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Editorial

Appropriate and responsible use of opioids in chronic non-cancer pain

During the last two years several publications in *The European Journal of Pain* have focused on the use of strong-acting opioids for chronic non-cancer-related pain (Bleeker et al., 2001; Carr, 2001; Cousins, 2001; Dellemijn, 2001; Eriksen, 2001; Gouwe, 2001; Kalman et al., 2002).

A group of distinguished pain clinicians from nine European countries have discussed the appropriate use of strong-acting opioid analogues for chronic non-cancer pain. They summarize their experience and advice in this issue of *The European Journal of Pain* (Kalso et al., 2003). I would like to emphasize some aspects of the recommendations from these experienced academic pain clinicians:

1. **Reduce the stigma of potent opioids for chronic non-cancer pain.** It is important to reduce the stigma of using potent opioids for chronic non-cancer pain. Although there is only a meagre “evidence-base” from randomised controlled trials, the experience of pain clinicians shows that potent opioids can be used effectively and safely in patients with persistent pain where no other available and less risky therapy can improve the low quality of life. The appropriate use of potent opioids is accepted medical practice for chronic, otherwise intractable, pain in patients with normal life expectancy. However, this treatment is not without risks and can be very demanding on patient and doctor alike. It is only a minority of patients referred to a pain clinic that qualify for long-term treatment with potent opioids (Maier et al., 2002). The National Agency for Medicines, Sweden (2002) and National Agency for Medicines, Norway (2002) state that this is accepted medical practice, reserved for selected patients only.

2. **Signed written information.** The recommendations by Kalso et al. (2003) do not request a written contract with the patient. However, in my experience, verbal information and oral agreements are not good enough when problems of compliance and drug-related complications of addicting drugs develop – the patients forget! The patient, his/her family and family doctor must understand why an opioid trial period is started, agree to the aims of the therapy (reduced pain, improved quality of life and psychosocial functions), as well as the rules of prescribing, dispensing, controlling the opioid therapy and its effects and adverse effects. This, and the reasons for discontinuing the opioid therapy when necessary (insufficient pain relief and/or adverse effects that reduce quality of life), must be agreed upon and confirmed in writing (Breivik, 2002). The risk of inducing drug dependence and drug misuse (“addiction” or “psychological dependence”) and the difficulties that arise from this complication must be considered a real possibility. Strategies and resources for handling this complication must be at hand (National Agency for Medicines, Sweden, 2002; National Agency for Medicines, Norway, 2002).

3. **Use only slow-onset, prolonged duration, and slow-offset drugs.** Long-term treatment with potent opioids must be administered as sustained release formulations.

4. **Do not treat episodic, incident, break-through pain with injections or transmucosal lipophilic opioids.** Breakthrough pain should not be treated with potent opioids with rapid onset, short-duration, and rapid offset of effect: Parenteral injections as well as transmucosal administration of potent opioids are notoriously difficult to control. Psychological drug dependence, escalating doses, and drug-seeking behaviour (drug misuse) are real risks.

We do not know the long-term effects of these drugs on cognitive functions, other functions of the brain, endocrine, sex, and other organs. There are no published randomised controlled trials (RCTs) documenting the long-term effects and safety when this treatment goes on for years. The longest controlled studies have lasted a few weeks, at most. It is clear that RCTs of sufficient magnitude and duration are probably never going to be carried out to elucidate all the difficult questions arising during long-term opioid therapy. We hope to be a bit wiser when the long-term, open, follow-up study of the MONTAS study (Maier et al., 2002) is published.

Therefore, the clinician has to make the difficult decisions based on his/her knowledge of the patient and the observed beneficial and adverse effects on pain and quality of life: When to start strong-acting opioid therapy, how to know pseudo-addiction (with a real need of increased dose) from truly addictive behaviour,
when to stop opioid therapy, and how to handle the obligatory increase in pain during withdrawal. In this situation, I am sure that the clinicians will find the recommendations by Eija Kalso et al. (2003) helpful. They give good general advice and their recommendations can be adapted to local, national medicolegal conditions and particular medical cultures of most European countries (see National Agency for Medicines, Sweden, 2002 and National Agency for Medicines, Norway, 2002). They are highly recommended.

References


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Recommendations for using opioids in chronic non-cancer pain

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Abstract

1. The management of chronic pain should be directed by the underlying cause of the pain. Whatever the cause, the primary goal of patient care should be symptom control.
2. Opioid treatment should be considered for both continuous neuropathic and nociceptive pain if other reasonable therapies fail to provide adequate analgesia within a reasonable timeframe.
3. The aim of opioid treatment is to relieve pain and improve the patient’s quality of life. Both of these should be assessed during a trial period.
4. The prescribing physician should be familiar with the patient’s psychosocial status.
5. The use of sustained-release opioids administered at regular intervals is recommended.
6. Treatment should be monitored.
7. A contract setting out the patient’s rights and responsibilities may help to emphasize the importance of patient involvement.
8. Opioid treatment should not be considered a lifelong treatment.

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Keywords: Opioids; Opiate; Non-cancer pain; Guideline

1. Introduction

Many doctors will be faced with patients who have chronic pain. Opioids such as morpheeine and pentazocine (which are full opioid agonists and classified as being on Step III of the World Health Organization analgesic ladder, World Health Organization, 1996), are now an established part of the care of patients with cancer and in palliative care settings, but they are still relatively new and unfamiliar in many areas for the treatment of chronic non-cancer pain. In most countries, the use of such opioids is controlled (e.g., a special prescription form is required and their storage and dispensing is regulated). Guidance is therefore needed about their use. This document aims to provide a framework for the development of national or local guidelines (American Academy of Pain Medicine, 1996; Kalso et al., 1999; National Agency for Medicines Sweden, 2002; Perrot et al., 1999) but not to provide detailed advice about doses or formulations. It is designed to be a starting point for discussion and to be sufficiently flexible to gain practical acceptance in different regions. It aims to assist prescribers (whether in primary care or specialist

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settings) in the appropriate use of opioids in pain management.

One of the aims of the recommendations is to discuss the well-documented problems of undertreatment and avoidance of strong opioids, as well as to address possible problems of overuse or inappropriate use (Large and Schug, 1995; Melzack, 1990; Zenz and Willweber-Strumpf, 1993).

The decision to initiate or terminate long-term opioid therapy should, ideally, involve a multidisciplinary pain clinic with experience in this field. However, in many cases this is not practical, since there are insufficient pain clinics to be able to evaluate every patient. In such circumstances, referral to a pain clinic would result in patients waiting unacceptably long periods for treatment. These recommendations, while emphasizing the central role of specialist teams, therefore recognize the fact that, in many cases, treatment decisions will have to be made by other doctors without the support of a specialist team. However, prescribing clinicians are encouraged to contact pain clinics, multidisciplinary teams or other colleagues if they are unsure about any aspects.

Patients with severe, continuous pain are not a homogenous group and management will be more complex and problematic for some patients than others. Clinicians need to assess not only the likelihood of benefit from strong opioids, but also the potential for their misuse in each case. Other guidelines have recommended different approaches for patients considered at low or high risk of inappropriate use. However, we have not adopted this approach, but, rather, recommend similar assessment, initiation and termination procedures for opioid therapy in both straightforward and problematic patients. Despite this common framework, treatment should be individualized for each patient and patients should be involved in treatment decisions.

1. The management of chronic pain should be directed by the underlying cause of the pain. Whatever the cause, the primary goal of patient care should be symptom control.

Treatment of pain should be directed by the underlying cause. A clear-cut diagnosis of the cause of the pain seems to improve treatment outcome with opioids. A precise diagnosis of the cause of pain is the goal standard but this is often not attainable. Use of opioids without a clear diagnosis of the cause of pain is appropriate if the pain is severe and continuous, and is responsive to opioids.

Care should be individualized, and patients should be involved in treatment decisions. The consent process is useful for clarifying patient expectations and defining limitations of therapy. It can also be used to set out the consequences if compliance with medication is poor and to agree on the circumstances that will lead to treatment being stopped.

2. Opioid treatment should be considered for both continuous neuropathic and nociceptive pain if other reasonable therapies fail to provide adequate analgesia within a reasonable timeframe.

Division of pain into nociceptive and neuropathic may be out-dated (Woolf et al., 1998), but is probably still helpful. Opioids are considered to be effective in nociceptive pain (Allan et al., 2001; Caldwell et al., 1999, 2002; Moulin et al., 1996; Roth et al., 2000). The efficacy of opioids in certain neuropathic pains has also been shown (Attal et al., 2002; Dellemijn and Vanneste, 1997; Hark et al., 2001; Huse et al., 2001; Rowbotham et al., 1991; Watson and Babul, 1998). However, the benefit of opioids in terms of quality of life in long-term use is still a matter for debate. With the current state of knowledge, opioids should not be prescribed for chronic pain syndrome (idiopathic pain).

