Neuropathic Pain; Quality of Life, Sensory Assessments and Pharmacological Treatments

BY

ANN KVARNSTRÖM

ACTA UNIVERSITATIS UPSALIENSIS
UPPSALA 2003
Dissertation presented at Uppsala University to be publicly examined in Hedstrandsalen, Uppsala University Hospital entrance 70, Uppsala, Friday, December 19, 2003 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Neuropathic pain of central and peripheral origin presents a substantial clinical problem as it is often resistant to pharmacological treatment.

The health related quality of life of 126 patients with peripheral neuropathic pain was studied, to provide a cross sectional description from this point of view. Two generic health-related quality of life instruments, the SF-36 and the Nottingham Health Profile were used together with pain assessments, global rating of health and verbal rating scales of pain and other symptoms, as well as patient descriptors.

The analgesic effect of ketamine, lidocaine and morphine were assessed in a double blind, placebo-controlled, randomized study design. Three groups of patients were studied: patients with peripheral neuropathic pain of traumatic origin, patients with central post-stroke pain and patients with neuropathic pain after spinal cord injury. Somatosensory function was examined to see if this could predict response to treatment and to investigate if the drugs caused changes in thermal or mechanical sensibility.

The results shows that the intense pain, limited efficacy and tolerability of available treatments, the low overall rating of health, reduced work status and troublesome symptoms constitute a substantial impact on the quality of life for patients with peripheral neuropathic pain.

The NMDA-antagonist ketamine yielded substantial pain relief to patients with peripheral neuropathic pain and patients with neuropathic pain after spinal cord injury. However, the reported side effects limit the clinical usefulness of the treatment. Lidocaine did not give significant pain relief to the patients in the three studied groups. Morphine may represent a therapeutic alternative for some patients with central post-stroke pain, although only a small group of this category of patients responded with analgesia.

Assessment of baseline somatosensory functions could not be used to identify responders to treatment with either drug, nor did ketamine, lidocaine or morphine cause any changes in thermal or mechanical sensibility.

Keywords: neuropathic pain

Ann Kvarnström, Department of Surgical Sciences, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden

© Ann Kvarnström 2003

ISSN 0282-7476
ISBN 91-554-5798-3
urn:nbn:se:uu:diva-3766 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-3766)
List of Papers

I. Karin Meyer-Rosberg, Ann Kvarnström, Erik Kinnman, Torsten Gordh, Lars-Olof Nordfors, Ann Kristofferson
Peripheral neuropathic pain—a multidimensional burden for patients

II. Ann Kvarnström, Rolf Karlsten, Hans Quiding, Britt-Marie Emanuelsson, Torsten Gordh
The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain
Acta Anaesthesiolologica Scandinavica 2003; 47: 868-877

III. Ann Kvarnström, Rolf Karlsten, Hans Quiding, Torsten Gordh
The analgesic effect of intravenous morphine and lidocaine on central post stroke pain
Submitted

IV. Ann Kvarnström, Rolf Karlsten, Hans Quiding, Torsten Gordh
The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury
Accepted Acta Anaesthesiolologica Scandinavica

Reprints have been made with the permission of the publishers.
Contents

List of Papers ..................................................................................................4
Abbreviations .............................................................................................8
Pain terms according to the International Association for the study of Pain (IASP) (Merskey 94) .................................................................................9

INTRODUCTION ........................................................................................11

BACKGROUND ..........................................................................................12
Neuropathic pain states........................................................................12
Incidence and prevalence figures.........................................................12
Mechanisms of neuropathic pain states ...............................................13
Peripheral neuropathic pain: peripheral mechanisms......................13
Peripheral neuropathic pain: central mechanisms...........................14
Central neuropathic pain ......................................................................15
Quality of life.......................................................................................17
Assessment of sensory abnormalities in patients with neuropathic pain
Thermal testing ...............................................................................19
Allodynia/hyperalgesia to mechanical stimuli ................................19
Lack of effective pain relief.................................................................19
Three interesting lines of treatment ....................................................20
Ketamine for treatment of neuropathic pain ........................................22
Lidocaine for treatment of neuropathic pain ........................................22
Morphine for treatment of neuropathic pain ........................................23
Morphine instead of ketamine in patients with CPSP .........................24

THE AIMS OF MY THESIS........................................................................25

PATIENTS AND METHODS .....................................................................26
Study I ......................................................................................................26
Patients.................................................................................................26
Recruitment .........................................................................................26
Data collection.....................................................................................27
Pain ......................................................................................................27
Symptoms related to pain and side-effects from treatments..............27
Success of previous therapy ................................................................28
Employment status ............................................................................28
Patient-perceived quality of life impairments..................................28
Health related quality of life ...............................................................28
Global rating of health (rating scale) ..................................................29
Statistics...............................................................................................29
Study II-IV ...............................................................................................30
Patients.................................................................................................30
Drugs ...................................................................................................31
Blood sampling and bioanalysis .........................................................32
Assessment of pain ..............................................................................32
Quantitative sensory testing with thermal stimulation ......................32
Examination of sensibility to mechanical stimuli ..............................33
Assessment of adverse events ............................................................33
Statistical analysis................................................................................34

METHODOLOGICAL CONSIDERATIONS ..................................35
Patient selection ...................................................................................35
Health related quality of life ...............................................................36
Choice of dose .....................................................................................37
Pain and pain relief measurement.......................................................38
Thermal stimulation ............................................................................39
Assessing the sensibility to mechanical stimuli...................................40

RESULTS .....................................................................................................42
Study I ......................................................................................................42
Patients.................................................................................................42
Pain intensity .......................................................................................43
Bothered by discomfort from pain......................................................44
Symptoms related to pain and side-effects of treatment ....................44
Ongoing treatment ..............................................................................45
Success of previous therapy ...............................................................45
Employment status ............................................................................47
Patient-perceived QoL impairments ...................................................48
HRQoL .................................................................................................49
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ASIA</td>
<td>The American Spinal Injury Association</td>
</tr>
<tr>
<td>CDS</td>
<td>Central dysesthesia syndrome</td>
</tr>
<tr>
<td>CPSP</td>
<td>Central post stroke pain</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calcitonine gene related polypeptide</td>
</tr>
<tr>
<td>CCK</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>DCS</td>
<td>Dorsal columnal stimulation</td>
</tr>
<tr>
<td>DRG</td>
<td>Dorsal root ganglion</td>
</tr>
<tr>
<td>EAA</td>
<td>Excitatory amino acid</td>
</tr>
<tr>
<td>FASS</td>
<td>Farmacevtiska specialiteter i Sverige (Swedish Drug Compendium)</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma aminobutyric acid</td>
</tr>
<tr>
<td>GSRS</td>
<td>Gastrointestinal symptom rating scale</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>MPQ</td>
<td>McQuill Pain Questionnaire</td>
</tr>
<tr>
<td>NHP</td>
<td>Nottingham health program</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>N of 1</td>
<td>Number of 1</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non steroid anti inflammatory drugs</td>
</tr>
<tr>
<td>Q1</td>
<td>First quartile</td>
</tr>
<tr>
<td>Q3</td>
<td>Third quartile</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>QST</td>
<td>Quantitative sensory testing</td>
</tr>
<tr>
<td>PAG</td>
<td>Periaqueductal grey</td>
</tr>
<tr>
<td>PHN</td>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>PNP</td>
<td>Peripheral neuropathic pain</td>
</tr>
<tr>
<td>RVM</td>
<td>Rostral ventromedial medulla</td>
</tr>
<tr>
<td>SCI</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
</tbody>
</table>
SEM Standard error of the mean
SEP Sensory evoked potentials
SF-36 Medical Outcomes Study Short Form-36
SP Substance P
TCA Tricyclic antidepressants
TENS Transcutaneous electrical nerve stimulation
UK United Kingdom
VAS Visual analogue scale

Pain terms according to the International Association for the study of Pain (IASP) (Merskey 94)

**Pain**
An unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage.

**Allodynia**
Pain due to stimulus which does not normally provoke pain.

**Analgesia**
Absence of pain in response to stimulation which would normally be painful.

**Hyperalgesia**
An increased response to stimulus which is normally painful.

**Hypalgesia**
Diminished pain in response to a normally painful stimulus.

**Hyperesthesia**
Increased sensitivity to stimulation, excluding the special senses.

**Hypoesthesia**
Decreased sensitivity to stimulation, excluding the special senses.

**Hyperpathia**
A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

**Dysesthesia**
An unpleasant abnormal sensation, whether spontaneous or evoked.

**Nociceptor**
A receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged.

**Noxious stimulus**
A noxious stimulus is one which is damaging to normal tissues.

**Pain threshold**
The least experience of pain which a subject can recognize.
INTRODUCTION

Working as a doctor at a multidisciplinary pain centre, one meets many patients suffering from chronic neuropathic pain. Before I started to work at a pain clinic, I hardly knew this group of patients, even though I had worked as a doctor and anaesthesiologist for many years. In a pain clinic setting these patients gather, and they constitute around one third of the patients there.

The mentioned group made a deep impression on me for two reasons:
- my impression that the pain had an overwhelming negative effect on nearly every aspect of life in this category of patients;
- the patients were highly resistant to the available therapeutic approaches.

Many pharmacological and non-pharmacological treatments were tested, often with only adverse effects as the result.

This is the background to this work. These patients affected me a lot, and I wanted to see if their lives were influenced by their pain the way I suspected. I also wanted to study alternative treatment strategies, to see if they could lead to better pain relief and thus an improved quality of life for this group of patients.
BACKGROUND

Neuropathic pain states
Painful neuropathic conditions may accompany a lesion of the peripheral or central nervous system. Painful neuropathies are characterized by spontaneous and/or abnormal stimulus-evoked pain, associated with such a lesion. Evoked pain can consist of allodynia when caused by normally innocuous stimuli, e.g. light mechanical stimuli (Merskey 1994). In contrast to allodynia, hyperalgiesia is defined as increased pain intensity evoked by normally painful stimuli (Merskey 1994). Neuropathic pain states are also often associated with nonpainful abnormal spontaneous and evoked sensory phenomena such as paresthesia and dysesthesia as well as hypoesthesia in the affected area. Neuropathic pain has no value as a warning signal for tissue damage, and from this point of view it is of no value.

Incidence and prevalence figures
Studies on the prevalence of pain in the general population of several western countries indicate that 15-20 % suffer from acute pain, and between 25 and 30% suffer from chronic pain (Bonica 2001). It has been estimated that the incident of neuropathic pain in the UK is about 1% (Bowsher 1991). For the vast majority of neuropathic diagnostic entities the percentage of subjects reporting neuropathic pain is not precisely known (Hansson 2001). However, according to one estimate 5% of patients with traumatic nerve injury suffer from pain (Sunderland 1978). Further, about 8% of stroke patients suffer from central post-stroke pain, during the first year after the stroke (Andersen 1995). With the incidence of stroke in Sweden being 3000 per million, this figure gives an indication of the magnitude of the problem (National Board of Health and Welfare 2000).
The incidence of spinal cord injuries in Sweden is 13 per million and in USA 40-50 per million (Surkin 2000). Studies concerning the prevalence of chronic pain in patients with spinal cord injury indicate that around 65% experience chronic pain and that approximately one third of these patients rate their pain as severe (Levi 1995, New 1997, Störmer 1997, Sidall 1999). Neuropathic pain after SCI affects 30%-40% of the patients (Störmer 1997, Sidall 1999, Sidall 2003, Richards 1980). Neuropathic pain in patients with SCI can be divided in above-level, at-level and below-level pain (Sidall 2000a), according to Sidall the incidens of at-level pain is 41% and below-level pain is 34%, five years after the injury (Sidall 2003). Some authors suggest that neuropathic pain is more common in association with incomplete spinal cord lesion (Davidoff 1987, Beric 1988). Others have not found any significant relationship between the presence or severity of pain and completeness of the SCI (Richards 1980, Summers 1991, Sidall 1999, Sidall 2003).

Mechanisms of neuropathic pain states
The mechanisms behind the origin and continuation of neuropathic pain are diverse and largely unknown. As mentioned above only a minority of people develop a chronic pain state after a lesion to the peripheral or central nervous system. The reason for this variability is not known. There may be a genetically disposition for developing pain after nerve injury. Research using mice and rats has shown a great variability due to genotype (Wiesenfeld 1981, Mogil 1999).

Peripheral neuropathic pain: peripheral mechanisms
Several types of peripheral mechanisms corresponding to peripheral nerve lesions have been identified. One thoroughly studied mechanism consists of abnormal spontaneous activity (ectopic discharge) recorded in nociceptive fibres, neuromas and dorsal root ganglion (DRG) (Devor 1999). Such discharges have been recorded in human subjects using microneurography and have been correlated most often with paresthesias and sometimes with spontaneous pain (Torebjörk 1979, Nyström 1981, Ochoa 1982). The mechanism of these discharges involves dysregulation of the synthesis and distribution of the sodium channels that control membrane excitability (Devor 1989, Novakovic 1998). Another peripheral mechanism of neuropathic pain involves nociceptor sensitization but this is probably of less
importance in chronic peripheral pain. Pathological interactions between fibres (ephapses) of nociceptive and spontaneously active non-nociceptive nerve fibres could be an alternative explanation for ongoing sensory symptoms (Granit 1945, Selzer 1979). Low threshold sensory afferents, motor axons and sympathetic efferents may activate nociceptive afferents via a direct coupling (Selzer 1979, Meyer 1985). A sympathetic interaction with the nociceptive afferents could exist at the level of the dorsal root ganglion (DRG), where sprouting of sympathetic efferents has been shown around axotomized sensory neurons (McLachlan 1993).

**Peripheral neuropathic pain: central mechanisms**

Different types of central modifications can induce pathological activation at the central nociceptive neurons responsible for the genesis of neuropathic pain. One mechanism is represented by central sensitization which refers to abnormal hyperexcitability of central nociceptive neurons (Coderre 1993). These phenomena are highly dependent on the activation of the NMDA receptor. The NMDA receptor channel complex is unique in being both ligand and voltage dependent. At resting membrane potential the channel is blocked in a voltage dependent manner by binding of Mg²⁺ inside the ion channel (Mayer 1984). This block can be removed if the membrane potential is increased by activity at other excitatory amino acid (EAA) receptors or by neuropeptides, such as substance P (SP) or calcitonine gene related polypeptide (CGRP) (Urban 1994). Ligand stimulation at the NMDA recognition site will then allow an influx of Ca²⁺ (MacDermott 1986). This NMDA mediated influx of Ca²⁺ may initiate a cascade of intracellular events responsible for the development of neural plasticity (Cotman 1988). These events include phosphorylation of membrane (receptor) proteins, activation of nitric oxide synthase (Meller 1992) and activation of immediate early genes coding for factors regulating protein synthesis (Monaghan 1989). It should be noted that the function of NMDA receptors is not only confined to synaptic plasticity. EAAAs released in large amounts, for example during brain or spinal ischemia, contribute to neuronal damage by excessive activation of NMDA receptors. Excessive Ca²⁺ influx through NMDA channels initiates processes leading to death of the neuron (Faden 1988).

Another major mechanism is represented by central disinhibition resulting from loss of modulatory control mechanism, which in turn may result in abnormal excitability in central neurons. Segmental disinhibition at the dorsal horn level has been indicated by electro-physiologic experiments.
after peripheral nerve injury (Wall 1981). Furthermore, decreased levels of gamma-aminobutyric acid (GABA) and glycine (which act as inhibitory neurotransmitters) and down regulation of the GABA receptors have been reported at the spinal dorsal horn level after experimental peripheral nerve injury (Castro-Lopes 1993, 1995).

Damage to primary afferents in peripheral nerves also induces profound topographic reorganization of the primary afferent terminals in the spinal cord. The central terminals of C fibres atrophy creating vacant synaptic sites, allowing Aβ fibres to sprout and form novel synapses in the lamina II which create inappropriate functional connections leading to persistent hypersensibility (Woolf 1992).

