patients, all with chronic WAD and referred to our departments. They answered a questionnaire including the following psychometric instruments relevant for chronic pain: Beck Depression Inventory, Coping Strategies Questionnaire, Multidimensional Pain Inventory, Life Satisfaction Checklist, SF36 and EuroQol. The subjects also went through sessions with separate infusions of morphine (0.3 mg/kg), ketamine (0.3 mg/kg) and midazolam (0.05 mg/kg). Infusion time was 30 min followed by a 2-h post-infusion assessment. Assessments were made using a Visual Analogue Scale (VAS) for pain intensity and unpleasantness and by statements of per cent pain relieved. A categorical pain rating scale was also used. A positive response was defined as ≥50% decrease of the VAS-level on two consecutive assessment points during the test sessions, anything less was a non response. The placebo responders were defined as those with a positive response to the active placebo infusion.
Results: The tests were completed by 94 subjects and 26% of these were placebo responders. Among the placebo non responders, 47% responded to morphine, 41% to ketamine, 25% to both drugs and 37% to neither morphine nor ketamine (pain intensity assessments). Similar proportions were found in the assessments of pain unpleasantness and per cent pain relieved. Approximately one in four subjects (27%, pain intensity assessment) did not respond to any of the drugs tested. This relatively high proportion of non responders seemed to be worst cases in some aspects of the psychometric tests. Generally, this non responder group had a trend to score worse for most items in the psychometric tests with some reaching significance in a univariate analysis. This result was confirmed in a multivariate context, although the results indicated only small differences between the groups. All three substances showed significant pain relief compared to baseline on all assessment points. On most variables, morphine and ketamine were significantly more effective compared to the active placebo.
Conclusions: There are different subgroups among subjects with chronic WAD with variations in responses to i.v. morphine, ketamine, and midazolam (active placebo). Subjects with chronic WAD who did not respond to any of the drugs tested scored badly in some aspects of the psychometric instruments.
Implications: The present study confirms one aspect of the heterogeneity in the population with chronic WAD. The study does not elucidate precise pain mechanisms but taken together with other studies exploring other aspects, it stresses the importance of individualizing the assessment and treatment of subjects with chronic WAD. A common clinical experience is that depression, anxiety and maladaptive coping strategies often are obstacles for successful medical treatment of chronic pain. The present study supports this experience and emphasizes the need for assessment of psychometric variables when planning the treatment of chronic WAD.

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* Corresponding author at: Clinical Department of Operation and Intensive Care, Pain Unit, County Hospital Ryhov, SE-551 85 Jönköping, Sweden. Tel.: +46 (0) 36325050; fax: +46 (0) 36325055.
E-mail addresses: mats.persson@lj.se, mats.ge.pe@telia.com (M. Persson).

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1. Introduction

A sudden acceleration or deceleration due to impact can lead to a whiplash trauma and cause acute symptoms (pain and stiffness in the neck, often described as acute Whiplash Associated Disorder, WAD) and a significant subgroup develops chronic pain (chronic WAD) [1–3].

Apart from cases where the trauma causes verifiable lesions in the musculoskeletal or neural structures, most patients with chronic WAD do not present with such signs. In the majority of patients with chronic WAD, the pathogenesis of the persistent pain is poorly understood as is evident by the different views presented in the literature [4–6].

When describing and analysing chronic WAD according to a biopsychosocial model [7,8], different studies put various weight on different parts along the "bio", "psycho", and "social" axes. For example, emphasising the "bio" side, some researchers stress lesions in the zygapophyseal joints [9]; emphasising the "psycho" and "social" sides, some researchers stress factors such as anxiety, coping, and insurance issues, often as interconnected factors [10].

A possible approach is to view patients with chronic WAD as a heterogeneous group even though the basic concept is the bio-psycho-social model. Support for this can be found in studies where responses to pharmacological interventions have been investigated [11]. Studies focusing on the "psychosocial side" of the model also show heterogeneity among patients with chronic WAD [12–15].