As pain is such a complex process, its control is multimodal. Chronic pain is likely to benefit from a combination of pharmacological and non-pharmacological therapies.

Strong opioids should not be used as monotherapy, but in the context of a rehabilitation programme setting goals of improved physical and social function. The need for other pharmacological treatments (e.g., antidepressants) and non-pharmacological treatments (e.g., cognitive behavioural therapy and physiotherapy) should be evaluated regularly. Careful assessment and optimization of other pain therapies will reduce the need for opioids (Maier et al., 2002).

3. The aim of opioid treatment is to relieve pain and improve the patient's quality of life. Both of these should be assessed during a trial period.

The patient's current pain level, quality of life and functional status should be assessed carefully at the start of treatment (baseline). Sustained-release strong opioids should be introduced in the context of a trial period of 3-4 months (Dellemijn et al., 1998; Roth et al., 2000), during which the dose is titrated. Long acting, sustained-release opioids are usually the most practical preparations for dose titration.

The maximum length of the trial period should be agreed by the physician and the patient. At the end of
the trial period, the patient's pain level, the intensity of adverse effects, quality of life and functional status should be assessed again and compared to the baseline levels. In some cases, a pain diary is helpful to assess pain intensity and relief before and after treatment.

The use of an intravenous opioid infusion test can help to predict whether opioids will be beneficial. The negative predictive power of such tests is generally good, but a positive result may not predict long-term treatment success. If the test is performed in a double-blind fashion with saline, the placebo response can also be assessed. The assumption that a particular pain is unresponsive to opioids implies that the opioid dose has been individually titrated to the appropriate maximum level and that the opioid has reached the opioid-receptor. Acute intravenous testing allows the opioid to be titrated to the level of dose-limiting adverse effects for each individual under safe and controlled circumstances. The potential analgesic effect of the particular opioid in a specific pain syndrome and for the individual patient can be assessed. However, intravenous testing is not able to determine the balance between analgesic effect and adverse effects in long-term opioid use. If the result of intravenous testing is positive (maximum pain relief with opioid minus placebo response is greater than 50%), the likelihood of long-term treatment being effective is about 50%. If the response to intravenous testing is negative, the odds for a positive treatment result are negligible (Dellmijn and Vanneste, 1997; Dellmijn et al., 1998). Intravenous opioid testing may save a bothersome opioid titration period of several weeks with initial gastrointestinal adverse effects for patients who are unlikely to benefit.

In most cases, however, opioid therapy is initiated without intravenous testing. A prolonged trial period with gradual dose increments of oral opioids and aggressive treatment of opioid-induced adverse effects has the advantage of achieving a balance between pain relief and adverse effects for the individual patient. The balance between pain relief and adverse effects must be acceptable to the patient. Unless unwanted effects such as nausea, vomiting and constipation are treated immediately, many patients will stop opioid treatment in the early phase and not give it a fair trial. Most patients receiving strong opioids will require continuous prophylaxis against constipation, while tolerance to other adverse effects is likely to develop with continued treatment (Dellmijn et al., 1998).

The aim of treatment is to improve quality of life by relieving pain and improving functional status. Assessing a global measure such as quality of life ensures that both the beneficial and unwanted effects of treatment are taken into account. Relief of pain would be expected to be reflected in an improvement in quality of life, while the occurrence of adverse effects might decrease quality of life. However, clinical trials have shown that significant pain relief does not necessarily imply an improvement in physical function (Moulin et al., 1996). The optimum treatment will balance pain relief and adverse effects. The patient's views about the overall benefits of the treatment (in terms of analgesia, effects on functional status and quality of life, and any unwanted effects) should be determined and respected. A useful series of questions for pain assessment and a list of factors that may predict the outcome of opioid treatment are shown in Box 1. If the outcome of the trial treatment is unclear, a multidisciplinary pain clinic should be consulted.

**Box 1**

**Useful questions for assessing patients before opioid treatment**

- Has a realistic attempt been made to diagnose the underlying cause of pain?
- Have other reasonable treatments been properly tested and exhausted?
- Does the patient have a history of mental illness, or substance or alcohol abuse?
- What is the patient's current functional status?
- What improvement in functional status is desired, and how will this be measured?
- Has the patient kept a pain diary?
- Does the patient understand and accept the goals of treatment?
- What is the patient's physical and psychosocial status?

**Factors predicting outcome with opioid treatment**

**Adverse (negative) predictors:**

- Non-opioid responsive pain type
- Evoked pain, paroxysmal pain or pain on weight bearing
- History of drug or alcohol abuse
- History of psychotic illness
- Patient without a clear idea or desire for functional improvement

**Positive predictors:**

- Continuous pain with high pain intensity
- Clear-cut pain diagnosis
- Spontaneous pain
- Limited treatment period
- Positive outcome of intravenous opioid testing
- Younger age (fewer adverse effects)
- Patient accepts treatment goals
- Patient has kept a pain diary
- Patient makes attempts to maintain physical fitness
- Patient has good psychosocial status

4. The prescribing physician should be familiar with the patient's psychosocial status.
Full assessment of psychosocial status and history is an important part of the assessment before treatment is initiated. It may be helpful to involve a psychologist or psychiatrist. If the patient has a history of psychiatric illness, a full psychiatric analysis should precede initiation of opioid therapy. Patients with a history of drug or alcohol abuse should be referred to a multidisciplinary pain clinic.

Alcohol or drug abuse is a relative (not an absolute) contraindication for opioid therapy. Such patients can develop pain that is suitable for treatment with opioids. It is important for pain to be treated promptly and controlled in such patients, otherwise it can reactivate the addictive behaviour. The complex nature of these cases is probably best handled by a multidisciplinary team, ideally including an addiction specialist. If a multidisciplinary team considers that a patient's compliance would be inadequate, then the patient should not receive opioid therapy.

5. The use of sustained-release opioids administered at regular intervals is recommended.

The efficacy of sustained-release opioids in the management of chronic pain has been demonstrated in randomized controlled studies (Allan et al., 2001; Caldwell et al., 1999, 2002; Dellemijn et al., 1998; Milligan et al., 2001; Moulin et al., 1996; Peat et al., 1999; Roth et al., 2000). Such preparations should be taken regularly (by the clock) rather than as needed.

Breakthrough pain may occur on movement in patients with spinal or vascular pain. The use of short-acting opioids (acting on the same receptor as the main therapy, i.e., pure μ-agonists) should be considered carefully in such cases. As a rule, short-acting opioids should be avoided.

Opioid treatment is initiated at a low dose, and this dose is increased gradually if the patient reports unsatisfactory pain relief with acceptable or no adverse effects. The maximum dose is reached when the patient reports satisfactory pain relief or if unacceptable adverse effects persist despite symptomatic treatment. The optimum dose is essentially determined by the patient, who is the best judge of the balance between pain relief and adverse effects.

6. Treatment should be monitored.

Thorough monitoring of treatment includes measuring not only pain relief and adverse effects, but also the patient's functional status and quality of life. Quality of life may be perceived as difficult to measure, but published rating scales or simple tools such as visual analogue scales can overcome this. Absolute measures of quality of life or comparisons between patients are not the aim of such assessment. Rather, the aim is to use measures that compare the situation before and during opioid treatment for an individual patient.

Functional status, such as the ability to return to work, is an important goal of pain relief. However, functional goals must be individualized, and will depend on the patient. For example, return to work might be the most important outcome for a young woman with low back pain, but ability to sit comfortably might be an equally valid goal for an elderly man with hip pain (Follett, 1999; Rowland and Torgerson, 1998). In some countries reimbursement is dependent on measurement of functional status.

Ideally, a single physician or members of one team should be responsible for the prescription of opioids and should monitor the outcome of treatment. Changes in treatment/dosage are best handled by this physician/team who should also have information about the use of other drugs. Treatment by an individual physician ensures continuity of care and a good understanding of the patient's psychosocial background, but arrangements must be in place to ensure that patients are not left without pain control if access to specific physicians is not possible (e.g., during vacations or sickness).

For patients with a history of non-compliance or abusive behaviour, access should be restricted to one prescribing physician or team and one dispensing pharmacy. Such patients should not have the opportunity to 'shop around' different doctors for different drugs or to provide false information to obtain extra opioids (American Academy of Pain Medicine, 2001). The prescribing physician should monitor the patient's use of other drugs, such as recreational (illicit/lifestyle) drugs and alcohol, other analgesics and co-medications. These should all be checked and recorded prior to starting opioid therapy.

In many areas, access to multidisciplinary teams/pain clinics is limited and waiting lists for consultations may be long. This may mean that primary care physicians have to take responsibility for patient care and analgesic prescribing while they await referral. Box 2 suggests measures that should be taken with problem patients.