Altered supraspinal control mechanisms from descending pain modulatory neurons in the midbrain periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM) may be important for inhibition of nociceptive transmission (Fields 1999a). The PAG which is reciprocally connected with the RVM, also receives inputs from other brainstem areas; nucleus cuneiformis, the reticular formation and locus ceruleus as well as from the limbic forebrain and the hypothalamus (Herbert 1992, Bandler 1994). These connections can to some extent explain the analgesic effect caused by psychological mechanisms.

The combination of peripheral and central mechanisms contributes to a complicated clinical picture and involves therapeutically potentials.

**Central neuropathic pain**

Almost any kind of lesion in the brain or spinal cord can cause central pain. These include cerebrovascular and traumatic lesions, inflammatory processes, infections and tumours. The structure of the lesion is probably much less important than its location with regard to the risk of inducing central pain (Boivie 1999). Ever since the classical description by Dejerine and Roussy in 1906 there has been a particular interest in the role of thalamus in the development of central pain (Dejerine 1906). For several decades the impression from the literature was that central pain occurred mainly after thalamic lesions as shown by the use of the expression thalamic pain for all forms of supraspinal central pain.

Apart from thalamic lesions, cerebrovascular lesions with many locations have been shown to cause central pain, the most important being the lateral medulla oblongata, the posterior limb of the internal capsule, the subcortical
and cortical zones in the post central gyrus, and the insular region (Boivie 1999).

Several investigators have reported results indicating that central pain develops as a result of lesions that affect the spinothalamic pathways i.e. the pathways that are most important for the sensibility of pain and temperature (Boivie 1989, Tasker 1982, Bowsher 1996). These reports also show that the lesion can be located at any level of these pathways along the neuroaxis, from the origin in the spinal dorsal horn along the spino-thalamo-cortical projection to the cerebral cortex.

Two general pathophysiological processes have been hypothesized as possible causes of the severe spontaneous central pain and the painful over reactions to somatosensory stimulation that often accompany central pain:
1. An "irritative lesion" hypothesis that hyperactive cells at or adjacent to the lesion site produce increased activity of otherwise normal nociceptive pathways;
2. A "denervation hypersensitivity" hypothesis that neurons remote from the lesion, but within nociceptive processing pathways become hyperactive and hypersensitive because they have lost normal synaptic inputs (Head and Holmes 1911).

These hypothetical mechanisms are not mutually exclusive. Both may participate to varying degrees in the pathophysiology of central pain in different patients.

There is a complex constellation of activity and integration in many areas of the CNS that form the basis for the conscious pain experience. Probably these areas are highly interconnected; thus the elimination of a given pathway or a portion of this system such as by a lesion in the periphery, the spinal cord, or the brain could cause an imbalance in such integration, resulting in pain in the absence of a noxious stimulus (Craig 1999).

In pain states after spinal cord injury, two sensory levels of the nervous system are thought to be primarily affected; the segmental level i.e., the dorsal horn of the spinal cord at or near the site of injury, and the suprasegmental or forebrain level. The former are probably responsible for at-level pain, and the latter for below-level pain (Craig 2002).

The role of the thalamus in the development of central pain states is probably crucial. There is various evidence in support of this; It has been shown that after SCI there is an increase in the size of the thalamic representation of parts of the body adjacent to the anaesthetic area (Lenz 1994). Cells in this area are much less likely to have receptive fields than are cells in normal
controls (Lenz 1991). In the region of the border zone cells are more likely
to fire with a spike bursting pattern compared to other cells (Albé-Fessard
1983, Lenz 1989, Lenz 1994). Finally, thalamic stimulation in this region is
more likely to evoke sensations of pain (Tasker 1982, Lenz 1987,

Quality of life

Pain is not only a highly noxious experience per se, but it can also have an
overwhelming negative effect on nearly every other aspect of life, including
mood and capacity to function in daily roles (Rudy 1988). A summary of
key aspects concerning the patient's physical, psychological and social well-
being are often defined as the patient's health related quality of life (HRQoL)
(Schipper 1990). Generic questionnaires, designed to measure HRQoL of
patients with a diversity of diseases allow comparison with a background
population and with other patient groups (Patrick 1989).

Although its inclusion in medical research is relatively recent, quality of life
is increasingly being recognized as an important parameter to measure in the
evaluation of medical therapies, including those for pain management
(Skevington 1998, Katz 2002)

However, despite the fact that chronic pain is one of the most widespread
and difficult problem the medical community has to face (Latham 1994), the
features of pain and its burden on patients have been poorly described.
Neuropathic pain is thought to be a particularly distressing pain condition
and is associated with a high degree of suffering, not only because of the
intensity of the pain but also because of the long duration of the condition, as
the pain generally does not decline over time (Karlsten 1997). In many cases
no effective treatment exists (Fields 1999b). A wide range of therapeutic
regimens are often tried in an attempt to manage peripheral neuropathic pain.
Meta-analysis of the use of antidepressants (McQuay 1996) and reviews of
current pharmacological treatments (Karlsten 1997, Sindrup 1999) show that
currently available treatments are of limited efficacy and are associated with
side-effects that are poorly tolerated by patients, resulting in low compliance
(Kalso 1996).

Despite these findings, most experimental trials in populations with
peripheral neuropathic pain (PNP) are focused primarily on pain relief
outcomes (Kingery 1997, McQuay 1996). However, three experimental
studies assessing the efficacy of gabapentin of patients with post-herpetic
neuralgia and diabetic neuropathy included a measure of HRQoL (Backonja 1998, Rowbotham 1998, Serpell 2002). The authors used the general HRQoL instrument Short Form 36 (SF-36) which measures quality of life divided into eight dimensions. They found that three, five, and three of the eight dimensions, respectively were significantly improved by the treatment. The result of a recent study demonstrated impaired health-related quality of life using SF-36, in 150 patients with different aetiologies of pain referred to a multidisciplinary pain centre (Becker 1997). A shortcoming of these studies was that no evidence was presented that the instrument used was validated for the population studied.

Despite the extensive use of two descriptive generic HRQoL instruments, the SF-36 (McHorney 1993, Ware 1992, 1995) and the Nottingham Health Profile (NHP) (Hunt 1980), their reliability and validity have not been reported in a population with PNP or in any chronic pain population. Testing the psychometric properties of these two instruments thus seems mandatory before either can be recommended as outcome measures in PNP clinical trials.

The aim in the present study was to provide a cross sectional description of patients with PNP not previously described from an HRQoL point of view and to test the reliability and validity of the SF-36 and NHP in this group of patients. To reflect specifically pain-related symptoms and the side-effects from treatment often seen in PNP pain medication, questions regarding pain-related symptoms and side-effects were added. Employment status was also included in the present study to show the level of incapacity in the patient population examined. In addition, data were collected on pain intensity and distress from pain and the efficacy of previous and current pain treatments.

Assessment of sensory abnormalities in patients with neuropathic pain

Neuropathic pain is accompanied by sensory abnormalities (Lindblom 1979) due to lesions of sensory nerve fibres or sensory pathways within the central nervous system. Routine neurological sensory examination (testing of light touch with a cotton swab or pin-prick) can often detect these disturbances. However, hypoesthesia is often masked by allodynia to light mechanical stimulation. Hyperalgesia to mechanical stimuli is often reported as a different, more painful sensation, often with radiation and an unpleasant after-sensation. The diagnosis of neuropathic pain can in most cases be made
by a careful interview of the patient and a routine neurological examination. Quantitative sensory testing (QST) provides further diagnostic and descriptive characterization of the nerve pathology through quantitative evaluation of sensory qualities (Jörum 2002).

The sensations of touch, pressure and vibration are all mechanosensitive modalities transmitted in thick myelinated A fibres, dorsal columns and medial lemniscal pathways. These are all accessible to testing through conventional neurophysiological techniques such as neurography and electrically induced sensory evoked potentials (SEP). However, for testing the modalities of fast pain (A fibres), dull, burning, aching pain (C fibres), heat and heat pain (C fibres), cold (A fibres) and cold pain (A and C fibres) these methods are of no value.

**Thermal testing**

Quantitative testing of thermal thresholds is a widely accepted psychophysical method of evaluating small nerve fibre function and refines the diagnosis of neuropathies (Frusthorfer 1976, Yamitsky 1991, Verdugo 1992). It allows testing of warmth, cold, heat pain and cold pain sensations. This method describes the status of temperature sensitive somatosensory afferents all the way from the cutaneous receptors to the brain. Variability of threshold might be explained by differences in thickness of tissue overlying receptors, spatial distribution of receptors, physiologic properties of receptors, impulse transmission, or central processing (Light 1993).

**Allodynia/hyperalgesia to mechanical stimuli**

There are two types of allodynia/hyperalgesia to tactile stimuli, one to light touch (the dynamic type) and one to punctuate stimuli (the static type). Although both are caused by central sensitization mechanisms, they are mediated by different peripheral nerve fibres. The dynamic type is mediated by peripheral A fibres, whereas the punctuate type has been shown to be mediated by A fibres (Ziegler 1999). Punctuate allodynia/hyperalgesia can be mapped by the use of von Fray hairs, while dynamic allodynia is usually mapped by lightly brushing the skin (Ziegler 1999).

**Lack of effective pain relief**

Nociceptive pain, whatever its origin, can nowadays usually be successfully treated because of increasing knowledge of the underlying mechanisms and
better use of analgesic drugs. Patients with nociceptive pain often respond well to conventional pharmacological treatment, such as non-steroid anti-inflammatory drugs (NSAIDs), opioids and local anaesthetic drugs. Treatment of neuropathic pain is much more difficult (Finnerup 2002). Many patients suffer hard despite the best efforts of the medical profession. The arsenal of treatment available today for relief of chronic neuropathic pain is in part based on experimental research but mainly, on clinical experience and anecdotal evidence, since the number of clinical studies are limited (Fields 2001). This is particularly true for patients with central pain following stroke or spinal cord injury. Effective pain relief is lacking for the majority of patients, and for those who get some relief this is often partial and accompanied by considerable side effects (Fields 2001). It is not possible to predict whether or not a certain treatment will result in pain relief for the individual patient (Hansson 1998).

Three interesting lines of treatment

As a result of the multi-faceted pathophysiology, there are numerous possible entry points for therapeutic influence. We have chosen to study the three treatment alternatives described below.

In recent years, attention for subsequent pain relief has focused on glutamate’s action on the N-methyl-D-aspartate (NMDA)-receptor as a pivotal event in the transmission of persistent pain. Evidence suggests that NMDA receptors may be important for the development of long-lasting changes in neuronal excitability occurring after nerve lesions (Woolf 1991, Dubner 1992). These receptors are thought to be involved in the development of sensitization, “wind-up” and expansion of receptive fields (Dickenson 1987, Davies 1987, Woolf 1991). Persistent injury states such as neuropathy may produce a prolonged activation of the NMDA receptor subsequent to a sustained afferent input that enhances the evoked release of the excitatory amino acids. Ectopic impulse generation in peripheral nerves and in DRG, alterations in the phenotype of damaged nerves, and loss of inhibitory GABA controls (Fields 1997, Jensen 1996, Suzuki 2000) may all contribute to greater activation of the NMDA-receptor-channel complex.

Another approach for therapy is blocking of the sodium channels that play a role in neuronal hyperexcitability, and are thought to be one of the principal neurochemical mechanisms of neuropathic pain (Chen 1998). A principal mode of action of intravenous lidocaine is thought to be a dose-dependant
blockade of spontaneous ectopic activity in peripheral nerves and dorsal root ganglion cells (Chabal 1989, Tanelian 1991, Devor 1992). A central action of lidocaine and other local anaesthetics is indicated by their ability to reduce spinally mediated nociceptive withdrawal reflex in animals (Woolf 1985), by their ability to suppress dorsal horn wide-dynamic-range neurons in the spinal cord (Hao 1992, Sotgiu 1992), and by the ability of lidocaine injected in the rostroventromedial medulla and the periaqueductal grey to attenuate allodynia in neuropathic rats (Pertovaara 1996).

The opioids, as the principal and arguably most effective class of analgesic in use, are of many considered as ineffective in neuropathic conditions (Arnér 1988, Kupers 1991) whereas others claim that their effectiveness is just a matter of dose (Fields 1988, Portenoy 1990).

Opioid receptors are synthesized in the cell body of the sensory neuron and transported in both central and peripheral directions. Opioids have no peripheral actions at cutaneous sites in undamaged tissue, but there is good evidence that the consequences of inflammation can induce a novel peripheral site of opioid action that appears rapidly after the induction of the inflammation (Stein 1989). In the spinal cord, opioid receptors are found in the dorsal horn in the terminal zones of C-fibres. Stimulation of the presynaptic opioid receptor is associated with hyperpolarization of the terminal and reduced neurotransmitter (substance-P and glutamate) release (Hirota 1985, Kangrga 1991). Postsynaptic membranes also contain opioid receptors, which stabilize the membrane and make it less sensitive to neurotransmitters (Hylden 1983, Lombard 1989). Supraspinal sites of opioid analgesia are well established and have been localized to areas in the medial brain stem around the nucleus raphe magnus and extending rostrally to periaqueductal gray (Yaksh 1988).

Reduced response to opioids in neuropathic pain states may be explained by the induction of cholecystokinin (CCK) production in afferent fibres which occurs after nerve section, as CCK seems to be an opioid antagonist (Xu 1993). Another factor affecting the dose-response curve of opioid effectiveness may be associated with the action of the NMDA receptor-channel complex which enhances the excitability (Dickenson 1994).

Pathological transmission of pain by large-diameter A-fibres which do not possess opioid receptors (Dickenson 1986), could also explain reduced opioid efficiency. Moreover animal studies have shown that the amounts of opioid receptors in the dorsal horn are reduced after deafferentation, probably due to degeneration of the C-fibre afferents (Lombard 1989).
However, the postsynaptic opioid receptors as well as the supraspinal receptors will not be perturbed by primary afferent damage or dysfunction. The abovementioned is in accordance with reduced effect of opioid treatment in neuropathic pain states, but does not necessarily lead to an inherent resistance to these drugs.

Ketamine for treatment of neuropathic pain
In subanaesthetic doses, the oral, intramuscularly, intravenous, or subcutaneous administration of ketamine, has been shown in several controlled trials to relieve post herpetic neuropathy (Eide 1994, 1995a), phantom pain (Nikolajsen 1996), acute and chronic orofacial pain (Mathisen 1995), chronic post-traumatic pain (Max 1995), chronic ischemic pain (Persson 1998), and mixed neuropathic pain syndromes (Backonja 1994, Felsby 1996, Leung 2001). Eide showed an effect of ketamine on spontaneous and evoked pain following SCI (Eide 1995b). Several studies have also reported decreased intensity as well as reduced distribution of allodynia/hyperalgesia (Eide 1994, 1995ab, Felsby 1996, Max 1995, Nikolajsen 1996, Leung 2001, Jörum 2003).
While many studies are conducted with ketamine on neuropathic pain, we have only found the study conducted by Max concerning post traumatic neuropathic pain and Eides' study concerning pain of spinal origin.
It has been suggested that the analgesic effects of ketamine may be mediated by its interaction with other receptors and channels in the CNS (Meller 1996). However, since ketamine displays a much higher affinity for the NMDA receptor compared to other receptors or voltage-gated channels, it is unlikely that ketamine acts at other sites when distributed in clinically relevant subanaesthetic doses (Eide 1997). Furthermore, it has been shown that opioid receptor antagonists do not inhibit ketamine-induced reduction of secondary hyperalgesia (Mikkelsen 1999).

Lidocaine for treatment of neuropathic pain
The first controlled study to demonstrate the effects of i.v. lidocaine was conducted in patients with painful diabetic neuropathy (Kastrup 1987). The dose given was 5 mg/kg and pain relief lasted for 3-21 days after a single infusion. A study by Rowbotham conducted in 1991 revealed that both i.v. lidocaine (5 mg/kg) and morphine (0.3 mg/kg) were effective in relieving
post herpetic neuropathy (Rowbotham 1991). Marchettini showed an analgesic effect of a relatively low dose; 1.5 mg/kg in patients with peripheral nerve injury (Marchettini 1992). Galer administered both 2 mg/kg and 5 mg/kg of lidocaine with the same study design to a group of patients with neuropathic pain of various origins and reported significant VAS reduction with both doses (Galer 1996). In a study of the concentration-effect relationship for lidocaine, Ferrante showed that a large increase in pain relief was induced by a very small increase in dosage and blood-concentration. An all or nothing phenomenon with an abrupt analgesic effect over a narrow dosage range was demonstrated (Ferrante 1996). On the other hand, a study by Wallace in 1996 using a computer-controlled infusion pump demonstrated a dose-response relation in patients with traumatic neuropathy (Wallace 1996). Attal treated 16 patients with central post-stroke pain and pain from spinal cord pathology, demonstrating that lidocaine was more effective than placebo in relieving spontaneous pain and mechanical allodynia (Attal 2000). This was the first controlled study conducted in patients with neuropathic pain of central origin.