One way to investigate chronic pain is to study responses to pharmacological agents with known targets. This approach has been done for different patient groups including patients with chronic WAD [11]. Most studies deal with opioid agents and/or ketamine and assume the former acts on the central pain processing via the μ-receptor and the latter acts as an antagonist on the NMDA-receptor. Clearly, NMDA-receptors play an important role in central sensitization [16,17]. Several studies conclude that central hyperexcitability (sensitization) and/or disinhibiton of the somatosensory system may play a part in the pathogenesis of pain in chronic WAD [18–22], a conclusion that might explain why patients without detectable or minimal nociceptive input still perceive debilitating pain.

However, the pharmacological studies so far have been relatively small. Most studies incorporate a test with a placebo agent, commonly physiological saline, but sometimes benzodiazepines have been used as an active placebo [23,24] in order to simulate the sedative effects of other agents presuming no analgesic activity.

In the present study patients with chronic WAD were examined regarding the responses to different i.v. pharmacological challenges: morphine, ketamine, and "active" placebo (midazolam). The patients also answered a questionnaire including several psychometric instruments relevant for chronic pain.

The aim of the study was to describe the short term responses to drugs and the assumed heterogeneity in response patterns. Furthermore, we analysed whether the outcomes of the pharmacological challenges correlated with the psychometric results.

2. Patients and methods

2.1. Patients

Between May 2001 and October 2008, 95 subjects with chronic WAD were recruited from patients referred to the Pain Unit, Operation and Intensive Care Clinic, County Hospital Ryhov, Jönköping, Sweden and to the Pain and Rehabilitation Centre, University Hospital, Linköping, Sweden. For background data see Table 1. The study was conducted in accordance with the Declaration of Helsiniki and approved by the local Ethics Committee (00-283). All participants gave written informed consent.

Table 1
Background data of the recruited subjects ($n = 95$).

Area	Variables	
Gender/Age	Male (n (%))	39 (41%)
	Mean age (years (SD))	36.8 (9.8)
	Female (n (%))	56 (59%)
	Mean age (years (SD))	35.4 (9.5)
	All subjects (n)	95
	Mean age (years (SD))	36.0 (9.6)
Time from impact (mean (SD))	Months	28 (15)
Type of impact (n (%))	From the rear	41 (43%)
	Obliquely rear	4 (4%)
	From the side	6 (6%)
	Other	44 (46%)
Patient position at impact (n (%))	Driver	69 (73%)
	Passenger front seat	13 (14%)
	Passenger back seat	7 (7%)
	Other type of vehicle	6 (6%)
Time to symptoms (n (%))	Immediately	36 (38%)
	First 24 h	44 (46%)
	First week	14 (15%)
Use of analgesics (n (%))		
NSAID/Acetaminophen	None	19 (20%)
	Sporadic	22 (23%)
	Daily	42 (44%)
Weak opioids	None	40 (42%)
	Sporadic	17 (18%)
	Daily	26 (27%)
Strong opioids	None	83 (87%)
	Missing data	12 (13%)

2.1.1. Inclusion criteria

The subjects had a well-documented whiplash trauma or a whiplash-like accident with a minimum of six months and maximum of five years before inclusion (i.e., WAD grades II–III). They had a persistent pain in the neck – with or without spread of the pain to the head, shoulder, and arm regions – with a pain intensity of ≥40 mm on a 100 mm VAS. The minimum age was set to 18 years.

2.1.2. Exclusion criteria

All subjects were given a MRI of the cervical spine. If affections of medulla and/or nerve roots corresponding to neurological signs in the periphery were discovered, these subjects were excluded from the study. If the subjects had neuroorthopedic surgery done on the cervical spine, they were excluded. Subjects were excluded if they had a significant chronic pain problem before the trauma. Subjects with generalized pain after the trauma were also excluded. That is, subjects were only included if their pain was mainly localized to the neck with or without spread of the pain to the head, shoulder, or arm regions. Subjects were excluded if they had drug addiction problems, exhibited psychotic behaviour, or were pregnant.

2.1.3. Baseline screening

All subjects answered a comprehensive questionnaire including psychometric instruments relevant for chronic pain. The questionnaire asked the subjects whether they had been using analgesics the previous six months. If they answered "yes", they were asked for type of analgesic and whether they were using it sporadically or daily (Table 1).