**Box 2**

**Problem patients may require:**
- referral to a multidisciplinary team (including a psychologist and an addiction specialist)
- a contract/agreement
- a trial period of opioid therapy (e.g., 3 months)
  - with a predetermined, acceptable endpoint
  - with structured follow-up (e.g., efficacy, adverse effects, quality of life, drugs prescribed/consumed)
- one doctor/team/pharmacy.
7. A contract setting out the patient’s rights and responsibilities may help to emphasize the importance of patient involvement.

Patients have the right to be fully informed about the nature of their treatment and its possible benefits and harmful effects. Obtaining agreement from the patient about the conditions for stopping opioid therapy is as important as obtaining consent for the initiation of therapy. Agreeing a contract also shows that the patient is committed to the aims of treatment and understands that receiving opioid therapy entails certain responsibilities. Topics that should be covered in a contract are shown in Box 3, and sample contracts and consent forms are available from other organisations (American Academy of Pain Medicine, 2001, 2002; National Agency for Medicines Sweden, 2002; Fishman et al., 1999; Gitlin, 1999).

Box 3

**Topics that should be included in a patient contract** (adapted from guidelines issued by the National Academy of Medicine, Sweden (National Agency for Medicines Sweden, 2002))

1. An explanation of the nature of the treatment and its possible beneficial and adverse effects.
2. Patients’ should inform the doctor/team if they take any other analgesic or medication for a psychiatric condition, or if they take alcohol or recreational (illicit/lifestyle) drugs.
3. Patients should not request prescriptions for analgesics from another doctor.
4. The medication should be taken only as prescribed, and never passed on to anybody else.
5. The medication should be kept in a safe place (out of the reach of children) and the police should be informed if it is stolen.
6. Patients need a written document from the doctor when travelling abroad and may be limited in the amount of opioid they can carry for their personal use (e.g., under the Schengen agreement).

8. Opioid treatment should not be considered a lifelong treatment.

Treatment may be stopped, or the dose reduced, if the patient experiences a significant improvement in the painful condition (such as improvement of the underlying disease), or a poor outcome of treatment (e.g., intolerable adverse effects). Treatment should be stopped in cases of poor compliance. Compliance problems might include uncontrolled dose increases or decreases, uncontrolled co-medication, or abandonment of non-pharmacological therapies.

2. Discussion/conclusions

Guidelines should be based on available evidence and this was the ambitious goal of this expert group. However, we soon realised that most of the key issues had to be discussed without evidence (Jadad and Browman, 1995). Several randomised controlled clinical trials have been performed with opioids in some chronic pain conditions. However, the opioid responsiveness of many chronic pain conditions has not been assessed in controlled settings and we know very little about the long-term (months to years) efficacy and adverse effects of opioids.

Our understanding of many basic factors such as the mechanisms of pain and their relevance to the responsiveness to opioids and true differences between opioids is still meagre. So is our understanding of pharmacogenetics and differences between individuals in pain perception and risk for addictive behaviour. Some specialists report successful treatment with methadone when other opioids have failed (Gardner-Nix, 1996). However, no clinical studies have been performed in this area. Another “phenomenon” that is much discussed but about which there is hardly any evidence is “opioid rotation” (Do Quang-Cantagrel et al., 2000; Thomsen et al., 1999). Another field for future research is the possibility of co-administering drugs that will increase the effectiveness of opioids or reduce their adverse effects including the development of tolerance.

In these guidelines the patient is considered the “key participant” in the management of his/her pain. The patient, together with the responsible physician, must take control of the pain. Pharmacists, pharmaceutical companies and society also have necessary and important contributions. The main object of guidelines such as these is to encourage the positive participation of all stakeholders in order to provide the maximum benefit to the patient.

3. Declaration of interests

Eija Kalso, Laurie Allan, Leon Plaghki and Michael Zenz have participated in clinical studies on opioids sponsored by Janssen-Cilag and Purdue Pharma (Napp Laboratories). They have also lectured at meetings organised by these two pharmaceutical companies. Michael Zenz has also worked with Mundipharma, Braun and Astra. Paul Dellemijn has participated in clinical studies sponsored by Janssen-Cilag and has lectured at meetings organised by Janssen-Cilag and Pfizer. Troels
S. Jensen has done consultancy for various medical companies including: GSK, Pfizer, Janssen-Cilag, Astra, Novartis, Pharmacia, and Schwartz. Clara C. Fauca has lectured at a meeting organised by Janssens-Cilag. Wilfried Ilias has no financial interest in companies that market opioid analgesics.

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Dispositional anxiety and the experience of pain: gender-specific effects

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Abstract

Aim of Investigation: Increased anxiety is believed to correlate with increased pain sensitivity in men and women. However, one laboratory-based study and one clinical-based study have offered evidence to suggest that the effect of anxiety in modulating pain sensitivity is specific to men only. The aim of the present study was to examine further whether anxiety differentially effects men and women’s report of experimentally induced pain.

Methods: One hundred forty-four healthy university students (75 women, 69 men) were exposed to a contact heat pain procedure (ascending method of limits procedure, baseline temperature 30 °C, ±0.2 °C, rate of change 2.0 °C/s, cut-off limit 52 °C) and a cold pressor pain procedure (constant temperature +1 °C, ±1 °C, cut-off limit 240 s).

Results: The results agreed with the previous two studies indicating a sex-specific effect of anxiety on pain report. Male participants scoring above the median on the Trait Anxiety Inventory reported significantly greater pain intensity, unpleasantness and showed lower pain tolerance compared to males scoring below the median on the cold pressor pain procedure, while no such differences in cold pressor pain report were found between high and low anxious women. No effect of anxiety was found on measures taken from the contact heat pain procedure, indicating that the sex-specific effect of anxiety on laboratory induced pain is dependent upon the method of stimulation used.

Conclusion: Anxiety is an important factor when considering gender differences in pain perception and warrants further investigation.

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Keywords: Gender; Anxiety; Pain

1. Introduction

The importance of investigating gender differences in pain perception was underscored recently by the establishment of a special interest group focusing specifically on developing a greater understanding of sex, gender and pain. This group was set up by the International Association for the Study of Pain (IASP) in response to growing interest in the area signified by the publication of a series of papers (Fillingim and Maixner, 1995; Unruh, 1996; Berkley, 1997; Fillingim et al., 1998), including a recent meta-analytical study showing important differences to exist between how men and women report pain (Riley et al., 1998). Identifying mechanisms underlying sex and gender differences, however, remain difficult. Differences in sample characteristics between men and women may prove to be clinically relevant in the understanding and treatment of pain and, therefore, worthy of continuing investigation.

1 The term “sex-differences” is generally used to refer to the biological aspects that differentiate men from women, while the term “gender-differences” is generally used to refer to the differences in social role expectations between men and women.
Many factors have been put forward as possible mechanisms underlying sex and gender differences in pain report. These include biological-sex differences such as gonadal hormones (Fillingim and Ness, 2000). For example, women’s response to noxious stimuli has been shown to vary across the menstrual cycle with significantly higher pain thresholds being consistently found during the follicular/postmenstrual phase compared to later phases (Riley et al., 1999). Other examples include psychosocial-gender differences such as willingness to report pain. For example, a study by Levine and De Simone (1991) found the sex of the experimenter to have an effect on the way male participants reported pain. Men reported less pain when the experimenter was female compared to when the experimenter was male. No significant effect of experimenter sex was found, however, on the pain report of female participants although women did tend to report higher pain to the male experimenter.

While such factors are likely to contribute toward creating differences in the way men and women report pain, findings are often inconsistent and do not seem to account adequately for the observed differences in pain sensitivity between men and women (Fillingim and Maixner, 1995). Other sources of variance between the sexes which may contribute to differences in pain report need to be explored.

One factor which has consistently been found to differ between the sexes is the level of reported anxiety. Women are often found to report greater dispositional and transient anxiety compared to men (Cattell, 1957; Murphy, 1986; Robin et al., 1987; Kroenke and Spitzer, 1998). Thus women compared to men appear predisposed to react more anxiously in situations that evoke an anxious response. Pain is normally appraised as a warning of bodily damage and a potential threat which is often a cause for anxiety. Anxiety toward a perceived threat such as impending pain is accompanied by a heightened awareness for information pertaining to the threat (Aldrich et al., 2000; Eccleston and Crombez, 1999). Heightened awareness to threatening information is believed to bias cognitive functioning resulting in altered perception (Mandler, 1984). Thus, cognitive evaluation of the intensity of nociceptive stimuli is considered distorted when anxiety is present (Cornwall and Donderi, 1988). Previous studies examining the effect of anxiety upon pain have shown increases in anxiety to correspond with increases in pain sensitivity (Schumacher and Veldan, 1984; Rhudy and Meagher, 2000) and with increases in affective measures of pain (Fowler-Kerry and Lander, 1991). Laboratory induced general anxiety (Cornwall and Donderi, 1988) and anxiety in relation to the threat of receiving painful stimuli (Dougher et al., 1987) have both been found to correspond with increased sensitivity toward painful stimulation. Thus the predominance for women in the general population to report higher levels of anxiety compared to men has led to anxiety being labelled as a potential source of variance in how men and women perceive and report pain (Robin et al., 1987).