Morphine for treatment of neuropathic pain

The question whether opioids have an analgesic effect in patients with neuropathic pain has been debated by several authors. Applying the concept of neuropathic versus nociceptive and idiopathic pain, Arnér and Meyerson demonstrated that opioids produced weak responses in patients with neuropathic pain (Arnér 1988). Others have raised doubts about the concept of non-responsiveness to opioids. The idea of a continuum of opioid responsiveness, rather than an all-or-nothing phenomenon, has been put forward, since studies have demonstrated a variable responsiveness of neuropathic pain to opioid analgesics (Portenoy 1990).

In patients with postherpetic neuralgia Rowbotham demonstrated an analgesic effect of morphine 0.3 mg/kg and Watson with oxycodone (Rowbotham 1991, Watson 1998). In a study of 53 patients with different types of neuropathic pain Dellemijn compared the analgetic effect of high doses of fentanyl (5 μg/kg/h for 5 hours) with placebo and found a significant analgesic effect (Dellemijn 1997).

Central pain is generally considered to be refractory to opioids (Boivie 1999). However, in a recent study of patients with central pain due to multiple sclerosis, 4 of 14 patients responded to morphine treatment (mean
dose 41mg) and none to placebo (Kalman 2002). Attal demonstrated lately, in a study including 15 patients with CPSP or pain due to spinal cord pathology, that morphine (mean dose 16 mg) reduced brush-induced allodynia (Attal 2002). However, the effect on spontaneous pain did not significantly differ from placebo. In patients with pain due to spinal cord injury Eide have shown that alfentanil significantly reduced the intensity of both continuous and evoked pain (Eide 1995b). In another study, intratechal morphine given to patients with pain after SCI had no greater analgesic effect compared to placebo, but morphine and clonidine in combination produced significant pain relief (Sidall 2000b).

Morphine instead of ketamine in patients with CPSP

Our original plan was to study the analgesic effect of ketamine and lidocaine on three types of neuropathic pain; peripheral neuropathic pain, CPSP and pain after SCI. The first patients to bee included were patients with peripheral neuropathic pain, followed by the patients with pain after SCI. About half of these patients experienced the ketamine treatment as unpleasant, and one patient had a very frightening experience of the treatment. Her hallucinations were not evident for the investigator during the treatment but were reported on the follow-up visit. She then became depressed for several months. This event made us reconsider the planned ketamine treatment of the post-stroke patients. Since they were elderly and suffered from brain damage, we alleged that they might have a reduced capacity to handle a potentially frightening experience. Some of the patients also had some degree of dysphasia, and this would further hinder their possibilities to communicate and thus deal with an experience of this kind. We therefore decided not to give this patient group ketamine. Instead we chose to study the analgesic effect of morphine, which provides an interesting therapeutic alternative, without the risk to give rise to the abovementioned side effects.
THE AIMS OF MY THESIS

We aimed to provide a cross sectional description of patients with peripheral neuropathic pain from a HRQoL point of view.

We aimed to assess the analgesic effect of ketamine, lidocaine and morphine in a double blind, placebo-controlled, randomized study design on patients with peripheral neuropathic pain of traumatic origin, central post-stroke pain and neuropathic pain after spinal cord injury.

We aimed to assess sensory abnormalities to see if this could predict response to treatment. We also aimed to assess whether the drugs caused changes in thermal or mechanical sensibility.
PATIENTS AND METHODS

Study I

Patients
Patients with neuropathic pain following a lesion of a peripheral nerve, spinal nerve or nerve root or patients with post-herpetic neuralgia (NHP) were included. Patients with peripheral neuropathic pain (PNP) were determined to be eligible for the study if they had symptoms of spontaneous pain in the nerve territories of peripheral nerves or nerve roots and coexistent signs of somatosensory nerve dysfunction such as hyperalgesia/allodynia, hypoaesthesia, or dysesthesia.

Recruitment
One hundred and sixty three patients with PNP treated at the Multidisciplinary Pain Treatment Center, University Hospital, Uppsala, Sweden, between January 1991 and May 1997 were identified from the centres register. The patients were informed about the study and given the opportunity to participate. Ninety-nine of the patients were willing and eligible to participate in the study. Of the remainder the pain diagnosis was no longer valid for 10 patients, eight patients had language difficulties and 46 patients declined to participate.

Thirty five patients who had recently been treated or were being treated during the study period for their PNP at the Multidisciplinary Pain Clinic, Danderys Hospital, Danderyd, Sweden, were informed about the study and given the opportunity to participate. Twenty-seven patients from the unit
were willing and eligible to participate, while eight patients declined to participate. Data on patients’ demographics, pain diagnosis, concurrent diagnosis, and previous and present pain medication were collected. Some of these data were collected retrospectively from the hospital records and checked with the patient at the time of the study visit. Approved consent was given by the local Ethical Committees of Uppsala University and Karolinska Institute Danderyd Hospital Stockholm.

Data collection
An electronic touch screen device–Apple® Newton® Message Pad™ 130–was used to collect data. One question appeared on the screen, to which the patient selected a single reply by tapping on the appropriate box or text or by drawing a line across a visual analogue scale (VAS). The selection made by the patient could be changed until the button for next question was tapped. The next question appeared on the screen only if the previous question had been answered, thus eliminating the risk of missing data.

Pain
The intensity of present pain was assessed for pain at rest and pain evoked by movement, touch and cold stimuli. The anchors of the VAS scale were ‘no pain’ (=0) and the ‘worst pain imaginable’ (=100 mm). In response to the question ‘Have you been bothered by pain during the past week?’ patients also rated the degree to which they were troubled by the four types of pain (at rest, evoked by movement, touch and cold) on a seven-point verbal Likert scale graded from ‘No discomfort at all’ (=1) to ‘Very severe discomfort’ (=7) (Likert 1932). Pain relief from current medical treatment was recorded using a VAS scale labelled ‘No pain relief’ (=0) and ‘Complete pain relief’ (=100 mm).

Symptoms related to pain and side-effects from treatments
A 25-item symptom rating scale (RS) was used to assess the extent to which patients were bothered by or experienced discomfort from symptoms related to pain and well-known side-effects from pain medications. The scale consisted of the Gastrointestinal Symptom Rating Scale (GSRS) with 15
symptoms (Dimenäs 1993), supplemented with 10 symptoms related to chronic pain or side-effects of drugs frequently used to treat PNP. The degree of discomfort was rated on a seven-point Likert scale (1= no discomfort at all, 7=very severe discomfort).

Success of previous therapy
Previous pain medication belonging to the following groups was recorded: tricyclic antidepressants (TCAs), opioids (strong and weak), anticonvulsants and antiarrhythmics. The patient was asked whether the treatment resulted in any pain relief and, if ‘Yes’; was asked to specify the reason for discontinuation by choosing one of the three alternatives: severe side-effects, insufficient effect or both severe side-effects and insufficient effect.

Employment status
Patients were asked whether they were currently working (yes/no). If no, the reason was clarified by choosing one of the three alternatives: retired, on sickness pension or unemployed. If the patient was working part-time, the reduction in working hours per week due to chronic pain condition was recorded.

Patient-perceived quality of life impairments
The investigator interviewed the patients regarding the interference of their PNP on their quality of life (QoL) (i.e. activities, relations, psychological well-being, quality of sleep), recording the five aspects that the patient felt were the most significant.

Health related quality of life
Two generic health-related quality of life instruments; Short Form Health Survey (SF-36) and the Nottingham Health Profile (NHP) were used to assess the health related quality of life (HRQoL) since they have previously been extensively studied and used to document health status of patients suffering from a large number of diseases (Ware 1993, Badia 1994, McEwen 1996, Essink-Bot 1997, Lukkarinen 1997).
The SF-36 is a shortened version of 149 health status questions developed and tested on a population of over 22,000 patients as part of the medical outcome study (Tarlow 1989, Stewart 1989). It consists of 36 items measuring health on the eight dimensions; physical function, role physical, bodily pain, general health, vitality, social function, role emotional and mental health. The scores range between 0 (worst HRQoL) and 100 (best HRQoL) for each dimension.

NHP consists of two parts, of which only the first was used in the present study (Wiklund 88, McEven 96). Patients responded either yes or no to 38 questions/statements aggregated to six dimensions: energy, pain, emotional reaction, sleep, social isolation and physical mobility. The scores range between 0 (best HRQoL) and 100 (worst HRQoL) (Ware 93). Reliability and validity testing of the SF-36 and NHP were performed using the evaluation methods and standards developed for these instruments (Hunt 1980, Ware 1993, Sullivan 1995).

Global rating of health (rating scale)
A vertical VAS was used for assessment of patients’ global rating of health. Patients were asked to draw a line across the scale where it best described their existing state of health. The anchors were ‘death’ at the bottom end (0) and ‘full health’ at the top end (100).

Statistics
Descriptive statistics were used to describe the study population. Ninety-five per cent parametric confidence intervals were used to illustrate the difference between the study population and the general Swedish population for SF-36 and NHP. To evaluate the relationship between the different assessments we calculated the Spearman correlation coefficients. Cronbach’s was used to describe the internal reliability of SF-36 and NHP in this study population. All analyses were performed using the SAS system version 6.12.
Study II-IV

Patients
In these studies we included patients with neuropathic pain at three different levels, peripheral neuropathic pain of traumatic origin, central post-stroke pain and neuropathic pain after spinal cord injury. Patients with peripheral pain were selected for inclusion based on the following criteria: the patient should be affected by peripheral nerve or root lesion of traumatic origin e.g. trauma, surgery or compression, with spontaneous and evoked pain in the cutaneous territory supplied by the injured nerve together with clinically demonstrable sensory deficit or sensory hyperfunction. Patients with CPSP were selected for inclusion based on the following criteria: 1) the patient should have had an unequivocal stroke episode; 2) the patient was seeking relief from constant or intermittent pain, which started after the stroke and with a duration of at least one year; 3) it was excluded based on clinical evaluation that the pain was of nociceptive, peripheral neuropathic or psychogenic origin. Patients affected by pain after traumatic spinal cord injury were included if they suffered spontaneous diffuse pain distally from the level of the lesion: below-level neuropathic pain according to the taxonomy proposed by the SCI Pain Task Force of the International Association for the study of Pain (IASP) (Sidall 2000a). For inclusion the below-level pain should have been their dominating pain for more than a year. The lesions were of partial or complete form at the cervical, thoracic or lumbar level. Patients with drug abuse, cardiovascular disease or previous treatment with the intended study drugs were not considered for the study. Patients with dysphasia severe enough to make an adequate evaluation impossible were not considered. Patients who were receiving other pharmacological treatments for their pain at the time of screening continued this medication with stable doses throughout the study. The nature and the purpose of the study were explained to the patients before they gave their informed consent. It was stressed that they could terminate the experiments at any time and that participation was voluntary. The protocol was approved by the Ethics Committee of Uppsala University and by the Swedish Medical Products Agency.
All tests were performed in a calm environment, each time at the same place and performed by the same two investigators using identical procedures. All patients were investigated in three separate sessions each one comprising about four hours, in addition all patients had one introductory session and one follow up session.

Drugs
The study had a randomised, double-blind, placebo-controlled, three periods, three treatment, cross-over design. The randomisation code assignments for different blocks of treatment were kept in sealed envelopes. A nurse not involved in the study randomly selected one blank envelope for each patient and prepared the infusion according to the written instructions in the envelope. Each test session was separated by at least four days. The patients continued with their regular medication including analgesics during the test period. The effects of ketamine hydrochloride (Ketalar®, Parke Davis, Morris Planes, USA) 0.4 mg/kg, morphine hydrochloride (Morfin®, Pharmacia Upjohn, Peacock, New Jersey) 0.2 mg/kg and lidocaine hydrochloride (Xylocain®, Astra, Södertälje, Sweden) 2.5 mg/kg were investigated. The patients with peripheral neuropathic pain and pain after spinal cord injury were given ketamine and lidocaine and the patients with central post-stroke pain received morphine and lidocaine. Saline (NaCl 9 mg/ml) was used as placebo. All substances were given intravenously. The drugs were diluted in saline and given by infusion over 40 minutes using an infusion pump (Gemini PC-1, Pharmacia, Stockholm). Lidocaine was given initially with 1.0 mg/kg during 10 minutes and then 1.5 mg/kg during 30 minutes. This was to ensure optimal loading of the compartments based on the pharmacokinetic properties of lidocaine (Roden 1990). Ketamine and morphine were given with a constant rate over 40 minutes. As the design was double-blind and lidocaine were given at two different rates, two bottles of each drug were given. Two intravenous cannulas were applied, one in each arm, one for the infusion and one for blood sampling. The given doses were based on previous reports (Dahlström 1982, Kupers 1991, Marchettini 1992, Eide 1995a, Felsby 1996, Wallace 1996), pilot studies and the use of the drug in clinical practise for other disorders. The doses were expected to have a pharmacological effect without too pronounced side effects.
Blood sampling and bioanalysis

Peripheral venous blood samples were collected just before the start of drug administration (time=0) and at 15, 45, 60, 120, and 150 min. (T:0, T:15, T:45, T:60, T:120, T:150) All plasma samples were stored in a refrigerator (4°C) and frozen within 2 h of collection. They were then stored at -70°C until assay.

The analysis of ketamine, lidocaine and morphine in plasma samples were performed using gas chromatography mass spectrometry (Dr Ulf Bondesson, Dept. of Chemistry, National Veterinary Institute, Uppsala, Sweden). The quality control samples for ketamine analyses at 62 ng/mL (n = 6) and 175 ng/mL (n = 6) gave a precision of 6.5% and 2.3%, respectively with a limit of quantification of 4.9 ng/mL. The corresponding figures for lidocaine at 2086 ng/mL (n = 10) gave a precision of 7.5% and the limit of quantification was 48 ng/mL. For morphine analyses at 32 ng/mL (n = 6) and 213 ng/mL (n = 6) gave a precision of 3.6 % and 6.5 % and the limit of quantification was 1.2 ng/mL.

Assessment of pain

The intensity of continuous spontaneous pain was measured by a visual analogue scale (VAS) (Huskinsson 1974). Pain rating was obtained on a 0-10 cm scale, with 0.0 = no pain and 10.0 = the worst pain imaginable. Measurements were taken before start of the infusion at T:0 and then at T:15, T:45, T:60, T:120, T:150.

We wanted to analyse the pain reduction expressed both as group mean values and as dichotomous outcome, presenting responders and non responders (Moore 1996). In order to detect a clinically relevant effect, response to treatment (responder) was defined as a more than 50% reduction in VAS-score compared to baseline at any time-point during and after infusion. All other patients were regarded as non-responders.

Quantitative sensory testing with thermal stimulation

Quantitative testing of thermal sensibility was carried out using a commercially available Peltier element based thermode with an area of 12.5 cm² (Thermotest Somedic AB, Hörby, Sweden) (Fruhstorfer 1976). All temperature stimulations started from the same temperature (32.0°C) (Hilz 1999). Perception thresholds for cold and warmth were tested using random
thermal pulses with a constant rise time (1°C/sec.). The patients were instructed to press a handheld button as soon as she/he experienced the stimulation as being cold or warm, respectively. This manoeuvre returned the probe temperature to initial thermode temperature. The mean of 5 values (warm/cold thresholds) was calculated. Heat and cold pain thresholds were determined by changing the probe temperature (2°C/sec) until the patient perceived the thermal stimuli as being painful. The mean of 3 values was calculated. The cut-off temperature was 52°C and 5°C, respectively. The testing started with familiarising the patient with the method on a healthy area not involved in the study. Thermal testing was then performed applying the probe to the most painful area and to a homologous control area on the contra-lateral side of the body or to a normal skin area above the lesion level (SCI). This was done before the infusion at T:0 and then immediately after infusion at T:45 and at T:150.

Examination of sensibility to mechanical stimuli
To assess the sensibility to touch we used a wisp of cotton which was gently stroked on the skin to test dynamic sensibility. For static sensibility we used calibrated von Frey filaments 0.1, 1.8 and 18.6 g (Aestesiometer Senselab® Somedic AB, Hörby, Sweden) which were gently applied to the skin with sufficient force to cause slight filament bulging. Pinprick was done by light prick with a pin. Sensibility to vibration was tested with a vibrameter (Somedic AB). This was done to test dorsal column function. The testing started with familiarising the patient with the method on a healthy area not involved in the study. The procedures were then carried out at the painful area and at a control area at the homologous contra-lateral side of the body or at a normal skin area above the lesion level (SCI). The patient reported if the sensation (compared to the control area) was normal, hyperesthetic, hypoesthetic or not felt at all. This was performed before the infusion at T:0 and at T:45 and T:150.

Assessment of adverse events
The adverse events were assessed in three ways; an open question about what was felt during the experiment was given at the end of each session, spontaneous reports about adverse effects during the experiment were registered, and this information was complemented with a checklist that the
patients were instructed to fill in at home after the experiment, when the risk that any patient was still affected was negligible.

**Statistical analysis**

Descriptive statistics included mean values, standard deviation and range whenever appropriate. The maximum percent decrease in VAS pain from baseline was modelled by an analysis of variance model (ANOVA) with period and treatment as fixed factors and patient as random factor. Estimates of treatment effects and pair wise differences between treatments were done in this model. The percent change in thresholds (cold-, warm-, cold pain-and heat pain-thresholds) from baseline were analysed using a separate ANOVA for each time point and side (pain site and control site) combination with period and treatment as fixed factors and patient as random factor. McNemar’s test was used for comparison of the proportion of responders in each group. Results are presented as estimates of differences and corresponding 95% confidence intervals. The 95% confidence interval (CI) for Numbers needed to treat (NNT) was obtained as the reciprocal value of the 95% CI for the difference between independent proportions. This was calculated according to the Wilson procedure without continuity correction (Newcombe 1998).

![Fig.1. The experimental protocol for studies II, III and IV.](image-url)
METHODOLOGICAL CONSIDERATIONS

Patient selection

The patients recruited to the treatment studies were all patients at the multidisciplinary pain clinic at Uppsala University hospital, all had neuropathic pain of long duration that had been resistant to other treatments and their VAS scoring were in most cases relatively high. These factors might decrease the possibility for analgesic effect of the studied drugs. The results may have been different if we had chosen patients consecutively when they first appeared at the pain clinic before any other medication had been tried, or if studies were done on patients treated for their neuropathic pain in the primary health care.

Some studies conducted to assess the analgesic effect of different substances include only patients that have already responded to the studied drug or a related drug. Belfrage studied adenosin given intrathecally to a group of patients that had shown a positive response to adenosin given intravenously (Belfrage 1999). A study of the analgesic effect of gabapentin on neuropathic pain syndromes had the inclusion criterion that the patients already had tried gabapentin with a positive response (Serpell 2002). Several studies on NSAIDs are designed in the way that only patients already treated with some conventional NSAID and who develop a "flare" state upon discontinuation are included in studies that compare the efficacy of a new NSAID drug (McKenna 2001, Bensen 2002). These criteria for patient selection establish the effect in relation to placebo but give no indication of the response rate in previously untreated populations. With this design a smaller population can be used to prove effect versus placebo.

One the other hand, I think that a considerable amount of studies conducted on patients with neuropathic pain are performed with a reverse selection, in comparison with those mentioned above. The patients which are primarily selected have pain conditions which are often both difficult to treat and long
lasting. This partly depends on the natural desire in clinical practise to administer drugs with a documented effect e.g. TCA without the delay that a study on the effect of new drugs would mean. This group of patients are also strongly motivated to participate in studies despite the risk of adverse effects and the requirement for several relatively long lasting treatment sessions. The latter also means that primarily patients who are not employed are available for participation. The patients included in the study of quality of life included a broader selection of patients. Like the treatment studies the quality of life study was not consecutive, but all patients that had been treated for neuropathic pain at the pain clinic during a certain period were considered for inclusion. This study was considerably less time consuming for the patients as it only required one visit of two hours duration. Furthermore the study was without medical intervention so it did not affect the patients’ drug use, and there was no risk for adverse effects.

Health related quality of life

In the present study two descriptive generic instruments, the SF-36 Health Survey (Ware 1995) and the Nottingham Health Profile (NHP) (Hunt 1980) were used. Both are widely used instruments that have been translated and validated for general population use in Swedish versions (Sullivan 1995, Wiklund 1990)

Generic instruments are intended to measure quality of life within a disease state as well as across disease states. They can also be administered to a general population to see how a particular condition causes the health profile to differ from a healthy standard (Steward 1989, Frater 1992). Their advantage is that they allow for groups of patients with various conditions to be compared with one another. Their disadvantage, however, is that because they are so general, they are often not very effective in measuring improvement in a specific disease state as a consequence of an intervention. Thus, they may not pick up subtle but important shifts in quality in life resulting from a given treatment (Katz 2002).

It may therefore be useful to complement a generic instrument with a questionnaire of disease-specific symptoms, which are considered more sensitive than generic instruments in differentiating the impact of various drugs on quality of life (Testa 1993). We chose to evaluate two commonly
used generic instruments and a specific questionnaire regarding pain-related symptoms. While SF-36 and NHP have been extensively used in numerous patient populations, their reliability and validity have not been reported in a population with peripheral neuropathic pain or in any chronic pain population. One of our aims was thus to evaluate the psychometric properties of these two instruments to test their validity and reliability in this group of patients.

Choice of dose
When planning a study of analgesic drugs the choice of dose is an important factor. If the dose is too low the desired effects may not occur and if the dose is too high the side effects may dominate over the desired effects. One method to choose the optimal dose is dose-titration. This method enables titration of the optimal dose both for desired effect and side effects. However, we judged that the resources needed to conduct dose titration were outside the scope of this study.

The choice of dose was ultimately determined by avoiding doses that could be toxic. Chronic pain implies a need for chronic treatment, and we considered that doses that might approach toxic levels were uninteresting in this context.

Lidocaine is a substance with relatively narrow therapeutic index and with considerable adverse effects on the nervous as well as the cardiovascular systems (Roden 1990). A major basis for our choice of dose was that a higher dose was not considered to be safe given the toxicity of lidocaine and hence the risk for severe adverse effects. In clinical practice, higher doses than the one we chose are rarely used at intensive care units even for life-threatening conditions like ventricular arrhythmias and status epilepticus. In the Swedish guidelines for administration and doses; the Swedish Drug Compendium (FASS), it is stated that doses of more than 200 mg should not be administered in less than one hour and that dose was administered during a mean of 40 min in our study.

Ketamine is also a substance with a narrow therapeutic index. In a study conducted by Öye (Öye 1992) side effects that indicated a sensory influence were registered in all cases of pain relief in a dose dependent way. In our studies we accepted a dose with an expected frequency of side effects, in
order to capture a potential effect since we did not consider that these side
effects would pose any potential risk for the patient.
Also for morphine the dose given was relatively high in comparison with
therapeutic doses e.g. in post-operative care. Other authors, who have
studied treatment with opioids of chronic pain, have used considerably
higher doses (Dellemjin 1997, Attal 2002). Also in this case we chose a
fairly high dose in order not to miss a potential analgesic effect, since we
judged the expected side effects to be manageable. On the other hand, side
effects of the scope we saw could be considered to be in the upper limit
during long time treatment.

Pain and pain relief measurement

Pain is a complex perceptual experience that can be quantified only
indirectly (Chapman 1985). Approaches to the measurement of pain include
verbal and numeric self-rating scales, visual analogue scales, behavioural
observation scales, and physiological responses (Gracely 1988). Because
pain is subjective, the patient's self report provides the most valid measure of
the experience.

Verbal or category scales consist of a series of verbal pain descriptors
ordered from least to most intense (e.g. no pain, mild, moderate, severe)
(Jensen 1992). Numerical rating scales typically consist of a series of
numbers ranging from 0 to 10 or 0 to 100 with endpoints intended to
represent the extremes of the possible pain experience and labelled ‘no pain’
and ‘worst possible pain’, respectively (Jensen 1992).
The visual analogue scale is one of the rating scales most widely used and
has been found to give valid and reliable data when used to measure
experimental pain as well as acute and chronic pain (Huskinsson 1983). It
consists of a 10 cm horizontal line with the two endpoints labelled ‘no pain’
and ‘worst imaginable pain’, respectively. The patient is required to place a
mark on the 10-cm line at the point which corresponds to the level of pain
intensity he presently feels. The distance in centimetres from the low end of
the VAS to the patient's mark is used as a numerical index of the severity of
pain (Huskinsson 1974). Sriwatanakul compared different types of scales
and found that horizontal VAS was more reliable and preferable to patients
than category pain scales (Sriwatanakul 1983). When category scales are
employed it is difficult to specify the size of each category and whether the
categories are of equal spacing (Heft 1984). VAS measurement of pain
intensity also seems to be more sensitive to smaller changes in effect than the categorical measures (Wallenstein 1980). Joyce concurred that the VAS is more sensitive, just as valid and may be more reliable than category scales in patients with chronic pain (Joyce 1975). On the contrary, in a study by Carlsson the reliability of VAS scales used to assess changes in chronic pain was unsatisfactory (Carlsson 1983). High correlations have been reported between VAS and numerical rating scales (Kremer 1981, Ekblom 1988). However, the VAS provides an advantage as it is a continuous scale. We have chosen to use the VAS because of its relative reliability, ease and brevity of administration and scoring (Jensen 1986).

We considered the option to instruct the patients to rate the amount or percentage of pain relief they experienced using a VAS after the drugs to be tested were administered. However, according to Carlsson this can introduce unnecessary bias (e.g. expectancy for change) which reduces the validity of the measure. She suggested therefore that a more appropriate measure of change may be obtained by having patients rate the absolute amount of pain at different time points during the experiment (Carlsson 1983). This was the way we chose to carry out the repeated measurements.

Some authors claim that the VAS has ratio scale properties (Price 1983, 1987) whereas others prefer to treat the data as ordinal scales and thus use non-parametrical statistical analysis (Chapman 1985).

Thermal stimulation

Measurement of thermal senses provides an estimate of the function of sensory small fibres. Being psychophysical parameters, sensory threshold values are not objective, and various test algorithms have been developed aiming at optimised results (Yarnitsky 1994).

Methods used for threshold determination can be divided into two basic groups: those that involve reaction time in the measurement, and those that do not. In the first, the subject is requested to stop a stimulus whose intensity is increasing linearly or exponentially. The time required for transmission of the peripheral impulse from the sensing site to the brain, processing, and transmission of the command to the signalling hand to halt the stimulus is the reaction time (Yarnitsky 1991). During this period, stimulus intensity keeps increasing. In the reaction time-exclusive methods, a stimulus of predetermined intensity is given, and the subject is requested to indicate whether perception occurred, after stimulus termination. Threshold values
obtained through this method are, hence, of less absolute value compared to the reaction time-inclusive ones. The thresholds of the method of limits, a reaction inclusive method, have a greater inter-individual and intra-individual variability than do thresholds determined with reaction time-exclusive ones. (Claus 1990, Yarnitsky 1994, Yarnitsky 1997). However, it has been shown (Claus 1987) that the method of limits demonstrates small-nerve fibre dysfunction as frequently as do the more time-consuming reaction time-exclusive algorithms. The method of limits is quick and easy to perform (Fruhstorfer 1976, Verdugo 1992), which is of importance in a study with repeated assessments.

Several authors have published their normative data by site, modality, method and age (Claus 1987, Verdugo 1992, Dyck 1993, Meh 1994, Yarnitsky 1994). As general rule, thresholds increase with age, there are minor differences between gender and between body sides but substantial diversity between different testing sites. Normative data are normally presented as the upper normal limit, using mean values ±2SD, such that hypoesthesia can be determined if one's threshold is above that range. For thermal pain normal data are given as a range with lower and upper ends, such that a threshold above the upper range represents hypoesthesia while that below the lower range stands for allodynia.

Normal values for different body sites differ considerably, e.g. Yarnitsky and Sprecher show hypoesthesia for warmth detection at the thenar region with a threshold of 3°C above baseline temperature whereas the threshold for hypoesthesia at the foot was 11°C above baseline (Yarnitsky 1994). Verdugo and Ochoa's criterion for warm hypoesthesia was 4°C above baseline temperature at the thenar region; for the tarsal region the values were very age-dependent (Verdugo 1992). Both studies used 32°C as baseline temperature.

Several authors have reported large variations between repeated measurements of thresholds of the same individual (Fagius 1981, Yarnitsky 1994, Rommel 2001).

The above mentioned variations make it difficult to classify and compare patients of different age, with diverse pain sites.

Assessing the sensibility to mechanical stimuli

One of our aims was to assess the sensibility to mechanical stimuli to determine if treatments gave rise to changes of sensibility.
We assessed dynamic sensibility using a wisp of cotton which was gently stroked on the skin and static sensibility using von Frey filaments. Pinprick was tested in the group of patients with central post-stroke pain. The assessments were qualitatively categorized as normal, not felt at all, hypoesthetic, allodynia/hyperalgesia, or hyperpathic. One can argue that this classification was too coarse to detect other than pronounced changes of sensibility. One way to detect more precise changes would have been to perform a quantitative determination of sensory and pain thresholds with von Frey filaments of different grading (Eide 1994, Felsby 1996). The allodynia evoked by von Frey filaments or stroke with wisp of cotton could have been recorded as change in pain intensity, measured by a VAS (Eide 1995b, Attal 2000). Another way to reach a more profound insight into possible drug-induced changes of sensibility would have been mapping the areas with abnormal sensibility before and after the treatments (Marchettini 1992, Felsby 1996, Wallace 1996).

However, as primary outcome, we wanted to study the pain relief of spontaneous pain. It would not have been possible to carry out all the potentially interesting sensory measurements within the time available. We gave priority to quantitatively measured temperature thresholds which were measured three times during each session and measured sensibility to mechanical stimuli qualitatively.

One noteworthy factor is our impression that patients who participate in this kind of studies cannot keep their focus and give reliable answers to psychophysical tests during more than a limited period. In our studies the patients were also given drugs that could further lower the ability to concentrate. We believe that studies with trained volunteers have a rather different point of departure in respect of this. In the latter group, distraction, fatigue and anxiety about the examination might be less pronounced. Furthermore the investigator's capacity to reliably carry out repeated measurements during a prolonged period of time is limited.
RESULTS

Study I

Patients
A total of 126 patients with PNP as their main diagnosis were included: 70 females, median age 50 years (range 24-82 years) and 56 males, median age 54 years (range 27-81 years). Neuropathic pain diagnosis, other pain diagnosis and other concurrent diagnoses are described in Table 1. For the ten patients experiencing other types of pain (such as migraine or back ache) in addition to neuropathic pain, the neuropathic pain was predominant. In summary 83 patients suffered from traumatic peripheral nerve injury, 7 had PHN and 30 had nerve root injury or spinal nerve injury, 6 had nerve injury of other origin, such as inflammation and tumours. The median time from onset of the PNP condition was 6 years (range 0.4-37.6 years).