There is growing evidence, however, to suggest that the effect of anxiety in modulating pain sensitivity is dependent upon gender (for review see Jones and Zachariae, 2002). Fillingim et al. (1996) examining the influence of gender and psychological factors on two different thermal pain procedures, found self-reported state anxiety to be associated with increased pain report among men but not among women. A similar relationship between anxiety and pain sensitivity for men and women was also found recently in a study investigating the sex-specific effects of pain-related anxiety on adjustment to chronic pain. Edwards et al. (2000) found pain-related anxiety and adjustment to chronic pain to be inversely related among male patients but unrelated among female patients. Additionally, a study by Keogh and Birkby (1999) recently reported that high anxiety-sensitivity, a sub-factor of trait anxiety, described by Lilienfeld et al. (1993) as a tendency to react anxiously to one’s own anxiety and anxiety-related sensations, was associated with enhanced cold pressor pain report in women but not in men.

Despite the modulatory effects of anxiety on the pain experience, surprisingly few studies have examined whether gender differences in pain report are anxiety dependent and even fewer studies have assessed whether the effects of anxiety on pain are specific to men or women. The present study was carried out, therefore, to explore specifically the role of anxiety in producing gender differences in pain report by examining the relationship between pre-disposed levels of anxiety (i.e., anxiety as a personality trait) and pain report in men and women exposed to experimentally induced noxious stimulation. To allow easier comparisons across studies the present study used similar thermal pain procedures to those used in previous studies reporting gender-specific effects of anxiety on pain report. A contact heat pain threshold and tolerance procedure similar to that applied in the Fillingim et al. study (1996) and a cold pressor pain procedure similar to that used in the Keogh and Birkby study (1999) were used.

As previously mentioned, biological-sex differences such as gonadal hormones have been found to produce differences in the way pain is experienced. In an attempt to control for the effect of hormonal influences on pain perception the menstrual cycle phase for all female participants was recorded and analysed to assess the effect of the following stages on pain outcome measures: menstrual, day 1–7; postmenstrual, day 8–14; ovulatory/luteal, day 15–21; pre-menstrual, day 22–28. An attempt

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The term “pain sensitivity” is used throughout as an umbrella term to describe variation in verbal pain report and in pain thresholds.
was also made to assess the participants' willingness to report pain by measuring social desirability. Social desirability is a stable trait which is defined as the need of an individual to respond in a culturally appropriate and acceptable manner in an attempt to gain approval (Cronwe and Marlowe, 1960). The more this trait is present in an individual the less reliable any self-disclosure will be. Also, to balance any effect experimenter sex may have on pain report both male and female experimenters were used to conduct each experimental session.

2. Materials and methods

2.1. Participants

Participants were 69 male (mean age = 25.78; SD = 5.41) and 75 female (mean age = 25.69; SD = 4.47) healthy university students who responded to local advertisements for the study. All respondents were screened for psychological and medical symptoms using the Brief Symptom Inventory (BSI; Derogatis, 1992; Derogatis and Melisaratos, 1983) and the Daily Habits and Health Questionnaire (Locke et al., 1994), respectively. The BSI is a 53-item questionnaire used to assess psychological symptoms. The Daily Habits and Health Questionnaire is a 48-item questionnaire designed to measure habits and health (1) in general, (2) within the last week and (3) within the last 24 h. Exclusion criteria included: feelings of pain or tenderness immediately prior to the experiment, chronic pain, recent alcohol use and/or use of other stimulants (e.g., marijuana), use of analgesic or antidepressant medication. All participants were asked not to drink excessive amounts of coffee or take aspirin or any other pain reliever on the day of the experiment. The experiment was approved by an ethics committee. Informed consent was obtained from all participants prior to the experiment. All persons received payment for participation.

2.2. Thermal stimulation apparatus and procedures

Two thermal pain procedures were used in this study: (1) the determination of contact heat pain threshold and tolerance and (2) the cold pressor test. The tests were performed on different sites of the body to avoid one test interfering with the other. The contact heat thermode was applied distally to the anterior side of the right forearm, while the cold pressor test was applied to the hand and wrist.

2.3. The determination of contact heat pain threshold and tolerance

Heat pain threshold and heat pain tolerance were determined by an ascending method of limits procedure (Yarnitsky and Ochoa, 1990) using a computerised version of the Thermostest device (Somedic AB, Stockholm, Sweden). A thermode consisting of series-coupled Peltier elements measuring 25 mm × 50 mm was used for stimulation. For each evaluation of heat pain threshold and tolerance a baseline temperature of 30 °C (±0.2 °C) and a rate change of 2.0 °C/s (heating and return to baseline) were used. The thermode was applied distally to the anterior side of the right forearm. To avoid skin damage, a cut-off limit of 52 °C was set. Each participant was instructed to press a button when pain was first perceived (pain threshold), and again when further increases in temperature could no longer be tolerated (pain tolerance). The temperature automatically returned to baseline once the button was pressed or once the cut-off limit of 52 °C was reached. The experimenters were careful not to stimulate the same area of skin for threshold and tolerance determinations. Participants were seated with their arm resting on top of the thermode. The weight of the arm pressed the skin against the stimulus areas. If any stimulus felt intolerable the participant could withdraw the arm. In each test (threshold and tolerance) three trials with 4–6 s intervals were performed in order to ascertain each participants average threshold and tolerance level.

2.4. The cold pressor test

The cold pressor test was conducted in a fashion similar to other experiments using the CPT (e.g., Walsh et al., 1989). A metal tank (48 × 30 × 15 cm) was filled with water continuously circulated using a circulation pump, and cooled to a constant temperature of +1 °C (±1 °C). Participants immersed their hand up to the wrist in the water-filled tank and were instructed to keep the hand resting. The pain outcome measures obtained during this test were pain threshold, pain tolerance, pain intensity and feelings of unpleasantness related to the painful stimulation. Pain threshold was defined as the length of time between the participant first submerging their hand into the cold water and verbal indication of the first sensation of pain. Pain tolerance was defined as the total length of time the participants' arm was submerged in the cold water. A 240 s ceiling on pain tolerance was adopted, after which time the participants were asked to remove their hand from the water. The participants were not informed of this ceiling in an attempt to reduce the risk of competitiveness and limit any misconceptions that the hand was expected to be submerged in the cold water for that specific length of time. Pain intensity and unpleasantness were assessed using two 11-point numerical rating scales, with verbal anchors. For the pain intensity scale the verbal anchors were “no pain sensation”–“extreme pain” and for the pain unpleasantness scale the verbal anchors were “not at all unpleasant”–“extremely unpleasant”. Intensity
and unpleasantness ratings were recorded in 10 s intervals from the time of submersion. The average rating across all time points was computed to obtain mean intensity and mean unpleasantness ratings.

2.5. Psychological measures

The State-Trait Anxiety Inventory was used in the present study (Spielberger et al., 1983). The State-Trait Anxiety Inventory (STAI) consists of two 20-item questionnaires using a 4-point Likert scale and is a standard measure of both situational (state = STAI-S) and dispositional (trait = STAI-T) anxiety.

The Marlowe Crowne Social Desirability scale was used in the present study (Crowne and Marlowe, 1960). The Marlowe Crowne Social Desirability Scale (MCSD) is a 33-item inventory that uses a true-false format. Respondents indicate their agreement or disagreement with each statement representing behaviours that are either socially desirable or undesirable.

2.6. Procedure

In order to reduce potential experimenter gender effects, two experimenters, one male and one female, conducted all experimental sessions. Both the male and female experimenter interacted with each participant. Prior to entering the laboratory, each participant completed a battery of psychological questionnaires. Following the completion of the questionnaires, each participant underwent two thermal pain procedures in the following order: (1) determination of contact heat pain threshold and pain tolerance and (2) cold pressor test (CPT). The procedures were given in order of estimated recovery time with significantly longer recovery times needed after the CPT compared to the contact heat pain procedure. The whole experiment lasted for an average duration of 50 min.