Table 1. Diagnosis

<table>
<thead>
<tr>
<th>Primary neuropathic pain diagnosis</th>
<th>n</th>
<th>Additional diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posttraumatic nerve injury (trauma, surgical, entrapment)</td>
<td>83</td>
<td>Hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Nerve root and spinal nerve injury</td>
<td>30</td>
<td>Asthma</td>
<td>6</td>
</tr>
<tr>
<td>Post herpetic neuropathic pain</td>
<td>7</td>
<td>Allergic reaction</td>
<td>5</td>
</tr>
<tr>
<td>Other reasons (trigeminus neuralgia, tumors, inflammation etc)</td>
<td>6</td>
<td>Migraine</td>
<td>4</td>
</tr>
</tbody>
</table>
Pain intensity

The median VAS score for current pain intensity was highest (53) for movement-evoked pain followed by pain at rest and cold- and touch-evoked pain (medians 40, 41 and 34 respectively) (Fig.2). The type of pain that was most intense varied between patients. Forty-three percent or the patients scored their highest pain evoked by movement, 25% evoked by cold, 24% evoked by touch and 15% at rest (the total exceeds 100% as nine patients scored their most intense pain for more than one type of pain). The median of the highest pain score reported by each patient was 74 (Q1 = 53, Q3 = 87). For the groups of patients with their highest pain scores evoked by movement, touch, cold and at rest respectively, the medians were 69, 78, 83 and 69 (Fig.2).

![Pain intensity at rest and evoked by movement, touch and cold. Median VAS pain scores and the 25th and 75th percentiles for all patients and scores for patients who rated their most intense pain at rest, movement, touch and cold, respectively](image)

Fig.2. Pain intensity at rest and evoked by movement, touch and cold. Median VAS pain scores and the 25th and 75th percentiles for all patients and scores for patients who rated their most intense pain at rest, movement, touch and cold, respectively.
Bothered by discomfort from pain

Most patients were considerably bothered by or experienced discomfort from pain experienced during the previous 7 days (Fig. 3). In addition to what can be seen in Figure 3, a high proportion of patients (94%) reported moderate to severe discomfort from at least one of the four types of pain. As with pain intensity, discomfort due to pain evoked by movement was rated highest by most patients, followed by pain at rest and pain evoked by touch and cold. Patients’ ratings of how troublesome the pain was showed a high correlation with the VAS scores for current pain intensity (Spearman’s rank coefficient $r = 0.82, 0.82$ and $0.74$ respectively for pain evoked by touch, cold and movement). For pain at rest $r$ was $0.50$.

Symptoms related to pain and side-effects of treatment

Of the 25 symptoms assessed the 10 most frequent are presented in Figure 4. Patients were most bothered by difficulty in sleeping, followed by lack of energy, difficulty in concentration and drowsiness; 88%, 86%, 76% and 71% respectively reporting they were troubled to some degree (Fig. 4). Sixty percent of the patients reported moderate to very severe discomfort from difficulty in sleeping during the previous 7 days. Only 6-15% of patients
reported moderate to severe problems with 15 different gastrointestinal symptoms (GSRS) (results not presented in Fig.4). The means for these symptoms were in the range 1.6-2.0, which is similar to that for the Swedish general population (Dimenäs 93).

Fig.4. The extent to which patients had been bothered by symptoms related to pain and/or side-effects during the previous seven days. (1= no discomfort, 7= very severe discomfort).

Ongoing treatment

Ninety-four patients (75%) were currently using at least one pain medication. Of these, 48 patients (51%) had two to four ongoing pain medications, often combined with physical therapy and/or afferent nerve stimulation (transcutaneous electrical nerve stimulation (TENS) or dorsal columnal stimulation (DCS) (Table 2).
Table 2. Current pain treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>39</td>
</tr>
<tr>
<td>Opioids</td>
<td>7</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>12</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>2</td>
</tr>
<tr>
<td>Weak opioids*</td>
<td>64</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>24</td>
</tr>
<tr>
<td>TENS</td>
<td>13</td>
</tr>
<tr>
<td>Dorsal columnal stimulation</td>
<td>8</td>
</tr>
<tr>
<td>Other interventions**</td>
<td>23</td>
</tr>
</tbody>
</table>

*tramadol, codeine, dextropropoxphene
**nerve blocks, physical therapy

Most patients experienced poor pain relief from their ongoing medical treatment. The median score ($n=94$) for pain relief from ongoing pain medical treatment was 41 (Q1=20, Q3=70; range 0-99) (0 = no pain relief, 100 = complete pain relief) (Fig.5).

![VAS painscoring](image)

Fig.5. Pain relief from ongoing treatment.

Success of previous therapy

In total, 66% of the patients had discontinued previous treatment(s) with TCAs, strong or weak opioids, anticonvulsants or antiarrhythmics. Twenty-one of these 84 patients were currently not using any pain medication. Of the total of 147 treatments tried, 60% (88) were discontinued owing to no pain relief (Table 3). Forty percent (59) of the treatments resulted in pain relief, and among these 24 were discontinued owing to insufficient effect, 23 owing to severe side-effects and 11 owing to both insufficient effect and severe side-effects. Patients who were on their second, third or fourth
treatment reported pain relief from ongoing pain therapy as poor in comparison with patients trying TCAs, opioids, anticonvulsants or antiarrhythmics for the first time.

Table 3. Reason for discontinuing previous treatment

<table>
<thead>
<tr>
<th>Previous treatment</th>
<th>Number of patients who tried*</th>
<th>Reason for discontinuation (number of patients*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No pain relief</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insufficient effect</td>
</tr>
<tr>
<td>TCA**</td>
<td>57</td>
<td>32 (56%)</td>
</tr>
<tr>
<td>Opioids</td>
<td>44</td>
<td>24 (54%)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>36</td>
<td>25 (69%)</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>10</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Total</td>
<td>147 treatments in 84 patients</td>
<td>88 treatments in 67 patients</td>
</tr>
</tbody>
</table>

* Patients had discontinued 1 to 4 different treatments
** One patient discontinued for other reason.

Employment status

In total, 52% (n =65) of patients had a reduced employment status as a direct consequence of the pain. Of the 104 patients (83%) within working age (<65 years of age), 43 received sickness pension and 22 worked part-time as a consequence of their neuropathic pain condition. Among part-time employees, the average reduction in working hours due to pain was 17 hours per week (Fig.6). The patients were not asked if they were on sick leave which is a limitation in respect of this issue.
Fig. 6. Present working status of the 126 patients, of which 104 were of working age. In total, 52% of the patients had reduced working hours due to their chronic pain condition (shaded area).

Patient-perceived QoL impairments

In the interview regarding interference of their PNP on their QoL, 49% (n = 32) of the patients who had reduced working hours due to PNP reported that they missed their job. Reduced outdoor activities, sports and physical activities in general were also frequently reported by the patients to interfere most significantly with their QoL. In Table 4, 25 of the 386 aspects that the patients felt severely interfered with their QoL are listed to give examples of the kinds of QoL impairments regarded as severe by the patients.

Table 4. Missing qualities of life

<table>
<thead>
<tr>
<th>Not being able to work</th>
<th>Miss physical and mental strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can’t do crochet work</td>
<td>too little garden work</td>
</tr>
<tr>
<td>Miss art work</td>
<td>difficult to sleep, always tired</td>
</tr>
<tr>
<td>Always feeling limited</td>
<td>not able to play the piano</td>
</tr>
<tr>
<td>Miss dancing</td>
<td>not able to go fishing or hunting</td>
</tr>
<tr>
<td>Can’t spend time outdoors</td>
<td>no longer able to take care of the motor boat</td>
</tr>
<tr>
<td>Increased irritation</td>
<td>can not provide fuel wood for the house</td>
</tr>
<tr>
<td>Miss myself</td>
<td>miss physical contact with grandchildren</td>
</tr>
<tr>
<td>Lack belief in the future</td>
<td>not being able to walk in high heels</td>
</tr>
<tr>
<td>Miss my good spirits</td>
<td>difficult not to be independent</td>
</tr>
<tr>
<td>Miss colleagues</td>
<td>pain with sexual intercourse</td>
</tr>
<tr>
<td>Too tired to read</td>
<td>not being able to plant potatoes</td>
</tr>
<tr>
<td>Miss love</td>
<td></td>
</tr>
</tbody>
</table>
HRQoL

Results from SF-36 showed that the patients had a significantly impaired HRQoL. The scores of all eight dimensions in SF-36 were significantly reduced compared with the Swedish general population. (Sullivan 95) (Fig.7). Physical function, role physical, bodily pain and role emotional were the most affected dimensions compared with the normal population. Of the different types of pain assessed using the VAS scores, pain on movement (VAS) was the type of pain with the highest correlation with the SF-36 dimensions. The highest correlation were with bodily pain and physical function ($r = -0.53$ and $r = -0.43$ respectively). Cronbach’s exceeded or equalled the recommended 0.7 (Ware 93) for all dimensions. The results from NHP are similar to SF-36 in that all dimensions were significantly reduced in the patient group compared with the Swedish general population (Fig.8) (Halling 95). The dimensions pain, energy, sleep and emotional reactions were most affected. Also for NHP, pain on movement (VAS) was the type of pain with the strongest correlation with the six dimensions. The correlation with the dimensions physical mobility and pain were 0.42 and 0.39 respectively. Cronbach’s exceeded or equalled 0.7 for three of the six dimensions.

![Fig.7. SF-36 mean score and 95% confidence intervals of our study population and the Swedish general population. A higher score represents better health.](image-url)
Fig. 8. NHP mean score and 95% confidence intervals of our study population and the Swedish general population. A higher score represents worse health.

Global rating of health (rating scale)

Results from the global rating of health revealed that the health status of patients with PNP is considerably impaired compared with the Swedish general population, which was rated at 83 (SD ± 16.0) in a study by Lundberg (Lundberg 1999). The mean VAS score in this study was 57.0 (SD ± 23.0).
Studies II-IV

In studies II, III and IV we used similar methods in the studied patient groups, and I have therefore chosen to present the results together.

Patients
Thirty-three patients, 17 males and 16 females, were included in the three studies. Twelve suffered from peripheral neuropathic pain of traumatic origin. Eleven suffered from CPSP, one of the latter did not fulfil the study because of difficulties in communication; hence the analyses were done on results from the remaining 10 patients. Ten patients with pain after SCI were included in the study. All of these reported below-level pain; some also suffered from at-level pain. In all patients sensory abnormalities such as allodynia, hyperalgesia and/or hypoaesthesia were found within the painful region. All patients had tried different treatments e.g. TCA, anticonvulsants, weak opioids or transcutaneous electrical nerve stimulation (TENS) with unsatisfactory results. All patients assessed their pain as severe, even those who scored low on VAS. Demographic and clinical data are summarised in Tables 5, 6 and 7.
Table 5. Patient characteristics in patients with peripheral neuropathic pain (study II)

<table>
<thead>
<tr>
<th>Pat no</th>
<th>Age</th>
<th>Sex</th>
<th>Site of pain/nerve territory</th>
<th>Etiology of pain</th>
<th>Duration of pain (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>f</td>
<td>Groins bilat</td>
<td>Postop</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>f</td>
<td>N radialis superficialis</td>
<td>Postop</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>m</td>
<td>N peroneus superficialis</td>
<td>Trauma and several op</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>f</td>
<td>N intercostalis</td>
<td>Postop</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>m</td>
<td>N peroneus superficialis</td>
<td>Trauma and several op</td>
<td>4,5</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>f</td>
<td>N saphenus</td>
<td>Postop</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>f</td>
<td>N saphenus</td>
<td>Postop</td>
<td>3,5</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>m</td>
<td>Right knee</td>
<td>Postop</td>
<td>1,5</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
<td>f</td>
<td>N cutaneus antebrachii lat</td>
<td>Dischernia</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>f</td>
<td>N ischiadicus</td>
<td>Postop</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>f</td>
<td>N radialis superficialis</td>
<td>Postop</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>f</td>
<td>N cutaneus antebrachii med</td>
<td>Postop</td>
<td>12</td>
</tr>
</tbody>
</table>

TENS=transcutaneous electrical nerve stimulation, TCA= tricyclic antidepressants, DCS= dorsal columnal stimulation
<table>
<thead>
<tr>
<th>Sensory abnormalities</th>
<th>Current analgesics</th>
<th>Previous analgesics</th>
<th>Initial VAS at rest</th>
<th>Responder in the study (type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat hyperalgesia, cold hyperalgesia, dynamic allodynia, static allodynia</td>
<td>Opiates, antiep</td>
<td>TCA, DCS, TENS</td>
<td>6.8</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>Heat hyperalgesia, cold hyperalgesia, dynamic allodynia, static allodynia</td>
<td>TENS</td>
<td>TCA, antiep, guanethidin-block</td>
<td>7.2</td>
<td>No response</td>
</tr>
<tr>
<td>Warm hypoesthesia, cold hypoesthesia, dynamic allodynia, static allodynia</td>
<td>TCA, antiep, guanethidin-block, DCS, TENS</td>
<td>4.7</td>
<td>Ketamine-responder, Lidocaine-responder</td>
<td></td>
</tr>
<tr>
<td>Static allodynia</td>
<td>TCA, antiep</td>
<td>DCS, TENS</td>
<td>5.2</td>
<td>Lidocaine-responder</td>
</tr>
<tr>
<td>Warm hypoesthesia, cold hypoesthesia, dynamic allodynia, static allodynia</td>
<td>TCA, guanethidin-block</td>
<td>5.0</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Warm hypoesthesia, cold hypoesthesia, dynamic allodynia, static allodynia</td>
<td>TCA, Antiep, TENS</td>
<td>3.5</td>
<td>Ketamine-responder, Lidocaine-responder, Placebo-responder</td>
<td></td>
</tr>
<tr>
<td>Warm hypoesthesia, cold hypoesthesia, dynamic allodynia, static allodynia</td>
<td>TCA, guanethidin-block, TENS</td>
<td>3.2</td>
<td>Ketamine-responder, Placebo-responder</td>
<td></td>
</tr>
<tr>
<td>Cold hypoesthesia, heat hyperalgesia, mechanical hypoesthesia</td>
<td>TCA, paracetamol, dextropropox</td>
<td>Antiep, TENS</td>
<td>5.4</td>
<td>No response</td>
</tr>
<tr>
<td>Heat hypoalgesia, mechanical hypoesthesia</td>
<td>Tramadol</td>
<td>TCA, antiep, mexitil, TENS</td>
<td>6.0</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>Warm hypoesthesia, cold hypoesthesia, mechanical hypoesthesia</td>
<td>TENS</td>
<td>TCA</td>
<td>4.7</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>Heat hyperalgesia, cold hyperalgesia, dynamic allodynia, static allodynia</td>
<td>Opiates, guanethidin-block, paracetamol, codeine</td>
<td>TCA, stellatum-block, DCS, TENS</td>
<td>8.5</td>
<td>No response</td>
</tr>
<tr>
<td>Mechanical hypoesthesia</td>
<td>TCA, guanethidin-block</td>
<td>8.0</td>
<td>Ketamine-responder, Lidocaine-responder</td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Patient characteristics in patients with central post-stroke pain (study III)

<table>
<thead>
<tr>
<th>Pat no</th>
<th>Age</th>
<th>Sex</th>
<th>Site of pain</th>
<th>Etiology of pain</th>
<th>Duration of pain year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>f</td>
<td>Hemibody pain</td>
<td>Thalamic hemorrhage</td>
<td>1,5</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>f</td>
<td>Hemibody pain</td>
<td>Periventricular infarctions</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>m</td>
<td>Hemibody pain except face, upper extremity most severe</td>
<td>Brainstem infarct</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>f</td>
<td>Hemibody pain</td>
<td>Brainstem hemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>f</td>
<td>Hemibody pain</td>
<td>Midbrain infarct</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>f</td>
<td>Upper extremity</td>
<td>Unidentified</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>73</td>
<td>m</td>
<td>Hemibody pain</td>
<td>Subarach hemorrhage, temporal</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>m</td>
<td>Foot</td>
<td>Intracerebral hemorrhage, frontal, temporal</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>m</td>
<td>Hand and foot</td>
<td>Unidentified</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>74</td>
<td>f</td>
<td>Upper extremity and foot</td>
<td>Thalamic infarct</td>
<td>3</td>
</tr>
<tr>
<td>Quality of pain</td>
<td>Non-sensory neurological signs</td>
<td>Current analgetics</td>
<td>Initial VAS at rest</td>
<td>Responder</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------------------------</td>
<td>---------------------------</td>
<td>---------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Burning, stabbing</td>
<td>Ataxia, oculomotor disorder</td>
<td>Amitriptyline, gabapentin</td>
<td>2,8</td>
<td>Morphine responder</td>
<td></td>
</tr>
<tr>
<td>Stabbing, tearing</td>
<td>Paresis</td>
<td>None</td>
<td>9,2</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Stabbing, aching</td>
<td>Paresis</td>
<td>Dextropropoxyphene TENS</td>
<td>2,1</td>
<td>Morphine responder</td>
<td></td>
</tr>
<tr>
<td>Aching, squeezing, stabbing, throbbing, shooting</td>
<td>Paresis, ataxia</td>
<td>Amitriptyline</td>
<td>3,4</td>
<td>Lidocaine responder</td>
<td></td>
</tr>
<tr>
<td>Burning, aching</td>
<td>Paresis, ataxia, dysphasia</td>
<td>Dextropropoxyphene</td>
<td>7,7</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Burning, stabbing</td>
<td>Paresis</td>
<td>None</td>
<td>5</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Aching</td>
<td>Paresis, ataxia, dysphasia, ataxia</td>
<td>Amitriptyline</td>
<td>1,4</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>Paresis, dysphasia, dysgnosia, dyspraxia</td>
<td>None</td>
<td>3,2</td>
<td>Morphine responder</td>
<td></td>
</tr>
<tr>
<td>Burning, aching</td>
<td>Paresis</td>
<td>None</td>
<td>6,3</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Burning, stabbing, aching</td>
<td>Ataxia</td>
<td>Gabapentin, tramadol</td>
<td>5,9</td>
<td>No response</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Patient characteristics in patients with pain after spinal cord injury (study IV).