2.7. Data analysis

Exploration of the data revealed that four of the dependent variables suffered from skewness (contact heat pain threshold; CPT pain intensity; CPT unpleasantness and CPT pain threshold). As a result, the data for all four variables were transformed using logarithmic transformation. Analysis was used to control for the effect of menstrual cycle phase on the pain report of high and low anxiety female participants. Multivariate Analysis of Variance (MANOVA) was used to assess the interaction of anxiety and gender on pain outcome variables. Based upon previous research showing gender differences in pain perception to be dependent upon the type of stimulation method used (Lautenbacher and Rollman, 1993), multivariate analysis was performed for each thermal pain modality separately. This was done in an attempt to reveal any differential main and interactive effects of anxiety and gender on pain report that may arise as a result of using two qualitatively different pain stimulus modalities. Correlation analyses between pain outcome scores and other variables were undertaken separately for male and female participants using Pearson’s correlation coefficients. To test the significance of between group differences in correlation coefficient magnitude, r was transformed into a Z-Score using Fisher’s Z-statistic.

On inspection of the data the combination of the scores from the variable trait anxiety with scores from pain outcome variables resulted in a single case (a female participant) that was noticeably discrepant from the rest. In accordance with the direction given by Tabachnick and Fidell (2001) in dealing with multivariate outliers the case was deleted from analysis.

3. Results

To examine the relation between anxiety and pain measures among men and women, participants were categorised as either high anxious or low anxious using gender-specific median splits on total STAI-T scores. The median STAI-T score was 35 for women and 33 for men. Participants scoring on the median value were included in the low anxiety sub-groups. Mean trait anxiety scores for each sub-group along with standard deviations are as follows: low anxiety men ($M = 27.58$, $SD = 3.55$); low anxiety women ($M = 29.45$, $SD = 3.62$); high anxiety men ($M = 40.30$, $SD = 5.16$); high anxiety women ($M = 43.61$, $SD = 5.80$). As expected due to sub-group allocation high anxiety groups measured significantly higher than low anxiety groups ($p < .001$) for trait anxiety. Low anxiety sub-groups did not differ significantly, however, high anxiety women were found to score significantly higher on measures of trait anxiety than high anxiety men ($p < .05$).

To control for the effect of menstrual cycle phase on the pain report of high and low anxiety female participants, analysis revealed that high anxiety female participants did not differ significantly in menstrual cycle phase compared to low anxiety females ($p > .05$). Low anxiety females = menstrual day 1–7, $n = 7$; postmenstrual day 8–14, $n = 17$; ovulatory/fertile day 15–21, $n = 8$; pre-menstrual day 22–28, $n = 6$. High anxiety females = menstrual day 1–7, $n = 5$; postmenstrual day 8–14, $n = 11$; ovulatory/fertile day 15–21, $n = 11$; pre-menstrual day 22–28, $n = 9$. Multiple comparisons on the effect of menstrual cycle phase on pain outcome variables revealed no significant differences between menstrual cycle phase for any of the pain outcome variables. Additionally, no significant gender differences were observed for age, or for measures of social desirability. Means and standard deviations for all pain
Table 1
Mean (and standard deviations) pain outcome scores between anxiety group (low vs. high) and gender (male vs. female)

<table>
<thead>
<tr>
<th></th>
<th>Heat threshold</th>
<th>Heat tolerance</th>
<th>CPT intensity</th>
<th>CPT unpleasantness</th>
<th>CPT threshold</th>
<th>CPT tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low anxiety male</td>
<td>42.66°C</td>
<td>48.03°C</td>
<td>6.78</td>
<td>6.39</td>
<td>14.37 s</td>
<td>178.09 s</td>
</tr>
<tr>
<td>N</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>SD</td>
<td>2.98°C</td>
<td>2.62°C</td>
<td>1.70</td>
<td>2.01</td>
<td>10.28 s</td>
<td>83.92 s</td>
</tr>
<tr>
<td>High anxiety male</td>
<td>41.60°C</td>
<td>46.90°C</td>
<td>7.80</td>
<td>7.51</td>
<td>11.03 s</td>
<td>115.32 s</td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>SD</td>
<td>3.23</td>
<td>2.97</td>
<td>1.58</td>
<td>2.06</td>
<td>7.22 s</td>
<td>78.46 s</td>
</tr>
<tr>
<td>Low anxiety female</td>
<td>42.12°C</td>
<td>46.05°C</td>
<td>8.01</td>
<td>7.89</td>
<td>10.97 s</td>
<td>97.87 s</td>
</tr>
<tr>
<td>N</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>SD</td>
<td>2.41°C</td>
<td>1.77°C</td>
<td>1.28</td>
<td>1.25</td>
<td>6.85 s</td>
<td>77.82 s</td>
</tr>
<tr>
<td>High anxiety female</td>
<td>42.60°C</td>
<td>45.82°C</td>
<td>7.54</td>
<td>7.56</td>
<td>16.42 s</td>
<td>111.65 s</td>
</tr>
<tr>
<td>N</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>SD</td>
<td>2.61°C</td>
<td>1.64°C</td>
<td>1.53</td>
<td>1.99</td>
<td>12.80 s</td>
<td>84.25 s</td>
</tr>
</tbody>
</table>

Note: Heat, contact heat (Thermotest); CPT, cold pressor test; CPT intensity, mean NRS-11 scores; CPT unpleasantness, mean NRS scores; CPT threshold, time in seconds from time of ice water immersion to first report of pain; CPT tolerance, time in seconds from time of ice water immersion to withdrawal.

outcome measures categorised by anxiety and gender groups are displayed in Table 1.

A 2 (anxiety group; high vs. low) × 2 (gender; male vs. female) factorial MANOVA was conducted for the two pain modalities separately. Multivariate analysis on the pain outcome variables from the contact heat pain procedure showed a significant main effect of gender [F(2, 138) = 10.41, p < .001]. No significant main effect of anxiety or significant interaction between anxiety and gender was found. Multivariate analysis on the pain outcome variables from the CPT procedure showed a significant main effect of gender [F(4, 136) = 3.56, p < .01], and a significant interaction between gender and anxiety [F(4, 136) = 4.38 p < .01]. No significant main effect of anxiety was found.

In order to examine further the effect of gender on pain outcome measures univariate F tests were examined. Following Keogh and Birkby (1999) a Bonferroni type adjustment for inflated Type I error was used, setting the critical α-level at .05/6 tests = .0083. No significant gender difference was found for contact heat pain threshold. A significant gender difference was found for contact heat pain tolerance [F(1, 141) = 15.92, p < .001] with men tolerating 3.4% (9.7% difference from baseline) higher levels of contact heat pain (M = 47.49°C; SD = 2.8°C) than women (M = 45.94°C; SD = 1.7°C). No significant gender differences were found for CPT threshold and a trend difference only [F(1, 141) = 3.43, p = .06] was found for CPT pain intensity with men reporting 6.8% less intensity while undergoing the cold pressor test (M = 7.3; SD = 1.7) compared to women (M = 7.8; SD = 1.4). A significant gender difference was found for CPT unpleasantness [F(1, 141) = 5.98, p < .05] with men reporting 11.6% less unpleasantness while undergoing the cold pressor test (M = 6.9; SD = 2.0) compared to women (M = 7.7; SD = 1.6). A significant gender difference was also found for CPT tolerance [F(1, 141) = 9.65, p < .01] with men tolerating cold pressor pain 41.6% longer (M = 148.0 s; SD = 86.7 s) than women (M = 104.5 s; SD = 80.7 s).

Post hoc tests using a Bonferroni correction were performed to examine further the specific nature of interaction found between anxiety and gender on CPT pain outcome measures (see Table 1 for means and standard deviations; the percentages given below illustrate the differences between anxiety and gender groups on measures of mean pain response). High anxiety women were not found to differ from low anxiety women on any of the pain outcome measures. High anxiety men, however, were found to report significantly higher levels of pain intensity (15.0%) and pain unpleasantness

![Figure 1](https://example.com/figure1.png)

Fig 1. Scatter plots of trait anxiety and pain report measures taken from the cold pressor test for men and women.
(17.5%) as well as display lower pain tolerance (54.4%) when compared to low anxiety men on CPT measures (all p values <.05). Low anxiety men reported significantly less CPT pain intensity (p < .01; 18.1%) compared to low anxiety women. Low anxiety men also rated the CPT as significantly less unpleasant compared to low anxiety women (p < .01; 23.4%) and high anxiety women (p < .05; 18.3%), and were able to tolerate cold pressor pain significantly longer than low anxiety women (p < .001; 82%) and high anxiety women (p < .01, 59.5%). High anxiety men were not found to differ significantly when compared to low and high anxiety women on any of the CPT pain outcome measures. No significant differences were found between groups for measures of CPT pain threshold.

3.1. Correlation analyses

Gender-specific simple correlation analyses between anxiety and pain measures revealed that for men trait anxiety was significantly correlated with CPT measures indicating that increased anxiety is associated with increased pain intensity and unpleasantness, and with decreased pain threshold and tolerance (see Figs. 1-4). Anxiety was not found to be significantly associated

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Male participants</th>
<th>Female participants</th>
<th>Z-Scorea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 69</td>
<td>N = 74</td>
<td></td>
</tr>
<tr>
<td>Heat pain threshold</td>
<td>-0.14</td>
<td>-0.12</td>
<td>0.12 NS</td>
</tr>
<tr>
<td>Heat pain tolerance</td>
<td>-0.09</td>
<td>-0.005</td>
<td>0.5 NS</td>
</tr>
<tr>
<td>CPT intensity</td>
<td>0.32**</td>
<td>-0.08</td>
<td>1.47 NS</td>
</tr>
<tr>
<td>CPT unpleasantness</td>
<td>0.30*</td>
<td>-0.02</td>
<td>1.68 NS</td>
</tr>
<tr>
<td>CPT threshold</td>
<td>-0.31**</td>
<td>0.23</td>
<td>0.51 NS</td>
</tr>
<tr>
<td>CPT tolerance</td>
<td>-0.37**</td>
<td>0.11</td>
<td>1.63 NS</td>
</tr>
</tbody>
</table>

NS, non-significant difference when comparing men and women on the magnitude of correlation between trait anxiety and pain measures.  
Fisher’s Z-transformation method for testing the significance of difference between correlation coefficients. 0.05 level of significance = Z < -1.96 or Z ≥ +1.96  
Correlation between STAI-T and pain measure is significant at the 0.05 level.  
Correlation between STAI-T and pain measure is significant at the 0.01 level.
with any of the pain outcome measures for women. The between group differences in correlation coefficient magnitude failed to reach significance. Gender-specific correlations are presented in Table 2.

4. Discussion

The results of the present study confirm earlier findings indicating a gender-specific effect of anxiety on pain report (Fillingim et al., 1996; Edwards et al., 2000). More specifically, male participants scoring above the median on the STAI-T reported significantly greater pain intensity, unpleasantness and lower pain tolerance compared to males scoring below the median in response to cold pressor stimulation. No such effect of anxiety on pain report was observed for female participants however. This finding suggests that dispositional anxiety is significantly related to sensory, affective and motivational aspects of pain report among men but not among women. Furthermore, the pattern of correlation between anxiety and thermal pain responses differed for men and women. For men, increased anxiety was significantly related to increased pain intensity and unpleasantness and reduced pain threshold and tolerance on measures taken from the CPT, while no significant associations between anxiety and pain responses were found for females. Although gender differences did not reach significance when comparing the magnitude of association between anxiety and pain, the differential association between anxiety and gender discovered does provide evidence for a gender-specific effect of dispositional anxiety on pain report. Thus, the perceptual disruption of nociceptive information as a function of dispositional anxiety may be specific (or at least more strongly associated) to men.

It is unclear based upon the limited evidence available why anxiety may be related to pain sensitivity for men and not for women. Edwards et al. (2000) offer evidence from related studies to suggest that: (1) men compared to women may experience an increase in pain sensitivity as a result of greater adrenergic and vascular activity in response to situational and dispositional anxiety, and (2) men compared to women, through a greater ability to detect and interpret internal physiological stimuli, may be more influenced by the physiological manifestations of anxiety. Thus for men the physiological manifestations of anxiety may have more influence over the interpretation of painful stimuli compared to women resulting in altered perception. If anxiety is associated with pain sensitivity in men only, then a shift in perspective is needed when explaining the role of anxiety in producing gender differences in pain report. If low anxiety in men is associated with low pain sensitivity, then samples containing high frequencies of men predominantly low in anxiety will likely produce gender differences in pain report irrespective of the level of anxiety in women. Variance in the pain report of women may be better accounted for by factors other than anxiety such as anxiety sensitivity (Keogh and Birkby, 1999) and menstrual cycle phase (Riley et al., 1999).

When looking at differences between gender in pain report for the cold pressor task, no significant differences in pain outcome measures were observed when comparing men in the high anxiety group to women in the low and high anxiety groups. Men in the low anxiety group, on the other hand, reported consistently less unpleasantness and tolerated cold pressor pain significantly longer than women in both high and low anxiety groups. Men in the low anxiety group were significantly less sensitive compared to women in the low anxiety group as shown on measures of pain intensity, however, no significant gender difference in pain intensity was found between low anxious men and high anxious women. Why no difference in pain intensity was found between low anxious men and high anxious women is unclear. Women in the high anxiety sub-group were found to measure significantly higher on measures of trait anxiety compared to all other groups including high anxiety men. According to the Perceptual Disruption Theory the high level of anxiety experienced by high anxiety females may have resulted in reduced sensitivity as anxiety competed with nociception for attention (Cornwall and Donderi, 1988). Also, recent animal studies suggest that anxiety and fear may share the same neural circuit, with the level of activation determining the behavioural outcome (Walters, 1994; King et al., 1996). It is believed that moderate levels of activation may produce anxiety and hyperalgesia while high levels of activation may produce fear and analgesia (Rhoody and Meagher, 2000). It is possible, therefore, that women in the high anxiety sub-group may have experienced a higher state of central arousal while undergoing painful stimulation resulting in fear and subsequently analgesia. This would also help to explain the positive correlation (although non-significant) between trait anxiety and pain threshold observed for female participants (see Table 2 and Fig. 3).

Interestingly, trait anxiety was not found to be significantly associated with either men or women's report of contact heat pain. That anxiety was related in a gender-specific manner to CPT outcome measures but unrelated to heat pain outcome measures suggests that the gender-specific effect of dispositional anxiety on pain may be dependent upon the type of stimulation method used to induce nociception. It has been suggested by a recent study comparing the inter-individual variation of pain tolerance determined by five experimental pain modalities (including contact heat pain and CPT), that the level of stimulus intensity tolerated may not “primarily” be determined by psychological factors but by an internal cut-off mechanism that is set to avoid tissue
damage and that is dependent upon stimulus modality (Luginbühl et al., 2000). Luginbühl et al. found the inter-individual variability of heat pain tolerance (delivered by a Thermotest apparatus identical to the one used in the present study) to be significantly lower than the other tests including CPT. Individual sample characteristics such as anxiety may, therefore, have less impact on heat pain tolerances compared to cold pain tolerances, or put another way CPT procedures may be more sensitive to psychological factors than contact heat pain procedures. This may explain the difference in association between anxiety and the two pain modalities found in the present study. As in the Luginbühl et al. study, the present study evaluated heat pain tolerance using an ascending method of limits procedure with a rate of change set at 2.0°C/s (baseline temperature 30°C, cutoff limit 52°C). It is possible that the temporal parameters of the stimulus used to induce noceception may be an important factor in determining whether or not anxiety mediates pain response. Future studies may wish to examine the relationship between rate of change of heat pain intensity and the mediating effects of anxiety on pain tolerance.

Despite the lack of a main effect and a gender-specific effect of anxiety on contact heat pain threshold and tolerance, gender differences were still observed for heat pain tolerance measures. Men were better able to tolerate contact heat pain compared to women. It has been suggested that gender differences in pain report may be confined to behavioural differences rather than perceptual or biological differences. As previously mentioned, differences in pain report between men and women may be the result of a gender-specific report bias as a function of socio-cultural factors such as the effect of experimenter sex (Levine and De Simone, 1991). However, all tests in the present study were run by both a male and a female experimenter, thus reducing the likelihood of the observed gender differences being significantly influenced by experimenter sex. Also, a previous study failed to find an effect of experimenter sex on the pain report of men and women (Feine et al., 1991). In an attempt to control further for the effects of response bias on pain report, social desirability was measured for both male and female participants. Gender comparisons revealed no significant differences in social desirability, further ruling out the likelihood of differences in response bias accounting for the observed gender difference in heat pain tolerance. Another possible explanation for the observed gender difference in heat pain tolerance is given by a recent study highlighting the possibility of sex differences in CNS processing of certain thermal stimuli. Fillingim et al. (1998) reported sex differences in pain expression to be more robust for sustained, temporally dynamic thermal stimuli, similar to the heat pain procedure employed in the present study, than for discrete noxious thermal pulses. Thus, the temporal parameters of a pain stimulus may be an important factor in determining whether or not gender differences are observed. Further research is needed in this area, however, before any reliable conclusions can be drawn.

Although women generally exhibited greater thermal pain sensitivity than men, no significant gender differences were found for measures of pain threshold taken from both thermal pain procedures. This finding is supported by previous research showing gender differences in thermal pain thresholds to be non-significant (McCaul and Hugstedt, 1982; Kenehalo, 1986; Lutenbacher and Rollman, 1993; Fillingim et al., 1996), and reflects the inconsistency in observed gender differences for measures of pain threshold in studies using thermal stimulation procedures (Riley et al., 1998). Measures of sensory pain threshold are likely to be influenced more by physiologic and sensory factors and less by affective and motivational factors. This may be one reason why gender differences in pain perception are less robust for measures of thermal sensory pain threshold.