<table>
<thead>
<tr>
<th>Pat no</th>
<th>Age</th>
<th>Sex</th>
<th>Level of injury</th>
<th>Duration of pain years</th>
<th>ASIA class</th>
<th>Site if pain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>M</td>
<td>C 6-7</td>
<td>14</td>
<td>B</td>
<td>Buttocks, lower leg, feet</td>
<td>Stinging, boiling</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>C 3</td>
<td>4</td>
<td>C</td>
<td>Below injury level</td>
<td>Burning, breaking</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>Th 8-9</td>
<td>4</td>
<td>B</td>
<td>Below injury level</td>
<td>Throbbing, squeezing, burning, stabbing, cutting</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>Th 7-8</td>
<td>35</td>
<td>A</td>
<td>Back, buttocks, thigh</td>
<td>Aching, stabbing, burning</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>M</td>
<td>L 1</td>
<td>2</td>
<td>C</td>
<td>Buttocks, lower leg and foot</td>
<td>Burning</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>M</td>
<td>C 5-6</td>
<td>2</td>
<td>B</td>
<td>Lower leg, feet, hands, forearms</td>
<td>Squeezing, tightening</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>F</td>
<td>Th 6</td>
<td>3</td>
<td>B</td>
<td>Below injury level</td>
<td>Burning, bursting</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>M</td>
<td>Th 5</td>
<td>8</td>
<td>B</td>
<td>Buttocks, legs</td>
<td>Burning, squeezing</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>C 3</td>
<td>2</td>
<td>C</td>
<td>Buttocks, back</td>
<td>Burning, stabbing</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>M</td>
<td>C 5-6</td>
<td>9</td>
<td>B</td>
<td>Buttocks, trunk</td>
<td>Stabbing, cutting, burning</td>
</tr>
</tbody>
</table>

TCA = tricyclic antidepressants. ASIA classification. The American Spinal Injury Association (ASIA) Impairment Scale: A = complete. No sensory or motor function preserved in the sacral segments S4-S5; B = incomplete. Sensory but no motor
<table>
<thead>
<tr>
<th><strong>Current analgesics</strong></th>
<th><strong>Initial VAS at rest</strong></th>
<th><strong>Responder</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol, codeine</td>
<td>4.2</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>Paracetamol, dextropropoxifen</td>
<td>2.9</td>
<td>Lidocaine-responder</td>
</tr>
<tr>
<td>None</td>
<td>1.4</td>
<td>No response</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>3.5</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>None</td>
<td>5.7</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>TCA, ketobemidon, paracetamol</td>
<td>7.2</td>
<td>No response</td>
</tr>
<tr>
<td>TCA, tramadol</td>
<td>9.1</td>
<td>No response</td>
</tr>
<tr>
<td>Tramadol</td>
<td>2.7</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>TCA, baclofen</td>
<td>3.3</td>
<td>Ketamine-responder</td>
</tr>
<tr>
<td>None</td>
<td>8.2</td>
<td>No response</td>
</tr>
</tbody>
</table>

Function preserved below the neurological level extending through the sacral segments S4-S5; C= incomplete. Motor function preserved below the neurological level with muscle grade less than 3 in the majority of key muscles; D= incomplete: Motor function preserved below the neurological level with muscle grade greater than or equal to 3 in the majority of key muscles (Ditunno 94).
Pain rating

The initial mean VAS-score for continuous pain was:
5.7 (range 3.2-8.5) in the group of patients with peripheral neuropathic pain (Table 5)
4.6 (range 1.4-9.2) for the patients with CPSP (Table 6)
4.8 (range 1.4-9.1) for the patients with pain after SCI (Table 7)

Individual values

The individual VAS scorings for each patient, treatment and measurement are presented in Fig. 9, 10 and 11.

Fig. 9. (Next page) VAS scores in percent of the initial values for each patient with peripheral neuropathic pain, N=12, for the three treatments (ketamine - -, lidocaine - , placebo - -) at each point of measurement. The curves of the responders are marked with colours, red for ketamine, green for lidocaine and blue for placebo responders. Observe that the scale of the y-axis differs between patients.
Fig. 10. VAS scores in percent of the initial values for each patient with CPSP, N=10, for the three treatments (morphine - , lidocaine - , placebo - ) at each point of measurement. The curves of the responders are marked with colours, purple for morphine, green for lidocaine and blue for placebo responders. Observe that the scale of the y-axis differs between patients.
Fig.11. VAS scores in percent of the initial values for each patient with SCI pain, N=10, for the three treatments (ketamine - -, lidocaine - -, placebo - -) at each point of measurement. The curves of the responders are marked with colours, red for ketamine, green for lidocaine and blue for placebo responders. Observe that the scale of the y-axis differs between patients.
Mean values

The mean values for maximal pain reduction for the different drugs were as follows:

For ketamine the mean value was 55 % in the peripheral pain group and 38 % in the group with pain after SCI.

Morphine was given to the patients with CPSP and the mean value for maximal pain reduction was 14 %.

For lidocaine the mean values were 34 % in the group with peripheral pain, 22 % in the group of patients suffering CPSP and 10 % in the group of patients with pain after SCI.

When placebo (saline) was given, the mean values were 22 % in the peripheral group, 6 % in the CPSP group and 3 % in the SCI group.

The difference in VAS-reduction was significant between ketamine and placebo in both the peripheral group (p = 0.009) and the SCI group (p = 0.01). When lidocaine and morphine were given there were no significant differences in mean values compared to placebo (Fig.12).

Fig.12. Mean values for maximal pain reduction as percent of baseline VAS for the different treatments ketamine, lidocaine, morphine and placebo in the three studies (mean SEM). Maximum pain relief with ketamine treatment versus placebo was significant in both the peripheral group (p=0.009) (study II) and the SCI group (p=0.01) (study IV).
Responders / non-responders

According to our definition of being a responder to drug-treatment (>50 % reduction in VAS-score), a significant difference in number of responders was registered between ketamine and placebo both in the peripheral group (p = 0.025) and the SCI group (p = 0.025) (Fig. 13).

Fig.13. Number of responders to ketamine, lidocaine, morphine and placebo, in the peripheral group N=12, CPSP group N=10 and SCI group N=10. Ketamine versus placebo showed a significant difference (p=0.025) in both the peripheral and the SCI group. Morphine showed a tendency toward significance compared to placebo (p=0.08).

There was no significant difference in number of responders between lidocaine treatment and placebo treatment in any group. The difference in number of responders to drug treatment showed a tendency toward significance comparing morphine and placebo (p = 0.08) in the CPSP group.

When numbers needed to treat (NNT) were calculated on the figures of response, the results were as shown in table 8.

Table 8. NNT (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Ketamine</th>
<th>Lidocaine</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathic pain</td>
<td>2.4 (1,5-32)</td>
<td>6 (2,1- )</td>
<td></td>
</tr>
<tr>
<td>Central post-stroke pain</td>
<td>10 (2,5- )</td>
<td>10 (2,5- )</td>
<td>3,3 (1,6- )</td>
</tr>
<tr>
<td>Pain after spinal cord injury</td>
<td>2 (1,4-8,5)</td>
<td>10 (2,5- )</td>
<td></td>
</tr>
</tbody>
</table>
Quantitative sensory testing with thermal stimulation

In all 32 patients, sensory abnormalities were registered either to thermal or mechanical stimuli within the painful region.

Peripheral neuropathic pain

In the group of 12 patients with peripheral neuropathic pain there was a heterogeneous pattern in QST values for innocuous and noxious temperatures. At baseline the following patterns were displayed for the 12 individual patients:
- Three patients showed normal thresholds for warm and cold detection but lower thresholds for heat and cold induced pain on the pain side compared to the healthy side.
- One patient had normal thresholds for warm and cold detection but higher thresholds for heat induced pain on the pain side than on the healthy side.
- Two patients had higher thresholds for warm and cold detection on the pain side than on the healthy side.
- One patient had a higher threshold for cold detection on the pain side and higher thresholds for heat induced pain on the pain side than on the healthy side.
- Three patients had increased detection thresholds for warm and cold on both the pain and the healthy side.
- Two patients had normal thresholds.

In table 9 the results are shown in another way

Table 9. Assessment of temperature thresholds in patients with peripheral neuropathic pain (n=12)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Anaesthet</th>
<th>Hypoaesthet</th>
<th>Alldynia</th>
<th>Hyperpathia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm detection</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cold detection</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heat pain</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cold pain</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Central post-stroke pain

The group of patients with CPSP also showed a heterogeneous pattern in their sensibility for innocuous and noxious temperatures. Before treatment (baseline) the following were found: One patient had thresholds which varied without any discernible pattern, both on the pain side and on the other side.
Warm detection: One patient could not detect any warmth, four had high thresholds and four had normal thresholds.
Cold detection: Two patients could not detect any cold, two had high thresholds five had normal thresholds.
Heat pain: One patient had no feeling of heat at all, one patient had heat allodynia, two had high thresholds and five had normal thresholds.
Cold pain: Two patients had no sensation of cold pain, one had cold pain allodynia, one had high thresholds and five had normal thresholds.
In Table 10 the results are presented.

Table 10. Assessment of temperature thresholds in patients with central post-stroke pain (one patient had thresholds which varied without any discernible pattern, the results from the other nine are presented)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Anaesthetich</th>
<th>Hypoaesthesia</th>
<th>Allodynia</th>
<th>Hyperpathia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm detection</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cold detection</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Heat pain</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cold pain</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Pain after spinal cord injury
Among the patients with pain after SCI six of ten patients did not perceive temperature at all in the 5°C -52°C range at the painful denervated skin. Of the other four, two showed a pattern of hypoaesthesia, with higher thresholds for warmth, cold, heat pain and cold pain at painful denervated areas than at normal skin area. Two showed normal detection thresholds for warmth and cold but lower thresholds for temperature induced pain; one for heat and one for cold pain. The results are presented in Table 11.

Table 11. Assessment of temperature thresholds in patients with pain after spinal cord injury (n=10)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Anaesthetich</th>
<th>Hypoaesthesia</th>
<th>Allodynia</th>
<th>Hyperpathia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm detection</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cold detection</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heat pain</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cold pain</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The results from thermal stimulation showed large inter-individual differences. No significant differences between responders and non-
responders could be seen in the results from thermal stimulation. The drug treatment did not result in any significant changes.

Intra-individual differences of thermal thresholds

As the patients were studied on three different occasions the baseline registration was repeated three times. We found that the patients’ reaction to the thermal stimulation at baseline varied for the same patient on different occasions. The mean range and SD for differences between the three baseline measurements are presented in Table 12 and 13. When we assessed the temperature thresholds for innocuous and noxious stimuli in ten healthy volunteers, on three different occasions, we also registered a variability in thresholds. The variation was not as pronounced as in the patient groups. Notably the differences between measurements were larger when tested on the legs compared to the arms, when detection was tested. The results are shown in Table 14.

Table 12. Intraindividual threshold differences at three separate baseline measurements at different occasions for 12 patients with peripheral neuropathic pain (mean range±SD).

<table>
<thead>
<tr>
<th></th>
<th>Pain side</th>
<th>Healthy side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warmth threshold</td>
<td>3,0±3,7</td>
<td>2,3±2,1</td>
</tr>
<tr>
<td>Cold threshold</td>
<td>4,1±6,8</td>
<td>2,7±2,6</td>
</tr>
<tr>
<td>Heat pain threshold</td>
<td>4,5±4,0</td>
<td>4,8±2,6</td>
</tr>
<tr>
<td>Cold pain threshold</td>
<td>6,0±5,7</td>
<td>6,3±5,8</td>
</tr>
</tbody>
</table>

Table 13. Intraindividual threshold differences at three separate baseline measurements at different occasions for 10 patients with central post-stroke pain (mean range±SD).

<table>
<thead>
<tr>
<th></th>
<th>Pain side</th>
<th>Healthy side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warmth threshold</td>
<td>2,4±2,6</td>
<td>3,2±2,4</td>
</tr>
<tr>
<td>Cold threshold</td>
<td>3,2±5,9</td>
<td>1,5±1,2</td>
</tr>
<tr>
<td>Heat pain threshold</td>
<td>2,7±2,3</td>
<td>3,5±2,2</td>
</tr>
<tr>
<td>Cold pain threshold</td>
<td>3,3±4,5</td>
<td>6,4±4,8</td>
</tr>
</tbody>
</table>
Table 14. Intraindividual threshold differences at three separate baseline measurements at different occasions for 10 healthy persons (mean range ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Forearm</th>
<th>Calf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warmth threshold</td>
<td>0,9±0,7</td>
<td>3,2±1,9</td>
</tr>
<tr>
<td>Cold threshold</td>
<td>0,8±0,8</td>
<td>1,7±1,0</td>
</tr>
<tr>
<td>Heat pain threshold</td>
<td>3,6±2,3</td>
<td>3,1±1,6</td>
</tr>
<tr>
<td>Cold pain threshold</td>
<td>2,5±2,2</td>
<td>2,1±3,0</td>
</tr>
</tbody>
</table>

Sensibility to mechanical stimuli

The assessment of reactions to mechanical stimuli was done using stroke with a wisp of cotton for dynamic sensibility, von Frey filaments for static sensibility, pin-prick (only CPSP), and vibration (only pain after SCI). The reactions did not significantly differ between responders and non-responders before infusion. All patients showed sensory abnormalities with hyper- and / or hypoesthesia. The pattern of sensory abnormalities found at baseline is seen in Table 15, 16 and 17. Changes induced by infusion were small and without a specific pattern.

Table 15. Assessment of mechanical sensibility in patients with peripheral neuropathic pain (n=12)

<table>
<thead>
<tr>
<th>Normal</th>
<th>Anaesthetic</th>
<th>Hypoesthetic</th>
<th>Allodynia/</th>
<th>Hyperalgesia</th>
<th>Hyperpathia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic sensory</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Static sensory</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 16. Assessment of mechanical sensibility in patients with central post-stroke pain (n=10)

<table>
<thead>
<tr>
<th>Normal</th>
<th>Anaesthetic</th>
<th>Hypoesthetic</th>
<th>Allodynia/</th>
<th>Hyperalgesia</th>
<th>Hyperpathia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic sensory</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Static sensory</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pin prick</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 17. Assessment of mechanical sensibility in patients with pain after spinal cord injury (n=10)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Anaesthetic</th>
<th>Hypoaesthetic</th>
<th>Allodynia/ Hyperalgesia</th>
<th>Hyperpathia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic sensibility</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Static sensibility</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vibration</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Drug concentrations

In Fig.14 (A, B, C, D, E, F) mean concentrations of ketamine, lidocaine and morphine in the three different groups are shown. All drugs show a peak after end of infusion (45 minutes) followed by a decrease until the end of the experiment (150 minutes). The registered plasma concentrations were at levels which indicated that clinically relevant doses had been given.
Fig. 14. A, B, C, D, E, F. Plasma concentrations for the drugs in the studies. A and B show the peripheral group. C and D show the CPSP group. E and F show the SCI group (mean±SD).
Adverse effects

Side effects after infusion were common both after ketamine, lidocaine and morphine infusions (Fig. 15 A, B, C). They were most frequent and most intense after ketamine infusions. All patients with peripheral neuropathic pain perceived at least one side-effect from ketamine infusion and a sum of 62 side-effects were registered among these 12 patients. Half of the patients in this group had an unpleasant experience from ketamine and one patient stated that this was extremely unpleasant. In the group of patients with pain after SCI, ketamine produced side-effects in nine of 10 patients and a sum of 39 side-effects were registered, somnolence and dizziness being the most common.