It is clear from this and other studies that have investigated the effects of anxiety on the pain report of men and women, that anxiety does not account for the total observed variance in pain report between the sexes. It is likely that differences in the way men and women experience pain are due to a complex interdependent array of biological and psychological mechanisms. Identifying the sources of variance in the transmission, perception, and report of pain between men and women will be an important step toward understanding the total pain experience. Clinical implications are as yet unclear. To our knowledge only one study to date has investigated the gender-specific effects of anxiety using a chronic pain population (Edwards et al., 2000). More clinical studies identifying gender-specific modulators of pain are clearly needed. The information gained from such studies may prove useful in the modification and improvement of pain treatment programs.

In conclusion, the findings from the present study, together with findings from the Fillingim et al. (1996) and Edwards et al. (2000) studies, identify a gender-specific effect of anxiety on pain response and a potential mechanism for producing gender differences in the experience of pain. Furthermore, the effect of anxiety in modulating pain report may be further dependent upon the method of thermal stimulation employed to induce noceception, with pain thresholds in response to sustained temporally dynamic thermal stimulation being influenced to a greater extent by sex differences in CNS processing and to a lesser extent by gender differences such as anxiety. The possibility that there are important differences in the way anxiety affects the pain report of men and women merits further investigation in both laboratory and clinical settings.
Acknowledgements

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Evaluation of a short duration behaviour-based post-operative pain scoring system in rats

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Abstract

We have recently demonstrated dose-related analgesic-induced reductions in the occurrence of 7 behavioural activities following midline laparotomy in rats. For these behaviours to be useful in evaluating pain in laboratory rats they must be shown to occur after different laparotomy, and frequently enough to allow rapid scoring of animals. Here, the relevant behaviours were used to test the analgesic efficacy of meloxicam with a variation of our previous laparotomy model. As part of an unrelated project, 57 male Fischer rats were divided into groups to receive either saline (0.2 ml/100 g s/c), meloxicam (0.5, 1 or 2 mg/kg s/c) or carprofen (2.5, 5, or 10 mg/kg s/c) 1 h before surgery. Behaviour data were collected for 10 min following 25 min of recovery from isoflurane anaesthesia. The cumulative frequencies of back arching, fall/stagger, writhing and poor gait were used to compute a composite behaviour score. Irrespective of whether analyses included only 5 or all 10 min of the observation period, the relevant behaviours occurred significantly more often in rats given saline or low dose meloxicam than in those given 1 or 2 mg/kg of meloxicam, or any dose of carprofen. We conclude that this technique of quantifying post-surgery behaviour is an effective pain scoring method following abdominal surgery in rats, and that 1 mg/kg meloxicam significantly attenuates laparotomy induced pain. Since only a short observation period is required, this approach represents an important practical advance in assessing abdominal pain severity and clinical drug potency.

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Keywords: Rat; Behaviour; Pain; Analgesia; Meloxicam; Carprofen

1. Introduction

It is generally accepted that if animals are to be used in biomedical research, any pain or distress that may result should be prevented or minimised. Post-surgical pain can be controlled using analgesics, however the use of an appropriate treatment regimen requires the development of methods of assessing pain. Pain in man is recognised as being a subjective experience but its nature in animals remains elusive. There is, however, a general acceptance amongst many research workers and veterinarians that alterations in animal behaviour are likely to accompany pain (Morton and Griffiths, 1985; Zimmerman, 1986; Roughan and Flecknell, 1996; Dobromylskiy et al., 2000; Roughan and Flecknell, 2000, 2001). This has prompted some recent efforts to develop behavioural analysis techniques for quantifying post-surgical pain in rats (Liles et al., 1998; Roughan and Flecknell, 2000, 2001) and dogs (Fox, 1995; Firth and Haldane, 1999; Fox et al., 2000), although most work has focussed on farm animals such as lambs (Molony et al., 1993; Kent et al., 1995; Molony and Kent, 1997; Graham et al., 1997; Kent et al., 1998; Thornton and Waterman-Pearson, 1999; Kent et al., 2000) and calves (Robertson et al., 1994; Molony et al., 1995). All of this work has been based on the assumption that pain severity and analgesic efficacy can be scored by quantifying the relative magnitude of the behavioural alterations that occur due to surgery and intervention therapy. To date, none of these behavioural assessment techniques have been developed into a practically useful scoring system.

The difficulties inherent in applying pain scoring systems include the time required for assessments, training requirements of observers, the occurrence of
large variations between observers, and a failure to validate the system by use of appropriate control groups (Leese et al., 1988; Reid and Nolan, 1991; Thompson and Johnson, 1991; Nolan and Reid, 1993; Holton et al., 1998; Lascelles et al., 1998; Griscaux et al., 1999; Firth and Haldane, 1999). Our inability to score pain effectively in animals has contributed to a lack of relevant clinical efficacy data for many of the analgesics available for animal use, and an under use of analgesics. For example, recent surveys report that analgesics are used relatively infrequently in dogs and cats following procedures such as ovariohysterectomy and castration, and are given to less than 25% of small mammals in UK veterinary clinical practice (Lascelles et al., 1998; Capuer et al., 1999). It is difficult to judge the frequency of analgesic use following experimental surgery in animals, but it is at best likely to be similarly low. This situation represents a serious welfare concern.

With a view to addressing this problem we have studied post-operative pain related behaviour in rats in considerable detail (Roughan and Flecknell, 2001) and demonstrated significant changes in some specific behaviours following surgery. The activities concerned (arching of the back, loss of balance during grooming or rearing, a transient ‘witching’ while inactive and abdominal writhing) were most prominent in animals that received only saline, but were significantly attenuated for between 4 and 6 h in analgesic treated animals. These key behaviours were unaffected by drug treatment in unoperated control groups, and this further supported our belief that their occurrence could be used to assess pain and the effectiveness of analgesic treatment. The behaviours also occurred sufficiently frequently to enable them to be used to develop a pain scoring scheme. To be of practical value, a pain scoring system must be easy and rapid to undertake, and ideally be applicable to a range of strains and ages of animal, and to different surgical procedures. These features have not been demonstrated for any of the pain assessment techniques currently available. Our previous study had utilised a single age and strain of rats, and a standardised surgical procedure (laparotomy). In addition, animals were observed for prolonged periods. The present objective was to gauge the limits of the scoring procedure, by assessing whether similar behaviour changes could be used to determine pain severity and analgesic efficacy in a different age and strain of rats subjected to different surgical procedures. We also wished to determine the minimum observation period necessary to conduct reliable assessments since this would greatly increase the practical value of the proposed scoring technique. We had the opportunity to assess these possibilities by studying Fisher rats that were required to undergo laparotomy as part of an unrelated project examining the growth of tumour cells implanted in the wall of the bladder.

2. Materials and methods

All procedures were conducted in accordance with the Animals (Scientific Procedures) Act 1986 (1989) (project and personal licence numbers PPL 60/2255 and PIL 30/177) and with the approval of a local ethical review committee.

2.1. Animal husbandry and study design

The animals were 57 male Fischer inbred rats (F344/Nttac). All were obtained from the same commercial supplier (Charles River, UK) and weighed 56 ± 12g (mean ± 1 SD) upon delivery. They were maintained on sawdust (Gold Chip, BS and S, Edinburgh, UK) in groups of 4 or 5 in cages (Tecniplast Type 2, North Kent Plastics, Erith, UK) during a 2 week acclimatisation period. Room temperature was maintained at 24 ± 1°C with 15–20 air changes per hour. A 12 h light–dark light cycle was used, with lights going off abruptly at 19:00 h. Food pellets (R and M No. 1, SDS, Essex, UK) and water were replenished as necessary.

The animals were weighed between 09:00 and 09:30 h for 2 days prior to surgery and every subsequent day until the end of the unrelated project (4–6 weeks approx.). On the day of surgery they were assigned to groups that were to receive a subcutaneous (sc) injection of either saline (0.2 ml/100 g), meloxicam (0.5, 1 or 2 mg/kg; M0.5, M1 and M2, respectively) or carprofen (2.5, 5 or 10 mg/kg; C2.5, C5 and C10, respectively). The timing of surgery was determined by the protocol for tumour implantation, but in general, between 6 and 15 animals were allocated for surgery on each of two days of alternate months beginning in March and ending in September 2001. The animals were age matched to within approximately 1 month at the time they underwent surgery. Upon completion of all surgery, the study design gave 7 treatment groups with between 7 (saline group) and 9 animals per group. Treatment order was determined by a randomised block design. This ensured that both the type of treatment administered and the time elapsed prior to behaviour recording were randomised between groups.