Also lidocaine infusions resulted in a substantial number of side-effects. In the peripheral group a total number of 29 side-effects were registered. Patients with CPSP reported 16, and patients with pain after SCI 13 side-effects. In the whole group somnolence appeared in 18 of 32 patients and perioral paresthesia in eight out of 32.

Morphine induced side-effects in six of 10 patients (morphine was only given to the CPSP group); the total number of registered side-effects was 21 and somnolence, dizziness and nausea were the most frequent.

Even placebo-infusions induced side effects. A total of 11 side effects were registered in the PNP group as well as in the CPSP group whereas only two were registered in the SCI group.

In none of the patients was there need to end the infusion because of adverse effects, no specific treatment were given and we judged that the side effects did not disturb the evaluation of the patients.

Fig.15. Side effects after infusion of ketamine, lidocaine and placebo in the peripheral group A; (Study II). Side effects after infusion of morphine, lidocaine and placebo in the CPSP group B; (Study III). Side effects after infusion of ketamine, lidocaine and placebo in the SCI group C; (Study IV).

<table>
<thead>
<tr>
<th>Ketamine</th>
<th>morphine</th>
<th>lidocaine</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Number of patients

A Study II
PNP

Somnolence
Dizziness
"Out of body sensation"
Changes in hearing
Changes in vision
Nausea
Unpleasant experience
Perioral paraesthesia
Itching

A Study III
CPSP

Somnolence
Dizziness
Changes in vision
Nausea
Unpleasant experience
Perioral paraesthesia
Itching

B Study III
CPSP

Somnolence
Dizziness
"Out of body sensation"
Change in hearing
Change in vision
Nausea
Unpleasant experience
Perioral paraesthesia

B Study III
CPSP

C Study IV
SCI

Somnolence
Dizziness
"Out of body sensation"
Change in hearing
Change in vision
Nausea
Unpleasant experience
Perioral paraesthesia

C Study IV
SCI

71
DISCUSSION

The main findings of this thesis were the following: The patients with peripheral neuropathic pain had a significantly impaired health-related quality of life. Ketamine yielded significant pain relief to patients with peripheral neuropathic pain and pain after spinal cord injury, although the pain relief was accompanied with considerable adverse effects. A small group of patients with central pain after stroke responded with pain relief with morphine infusion: these results were however not significant. Lidocaine in the dose we gave did not give significant pain relief to any of the groups studied in this thesis.

Health related quality of life (study I)

The limited clinical efficacy and tolerability of available treatment of peripheral neuropathic pain leads to a substantial burden on the affected patients. The unrelieved pain affects physical as well as mental dimensions of patients' lives and limits their ability to work. These aspects of patient well-being can be measured using the instruments described in this study. Only patients whose primary diagnosis was PNP were included. We hypothesize that the results observed are mainly related to continuous and evoked pain and side-effects from ongoing treatment.

Symptoms related to pain and side-effects of treatment

In addition to the pain and ineffective treatment, patients were to a high extent troubled by difficulty in sleeping and concentrating and by lack of energy. Feelings of depression and anxiety were also frequently reported. Difficulty in concentrating, drowsiness, dry mouth, lack of appetite, dizziness and problems in urinating are known side-effects of the treatments used and were frequently reported as bothersome by the PNP patients. The
degree of causality between the distress from these symptoms and PNP or each pain treatment cannot be ascertained from this study, since data are not available on the burden in the general population. The degree to which patients were bothered by gastrointestinal symptoms was similar to the results from a general Swedish population study (Dimenäs 1993). This may be because patients who had experienced these side effects had already discontinued the treatment which caused them; in addition, only few patients were taking strong opioids.

Efficacy and tolerability of treatments
Despite receiving treatment at specialized pain clinics, the PNP patients in the study suffer a high intensity of pain, bothersome pain-related symptoms and side-effects from ongoing treatment. A large proportion of them tries various treatments, but often discontinues the treatment due to bothersome side effects and inadequate pain relief. In this study patients reported pain relief from 40% of the previously tried treatments, but even those treatments were discontinued owing to insufficient effect and/or troublesome side-effects. These results are in accordance with a study evaluating the effect of amitryptiline in patients with neuropathic pain following treatment of breast cancer (Kalso 1996). Although most patients in the amitryptiline group experienced adequate pain relief, and a reduction in the effect of pain on daily life, only 20% of the patients were willing to continue the medication owing to the side effects. A decreased pain intensity is thus not the only predictor of treatment success. Lower frequency of side-effects, improved function, reduced distress and improved QoL should be viewed as an important outcome in addition to reduced pain. Improving these components will also result in improved compliance.

Reduced work status
In addition to patient suffering, the cost to society is high since a majority of patients (52% of those included) had a reduced employment status owing to their PNP condition. These numbers are similar to the results from a Danish study of pain epidemiology and HRQoL in chronic non-malignant pain patients where 45% had disability pension (Becker 1997). Enabling PNP patients to stay at and/or return to work could result in savings for society as well as an improvement in patient well-being. When the patients were asked
to list in what respect their pain condition restricted them in doing things they valued, a large proportion of them reported that they missed work most of all. Different outdoor leisure activities were also frequently missed. More effective treatments with fewer side effects would improve these aspects of HRQoL.

HRQoL
The results clearly demonstrate that patients with PNP have multidimensional impairment as a consequence of their pain. Scores from SF-36 and NHP show that pain affects all dimensions of well-being, physical as well as mental. Comparing scores with those reported for other serious diseases such as recent myocardial infarction, chronic heart failure and poorly controlled diabetes with complications, confirms the severe burden of PNP. The physical dimensions were comparable and the emotional dimension scores were worse for PNP patients (McHorney 1993). In addition, the SF-36 scores in patients with PNP in all but one mental dimension are as low as in patients with serious psychological conditions (endogenous depression) (McHorney 1993) (Fig 16). The results in the present study were comparable to the SF-36 scores in a study conducted by Becker on chronic non-malignant pain patients (Becker 97).

Overall, the SF-36 was found to have sufficient reliability for measuring the HRQoL of patients with PNP as Chronbach's was greater than or equal to 0.70 for all dimensions. Patient scores were significantly lower than those of the Swedish general population, which indicates that the instrument can be used as an indicator of chronic pain states. Dimension scores also diverged in the expected direction when comparing working and non-working subgroups in the sample, with the dimensions physical function and bodily pain reaching a statistically significant difference. All dimensions of the SF-36 were significantly correlated with the patients' global health state ratings (rating scale). Item-same dimension and item-other dimension correlation indicated that the 35 items in the scales had captured the concepts hypothesized by the scale developers and translators (Ware 1993, Sullivan 1995). The fact that the correlations were higher within the same dimension than with other dimensions lends credibility to the internal consistency and discriminant validity of the SF-36 in the PNP population (Meyer-Rosberg 2001).

NPH had a lower reliability, three of the six dimensions did not reach the
generally accepted standard of 0.70. Several other studies e.g. Badia (1994) and Essink-Bot (1996) in renal patient populations and Essink-Bot (1997) in migraine patients have all reported internal consistency weaknesses in some of the NPH dimensions. The original authors of the NHP acknowledge that the instrument because of its binary response format (yes-no) taps only the extreme end of perceived health problems and thus tends to yield many low scores (Hunt 1986). On the other hand NHP has other advantages which might be useful for patients with PNP. The pain dimension in NHP includes eight questions/items compared with only two in SF-36. Furthermore, NHP has a sleep dimension which is not included in SF-36. A sleep dimension is desirable as the great majority of patients (88%) reported they were bothered by difficulty in sleeping.

Fig.16. A comparison of scores from SF-36 between the groups; serious medical condition, psychiatric illness and our study population.

Although the scales contain comparable dimensions, in every comparison except one (pain) the SF-36 had higher internal consistency estimates. The SF-36 has the advantage of using a Likert-type scale scoring format which allows patients to respond with a range of scaling choices. Both the SF-36 and the NHP have acceptable degrees of convergent and construct validity. However, we like others (VanderZee 1996, Bouchet
have concluded that the SF-36 has, overall, superior psychometric properties. We suggest that further studies of the PNP population consider using the SF-36 as the major HRQoL outcome measure. Additional measurement of variables of importance to this population, such as sleep and pain intensity should also be included in any experimental treatment study.

Treatment studies II-IV

When analysing the data in the treatment studies we decided to present mean and dichotomous data together, the former being the usual way of presentation but the latter offering certain advantages. Since the result of pain reduction in neuropathic patients is usually neither continuous nor normally distributed, the mean has limitations. Moreover the dichotomous outcome has the advantage of being more clinically informative since it provides information about the percentage of patients likely to achieve a clinically important level of improvement (Moore 1996, Farrar 2000). The analgesic effect of ketamine was significant both using the mean values and dichotomous distribution. The treatment with lidocaine did not show any significant effect in the doses we used, either using mean or dichotomous values. When evaluating morphine the difference in proportion of responders showed a trend toward statistical significance between morphine and placebo whereas no difference was found looking at mean values.

A patient with a more than 50% reduction of pain assessed by a VAS-scale was defined as a responder in our study. This is quite a strict definition and one could argue that this will result in an underestimation of the efficacy of the treatment. Farrar claimed in a study in 2001 that 33% pain relief was a good cut-off point based on patient’s evaluations of a clinically important analgesic effect (Farrar 2001). If we had decided to classify patients with 33% pain relief as responders, this would have resulted in only minor changes in our present results. We chose the criterion >50% pain reduction because our aim was to show unequivocal results. As claimed by Moore and McQuay 1996 it is a simple, convincing, clinical endpoint. Moreover, other authors using the dichotomous method to present their material in general use 50%. Our choice of 50% pain reduction thus facilitates comparison with other studies, e.g. using NNT calculations.
The analgesic effect of ketamine in patients with peripheral neuropathic pain and pain after spinal cord injury, studies II and IV

Clinical studies have demonstrated that systemic administration of the NMDA receptor antagonist ketamine in patients with peripheral neuropathic pain reduces spontaneous pain and hyperalgesia (Backonja 1994, Eide 1994, 1995a, Max 1995, Felsby 1996, Leung 2001). Of these, the study conducted by Max is the only one concerning peripheral neuropathic pain of traumatic origin. He investigated the analgesic effect in 7 patients, with a dose approximately double compared to the one we used, and obtained response according to our criteria 50% reduction, in 4 patients. His results are thus comparable to ours.

There are a limited number of studies on patients with central pain in the literature. Backonja showed in 1994 in a study of patients with both peripheral and central pain, that the two patients suffering central post-stroke pain (CPSP) obtained an analgesic effect from ketamine. Yamamoto showed in an open, uncontrolled study that 11/23 patients with CPSP obtained pain reduction of more than 40% during ketamine treatment (Yamamoto 1997).

The only study, to our knowledge, of ketamine in patients suffering pain following SCI was conducted by Eide in 1995 (Eide 1995b). He studied 9 patients with central dysesthesia and evoked pain and observed an analgesic effect on both spontaneous and evoked pain. The results in the present study are in accordance with those of Eide who showed that seven out of nine patients reported that ketamine most effectively reduced continuous pain, while 2 of 9 patients reported pain relief with placebo infusion. Our doses were different, as Eide used approximately half the dose given in our studies.

The ceiling analgesic effect of NMDA-receptor antagonists in clinical studies as well as in clinical practice is given by the dose-limiting side effects such as sedation, dizziness and visual distortions. Only one of the patients in the present study did not note any adverse effects, and most of the patients experienced quite disturbing side effects. Substantial side-effects were registered, also in the study by Max (Max 1995), and it was noted that moderate-to-severe side effects preceded the analgesic effect and also outlasted the declining analgesic effect. Eide states that his treatment was not associated with severe side effects, which can be due to the lower total dose and shorter infusion period; the serum concentrations in his study were also lower than in these studies.
The side effects limit the clinical usefulness of the treatment as we have used it. However, the high ratio of pain relief in this group of patients with intractable pain raises interest in other ways of administration, or that development of new subtypes of NMDA-receptor antagonists could widen the therapeutic ratio.

The analgesic effect of lidocaine in patients with PNP, CPSP and pain after SCI, studies II-IV

Concerning the therapeutic effect of lidocaine, there are studies showing a clear analgesic effect in patients with neuropathic pain of peripheral origin (Kastrup 1987, Rowbotham 1991, Galer 1996, Wallace 1996). This is in contrast with the moderate analgesic effect in our study including patients with peripheral neuropathic pain of traumatic origin (4 responders of 12). Considerably fewer studies have been conducted on central pain states. Small open or single blinded trials have suggested that lidocaine is effective in these pain patients (Backonja 1992, Edmonsson 1993). The only randomised, controlled study of the effect of lidocaine in CPSP and SCI patients was conducted by Attal (Attal 2000). She studied the effect of intravenous lidocaine in 16 patients, 6 with CPSP and 10 with SCI pain. Spinal cord injuries included syringomyelia, post traumatic myelomalacia and spondylisis with myelopathy. For the whole group, lidocaine significantly decreased spontaneous ongoing pain when looking at mean VAS values. Brush-induced allodynia and static mechanical hyperalgesia were also significantly decreased. Her results are in contrast with the results in the present study which showed negligible analgesia with lidocaine in both patients with CPSP and SCI (one responder of 10 in each group). One explanation for the divergent results could be the chosen dose; the total dose of Attal was twice as high as the one used in our study. However, looking at the results as proportion of responders, only 9 of the 16 patients in Attal's study had a decrease in VAS of more than 50% at the end of infusion, compared to 6 of 16 with placebo. Also in other lidocaine studies in patients with peripheral neuropathic pain, higher doses were given (Rowbotham 1991, Galer 1996, Wallace 1996) and one can speculate that the low analgesic effect in our study was because our dose was too low to obtain an effect. However other studies using even lower doses than ours have showed an analgesic effect. Marchettini reported an analgesic effect with a dose of 1.5 mg/kg (Marchettini 1992). Galer administered both 2mg/kg and 5mg/kg
to patients suffering peripheral neuropathic pain, and reported significant VAS reduction with both doses (Galer 1996). In a study of the analgesic effect of lidocaine in patients with postherpetic neuropathic pain conducted by Baranowski in 1999, he investigated both 1 mg/kg and 5 mg/kg. That study showed a positive analgesic effect with both doses (Baranowski 1999). We want to emphasize that we believe that the chosen dose was prudent, given the toxicity of lidocaine and hence the risk for severe adverse effects from the nervous and cardiovascular systems. Half of our 32 patients reported side effects, 9 light-headedness and eight perioral paresthesia, the latter of which we regard as a warning signal to other more severe side effects. We aimed to test effects with clinically applicable doses.

The analgesic effect of morphine in patients with CPSP, study III

The limited analgesic effect of morphine infusion was not unexpected. Other studies have shown similar results (Kupers 1991, Kalman 2002, Attal 2002). According to clinical experience (Gonzales 1995, Boivie 1999) only a minority of patients with CPSP responds positively to opioid treatment. If we had given the infusion of morphine with individual dose titration there is a possibility that more patients would have responded to the treatment. However, in the study conducted by Attal where the dose of morphine was individually titrated, the effect on spontaneous pain was similar to our results. The plasma concentrations of morphine in our study were in the range of 23 to 52 ng/ml. This may be compared with concentrations that have been found to reduce postoperative pain, namely a mean of 20 ng/ml (Dahlström 1982, Derbyshire 1985). Our doses are thus within the limits where an analgesic effect could be expected according to the literature. The dose titration of effective drug may also make the blinding procedure difficult and thereby also the interpretation of the results. Some studies of the responsiveness of neuropathic pain to opioids have used much higher doses compared to ours. Dellemjin used fentanyl given at a dose equivalent to 80 mg of morphine and reported more than 50% responders in patients with different types of neuropathic pain (Dellemjin 1997). Kalman administered morphine at a mean dose of 44 mg with an infusion rate of 1 mg / minute to patients with central pain due to multiple sclerosis with a response rate of 4/14 (Kalman 2002). Both authors claimed that relief from pain was not obtained until high doses had been infused. In comparison, the mean dose of 14 mg in the present study was considerably lower. However, long-term
administration of opioids has troublesome side-effects (McQuay 1992). Hence we focused on doses which could be of interest for daily use and in that perspective even our doses could be considered to be in the upper limit. The three patients responding to morphine treatment in the present work had a clear response with marked pain relief. A reasonable conclusion from the evidence available seems to be that a few patients with central pain may benefit from opioid analgesics and that it is important to evaluate the effects in each individual. An interesting way to confirm the notion that our responders had a genuine analgesic effect would be to let them undergo studies using the N of 1 design (McQuay 1991).

The total number of registered side effects was lower than expected given that most patients were old and that all had suffered a cerebral injury. In contrast the group of patients with peripheral neuropathic pain, who were considerably younger, experienced more frequent side effects both after lidocaine and placebo infusion. In view of this, one can question our decision not to give these patients ketamine in fear of unmanageable adverse effects.

General considerations of analgesic effects

The patients recruited in this study all had severe neuropathic pain of long duration that had been resistant to other treatments. These factors might decrease the likelihood of treatment response. This category of patients is often recruited for trials of neuropathic pain; the results could have been different if we had recruited patients consecutively when they first appeared at the pain clinic. On the other hand, the categories of patients studied are in particular need of treatment and several of the responders claimed that this treatment was superior to any other they had previously experienced.

Six of the patients with CPSP and SCI scored less than three on the VAS before treatment. It can be argued that the pain of these patients was not severe enough to be a substantial burden. However, these patients claimed that their pain was severe, and they were therefore included in the studies. This is consistent with Boivie (Boivie 1999) who states that even patients in this category who rate their pain as low may be severely affected.

Pharmacological trials with this category of patients are few and with a small number of subjects per trial. This is a general problem of studies on patients with chronic neuropathic pain. A way to increase the efficiency of a clinical trial, thereby providing adequate power to use small samples, includes the
use of selection methods to create groups that are as homogeneous as possible. In the study of peripheral neuropathic pain we chose patients with traumatic origin to the nerve injury in an attempt to select a homogeneous group. On the other hand patients with peripheral neuropathic pain of traumatic origin are probably a complex and heterogeneous group per se with different types of fibre lesions, different magnitude of deafferentation and disinhibition, as well as different relations between peripheral and central mechanisms. In the study of patients with CPSP all patients with a clear diagnosis was included with no further selection. In the study of patients with pain after SCI we had a traumatic origin as a inclusion criterion. Moreover we chose patients whose main concern was continuous, spontaneous pain below the level of injury, according to the taxonomy proposed by the SCI Pain Task Force of IASP (Sidall 2000a), even though some of the patients also suffered from evoked pain and pain at the level of injury.

When analysing effects of treatments of neuropathic pain, meta-analyses of a number of comparable trials are important. An index that is being used with increasing frequency in the pain literature is the number needed to treat (NNT) (Cook and Sacket 1995). In the pain literature NNT is typically calculated as the number of patients who report at least 50% pain relief following an active treatment relative to the number who report at least 50% pain relief following a control treatment (Moore 1996). Generally NNTs between 2 and 5 are indicative of effective analgesic treatments (McQuay 1999) and this was achieved with ketamine and morphine but not with lidocaine in this work.

The long-time objective of studying intravenously administrated drugs is to find drugs that can be given orally during long periods. Whether an intravenous pharmacological test may predict the long term effect of oral treatment is an interesting issue that remains to be settled, and further studies with long term follow-up are needed to evaluate this concept. Galer claimed a correlation for response to intravenous lidocaine and mexiletine treatment; three lidocaine responders claimed good pain relief with mexiletin, while among six poor lidocaine responders only two received good pain relief with mexiletine (Galer 1996). In the lidocaine trial by Attal (Attal 2000), 12 patients received a lidocaine infusion followed by a 4-12 week oral mexiletine trial. Only 2 of 8 (25%) patients who responded with pain relief to the lidocaine infusion went on to have a positive response to the mexiletine trial. Furthermore one of 4 (25%) non responders to lidocaine
infusion went on to have a positive response to oral mexiletine. None of these patients was willing to be long-treated with mexiletine, essentially because of the side effects. The six patients in our studies that achieved a pain relief of more than 50% all tried mexiletine outside the studies and none of them found the balance between pain relief and adverse effects good enough to continue that treatment. Furthermore, in follow up studies of long-term opioid treatment by Attal and Dellemijn only 20% of the patients chose to continue treatment after one and two years, respectively (Attal 2002, Dellemijn 1998).

Diagnostic capacity

Some authors claim the usefulness of ketamine, lidocaine and morphine to be used in intravenous pharmacological pain analysis to separate nociceptive, neuropathic and idiopathic pain (Marchettini 1992, Sörensen 1995). This is also a diagnostic routine in many clinics. In studies II, III and IV the response rate was 6/32 for lidocaine and 12/22 for ketamine. Hence lidocaine and ketamine treatment can hardly be used as diagnostic tools for neurophatic pain, as the sensitivity is too low. Moreover since both ketamine and lidocaine have an analgesic effect in nociceptive pain (Domino 1965, Cassuto 1985), the specificity is most certainly low as well. Because of this we question the usefulness of these drugs as pharmacological diagnostic tools.

Sensory abnormalities at baseline

When we assessed baseline data of somatosensory functions before treatment, we found a wide variety of sensory disturbances. One of our hypotheses was that examination of patients with different sensory abnormalities using tests of thermal thresholds and other sensory tests could predict response to treatment. This hypothesis could not be confirmed. The performed assessments can help to distinguish between different sensory disturbances. One possible explanation for the limited value of prediction could be that the available tests do not give sufficient information about the type of nerve lesions. As mentioned above, patients with neuropathic pain are probably a complex and heterogeneous group with different types of fibre lesions, different magnitude of deafferentation and disinhibition, as well as different relations between peripheral and central components. The
duration of pain is probably also of importance for the heterogeneity as synaptic plasticity may lead to permanent changes in nociceptive processing (Coderre 1993). It is likely that a large number of patients are needed to identify specific patterns in such a heterogeneous group. However, the numbers of patients in our studies were determined with regard to the primary outcome variable, pain relief.

In a study of neurological symptoms in 27 patients with CPSP, Boivie found a decreased sensibility to innocuous temperatures in all patients (Boivie 1989). In his study, seventy percent could not differentiate temperatures between zero and 50°C. Approximately half of these patients had normal thresholds to touch and vibration. A similar but somewhat less pronounced tendency has been found in other studies (Vestergaard 1995, Bowsher 1998). These results are the basis for the hypothesis that CPSP is dependent on injury to the spinothalamocortical pathways.

The patients in our study showed a markedly varied pattern in temperature sensibility. These results differ notably from the results of Boivie, Bowsher and Vestergaard. Only two of our ten patients showed severe disturbances in temperature sensibility. In respect to the sensibility to mechanically evoked pain using of pin-prick and touch using cotton wool, the results from our study are in accordance with other studies. The majority of the patients had an abnormal reaction; hypoesthesia, hyperalgesia as well as allodynia were seen, similar to other studies.

The reason for the differing results of our study as compared to the previously mentioned studies with respect to abnormality of temperature thresholds is difficult to explain.

One might speculate that our patients did not suffer from CPSP, but this is unlikely since they were carefully examined and diagnosed both by a neurologist and/or a neurosurgeon before referral, and by an anaesthesiologist at the pain clinic.

The number of patients in our study is relatively small, precluding a closer analysis of the differences between this study and the others mentioned. However the moderate impact on sensibility to temperature is noteworthy.

Few studies of SCI pain have tested sensory function. Beric studied below-level pain in 13 patients with central dysesthesia syndrome (CDS) (Beric 1988). Two patients in their study had no sensation at all below the level of injury, while 11 had incomplete preservation of sensation. Ten of 13 patients did not perceive temperature sensation at all tested with QST.

Vibratory sensibility and touch were reduced, but not absent in 10 and 8
patients respectively. He found a significant difference between the temperature thresholds and those for vibration and touch. This is in accordance to the results in our study. Beric interestingly stated that in a large cohort of 243 SCI patients with and without altered sensation and pain, from which the 13 patients were drawn he found only 3 other patients, without CDS and with a similar combination of absent spinthalamic function and relatively preserved dorsal column function. This indicates a high incidence of pain in patients with this specific sensory profile. These sensory profiles are also in concordance with those found by Boivie in patients with CPSP (Boivie 1989).

We found a surprisingly high variability in the results from baseline measurements of sensory disturbances on different occasions in individual patients. Similar findings have been made by others (Fagius 1981, Rommel 2001). The investigation technique could play a role; however, the methodology was standardised as much as possible. All patients had been informed and educated in the same way and the experiments were all performed by the same investigator. The greater part of the variability observed in the present studies is probably due to central processing factors. Efferent pathways for facilitation and inhibition of afferent signals make it possible to focus attention on a particular sensation and a particular site of the body (Bannister 1976). Factors altering this attention would have a marked influence on threshold levels. Thus, factors such as motivation, psychological and physiological stress, distraction, fatigue as well as expectations have been found to affect the magnitude of the sensory thresholds both in the experimental situation with healthy subjects and in clinical practice (Lindblom 1974, Vallbo 1976, Dyck 1978). Patients can also be biased toward showing abnormal results due to a conscious or unconscious wish to demonstrate more disability than they have (Dyck 1998).

Sensory changes by treatment

We also wanted to study if ketamine, lidocaine and morphine gave specific sensory effects such as normalisation of pathologic thermal thresholds or normalisation of abnormal sensibility. No such effects were registered, not even in responders. As the intraindividual results from thermotests showed relatively large variation, also at T:0 and with placebo infusion, it was difficult to identify
other than major differences. No clinically relevant differences could be detected.

Normal values from temperature threshold measurements in a healthy population have shown variations both dependent on gender, age and site for testing (Verdugo 1992, Meh 1994, Hilz 1999). This makes the interpretation of our results more difficult because of difference in gender, age and site for testing (Table 5-7). On the other hand, we used the patients as their own control as we repeated the tests and also tested the contralateral (healthy) side or painless area above the lesion (SCI).

Few other studies have found changes in temperature thresholds after treatment, although Leung found an increase in both cold and cold-pain thresholds after ketamine and alfentanil infusions in patients with neuropathic pain. In a study conducted by Jörum alfentanil but not ketamine reduced cold allodynia, by increasing cold-pain thresholds in patients with neuropathic pain. At the same time a marked reduction of hyperalgesia to cold was seen following both ketamine and alfentanil administration (Jörum 2003).

Nor did we observe any changes in mechanical sensibility after infusion. This contrasts with Attal's studies where reduced intensity of brushed-induced allodynia was found both with morphine and lidocaine infusions. Also Eide in his study of SCI pain observed that allodynia to brush and “wind-up-like-pain” was reduced by ketamine as well as alfentanil infusions. One explanation of this difference may be that the above studies measured allodynia quantitatively with VAS while we only made a classification in four categories.

Future perspectives

The narrow therapeutic ratio associated with the use of the clinically available NMDA-receptor antagonists may be overcome by the development of more selective NMDA-receptor antagonists, which modulate binding sites within the NMDA-complex, or have affinity at specific NMDA-receptor subtypes.

Recent studies have shown that there exist at least nine different sodium channels encoded by different genes. The abnormal sodium channel activity and changes in sodium channel expression under neuropathic conditions have drawn much attention over the last several years (Waxman 1999). The
progress on studies of subtype-specific sodium channels and their link to certain neuropathic pain symptoms may lead to the possibility to target hyperexcitable sensory neurons along the nociceptive pathway without producing significant side effects.

The heterogeneity of the pain states following peripheral or central nerve injury may require an analgesic regimen that interacts at several selective sites with the potential for acting synergistically in terms of efficacy but not toxicity.

The development of an effective pharmacological treatment and thereby improving the quality of life of these patients would represent a fundamental breakthrough in clinical pain treatment.
CONCLUSIONS

The intense pain, limited efficacy and tolerability of available treatments, the low overall rating of health, reduced work status and troublesome symptoms constitute a substantial burden for patients with PNP. All dimensions of HRQoL are significantly impaired physical as well as mental indicating a multidimensional burden of these patients.

The NMDA-antagonist ketamine yields substantial pain relief to patients with peripheral neuropathic pain and patients with neuropathic pain below the level of SCI. The noted side effects limit the clinical usefulness of the treatment. However, the high degree of pain relief in these usually refractory pain states raises interest in the development of NMDA-antagonists with a wider therapeutic ratio.

Lidocaine, in the dose given in these studies did not give significant pain relief to patients with peripheral neuropathic pain, patients with CPSP and patients with neuropathic pain below the level of SCI.

Morphine may represent a therapeutic alternative for some patients with CPSP, although only a small group of this category of patients seems to respond with analgesia.

Assessment of baseline somatosensory functions could not be used to identify responders to treatment with either drug. Neither did ketamine, lidocaine or morphine cause any changes in thermal or mechanical sensibility.
ACKNOWLEDGEMENTS

This study would never have been possible without the assistance, encouragement and support most generously provided by a great number of people. The inspiring collaboration with all these dependable and positive persons who have shown confidence in my work and shared with me their knowledge and abilities in a variety of subjects, made this work worthwhile. I sincerely wish to thank you all.

This study was supported by grants from Astra Zeneca R&D, Södertälje, Sweden, Henning Larssons stipendie stiftelse, and the Swedish Medical Research Council (9077).
References


Castro-Lopes JM, Malcangio M, Pan BH, Bowery NG. Complex changes of GABAA and GABAB receptor binding in the spinal cord dorsal horn following peripheral inflammation or neurectomy. *Brain Res* 1995; 679: 289-297.


Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. *Neuropharmacology* 1987; 26: 1235-1238.


Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. *Neurosurgery* 1995b; **37**: 1080-1087.


Essink-Bot ML, Krabbe PF, Bonsel GJ, Aaronson NK. An empirical comparison of four generic health status measures. The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument. *Med Care* 1997; **35**: 522-537.


Farrar JT, Young Jr JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; **94**: 149-158.


Halling K. The Nottingham Health Profile age and sex comparison in a Swedish community. 1995. Manuscript performed at Department of Psychology, University of Göteborg.


Head H, Holmes G. Sensory disturbances from cerebral lesions. *Brain* 1911; **34**: 102-122.

Heft MW, Parker SR. An experimental basis for revising the graphic rating scale for pain. *Pain* 1984; **19**: 153-161.


Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; **73**: 123-139.


Lenz FA, Kwan HC, Dostrovsky JO, Tasker RR. Characteristics of the bursting pattern of action potentials that occurs in the thalamus of patients with central pain. *Brain Res* 1989; **496**: 357-360.


Likert R. A technique for the measurement of attitudes. Archives of Psychology 1932; 140: 1-55.


Lombard MC, Besson JM. Attempts to gauge the relative importance of pre- and postsynaptic effects of morphine on the transmission of noxious messages in the dorsal horn of the rat spinal cord. Pain 1989; 37: 335-345.


McHorney CA, Ware Jr JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; **31**: 247-263.


Meller ST. Ketamine: relief from chronic pain through actions at the NMDA receptor? *Pain* 1996; **68**: 435-436.


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to October, 1985, the series was published under the title “Abstracts of Uppsala Dissertations from the Faculty of Medicine”.)