2.2. Experimental procedure

Injections were given 1 h before moving animals to the operating theatre, where anaesthesia was induced with 4% isoflurane in oxygen (2 l/min) for 2 min or until the tail pinch reflex was absent, and maintained with 2% isoflurane in oxygen (2 l/min). The rats were then placed on heating blanket (Harvard Apparatus, Edenbridge, Kent, UK) that maintained body temperature at 37 ± 2°C. The lower abdomen was shaved and sprayed with chlorhexidine (Hydrex Derma Spray,
Adams Healthcare, Leeds, UK) and a 1 cm midline incision made in the skin and underlying muscles with a scalpel 1.5 cm anterior to the penis. The exposed bladder was held withatraumatic forceps (Debakey) and 0.1 ml phosphate buffered saline containing 2 x 10^6 tumour cells injected into the left lateral wall using an insulin syringe. The abdominal muscle and skin were closed separately using 4/0 polyglyactin 910 (Vicryl, Ethicon), the latter with subcuticular sutures. The total period of anaesthesia was 15 min, following which animals recovered in an incubator maintained at 28 ± 3°C for a further 12–15 min, or until normal exploratory activities commenced. Ten minutes later each animal was placed into a cage (Tecniplast Type 3) on its own and moved to a quiet room for filming prior to VAS assessment. Filming began immediately and continued for 10 min using a digital camcorder (DSR-PD1, Sony, Japan). At the end of this period, the rat was returned to its home cage and the digital film transferred to a standard VHS videocassette via a time code generator (AEC-BOX, Adrienne Electronics, Las Vegas, USA) for later analysis.

2.3. Monitoring

Following completion of filming, the rats were presented for clinical assessment by a qualified laboratory animal veterinarian. This second observer made a visual analogue score (VAS) of the condition of each rat, by marking an 'x' on a 10 cm line scaled from 0 (no pain) to 10 (severe pain). By measuring the distance between '0' and 'x' it was then possible to quantify the observer's impression of the degree of discomfort/pain experienced. The second observer also noted any clinical observations that influenced the VAS. Assessments were carried out over a 2–5 min period and involved observation of clinical signs of pain or distress (as described by Morton and Griffiths (1985)) both prior to interference, and during handling/wound palpation. To avoid subjecting control animals to unnecessary pain, upon completing filming and this first phase of post-operative VAS assessment the saline treated rats were given a subcutaneous injection of carprofen (5 mg/kg). All animals were offered softened diet as a complementary, and more easily obtainable food source. In a second phase of assessments (4–5 h later), each rat was re-examined by the laboratory animal veterinarian who recorded a second VAS. Following this, each rat was again assessed using the behavioural scoring system (Roughan and Flecknell, 2001) by the score system developer (Roughan). At this stage intervention analgesia was provided (5 mg/kg carprofen s.c) for any animal in which the combined frequency of twiching, staggering, back arching and writhing was between, or exceeded 6–8 occurrences in a 10 min observation period.

2.4. Behavioural observations and data collection

Behaviour data were collected by one treatment blinded observer who assessed the video footage of postsurgery behaviour (Roughan). Behavioural analysis software (The Observer Version 3.0, Noldus Information Technology, Wageningen, NL) was used for data collection. From experience gained and results obtained in our previous studies of the post-laparotomy behaviour of rats (Roughan and Flecknell, 1996, 2000, 2001), seven activities thought to be closely associated with abdominal pain were examined (Table 1). As shown, each behaviour was also defined by the animals' posture during execution of each act. Grooming was further qualified by the region of the body concerned. Also included was a simple assessment of gait (either 'normal' or 'abnormal') that we had not previously used. For each combination of posture and specific behaviour, 'The Observer' software was used to calculate the behaviour frequency (f). Changes in the duration of behaviour(s) are extremely difficult to estimate in a practical setting, hence, they would be unlikely to be a useful means of assessing pain. Nevertheless, to maximise the information obtained, both the duration (d) and relative duration (rd; duration/frequency) of time spent performing non-instantaneous events were calculated.

2.5. Statistical analysis

All statistical analyses were conducted using SPSS software (SPSS, Chicago, USA). Calculations of the mean change in body weight from 2 days prior to surgery, to the day following surgery were compared between treatment groups using the one-way analysis of variance procedure (ANOVA). As the animals were growing rapidly, a second analysis was made that attempted to account for this. The average daily growth of each individual (estimated from the 2 days prior to surgery) was added to each calculation for post-surgical weight loss. This 'growth adjusted' estimate of weight loss was then compared between the groups using ANOVA. These body weight analyses excluded animals that received intervention therapy, but included animals in the saline group that received 5 mg/kg carprofen at the end of filming(initial VAS assessment).

Each measurement of the occurrence of each behaviour and/or posture combination (described in Table 1) during the 10 min period following surgery was compared between groups using the two-way ANOVA procedure. For these analyses the 'within subject's factor' was analgesic dosage (mg/kg) and the 'between subject's factor' was drug type (saline, meloxicam or carprofen). These indicated that the data were not normally distributed, thus, they were first log(x + 1) transformed prior to further analysis. To gauge the limits of the assessment technique, identical analyses were
Table 1
Descriptions of the specific behaviours and postures adopted during execution of each act during data collection; a 10 min observation period at ca. 35 min following recovery from anaesthesia

<table>
<thead>
<tr>
<th>Specific behaviour</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back arching (f)</td>
<td>Vertical stretch from crouched position with arched back as seen in felines upon waking. Usually precedes or follows walking during the exploration phase (1st 1-2 min), or at any time thereafter. More often a partial loss of balance during grooming, resulting in lateral lying position from which recovery to balanced crouched posture occurs almost immediately.</td>
</tr>
<tr>
<td>Fall/stagger (f)</td>
<td>Stagger or fall during ambulation—a rapid transition to crouch from high or low rear. Often a partial loss of balance during grooming, resulting in lateral lying position from which recovery to balanced crouched posture occurs almost immediately.</td>
</tr>
<tr>
<td>Twitch (f)</td>
<td>Brief, seemingly spasmodic contraction, usually of the muscles of the back, travelling in an anterior-posterior direction. Posture usually crouch—most often occurs during ‘stop’ in walking or grooming.</td>
</tr>
<tr>
<td>Writhing (f)</td>
<td>Writhing involving lateral contortion of flank abdominal muscles. Posture, usually crouch, during transient break in walking or grooming.</td>
</tr>
<tr>
<td>Walking (f, d, rd)</td>
<td>Quadrupedal ambulatory movement. Posture; crouch.</td>
</tr>
<tr>
<td>Grooming (f, d, rd)</td>
<td>Qualified with region: body (including licking or scratching), ventral (wound licking), head (including paw licking, face washing and head scratching). Posture; usually crouch.</td>
</tr>
<tr>
<td>Stop (f, d, rd)</td>
<td>No ongoing activity. Posture; crouch or lying.</td>
</tr>
</tbody>
</table>

Posture adopted during behaviour execution

| High rear (f, d, rd)  | Fully erect bipedal stance—usually follows walking/exploration away from food hopper and water bottle. |
| Low rear (f, d, rd)   | Partially erect bipedal stance—usually follows walking, any cage region, also during ventral abdominal licking. |
| Crouch (f, d, rd)     | Normal stance (bis- or quadrupedal) for most activities such as walking, running, grooming, etc., back horizontal or angle of <45°. |

Also indicated are the measurement types that were applied to the data: f, frequency; d, duration; rd, relative duration.

Conducted using data obtained during only the first 5 min of the post-surgery observation period. All analyses incorporated an automatic (software) correction of probability level according with the number of comparisons between groups that were made (Bonferroni). Body weight data are quoted as means ± 1 SD. All behaviour data are given as back transformed (geometric) means with 95% confidence intervals.

3. Results

3.1. Body weight changes

There were no significant differences in the mean preoperative weights of the animals in each study group. Mean animal weight was 77 ± 12 g on the day surgery commenced. Animals in the saline group lost significantly more weight (−3.6 ± 1.5 g) in the first 24 h following surgery than animals in groups M0.5 or M2 where either a small loss, or little change in body weight occurred (1.2 ± 2.3, 1.1 ± 1.8 g, respectively). Animals in groups M1, C2.5, C5 and C10 experienced very little body weight change (−0.6 ± 2.5, −0.4 ± 1.3, −0.3 ± 2.1, −0.4 ± 2.3, −0.2 ± 2.4, respectively). Analysis of the ‘growth adjusted’ weight data gave very similar results in respect of treatment associated differences, but returned a larger estimate of weight loss in animals in the saline group (−8 ± 2 g).

3.2. Description of behaviours

Immediately following placement into the observation cage, irrespective of whether analgesics were administered, animals embarked upon a variable duration (30-90 s) exploratory phase during which they traversed between adjacent corners of the cage by slow walking; very rarely running. Intermittent bipedal rearing was recorded during exploration and this was when the animals’ gait was assessed. Abnormal gait was characterised by the animal walking with its back arched, occasionally hopping rather than walking. Following this the rat settled in one corner of the cage, usually below the food hopper or water bottle.

Records of each of the remaining behaviours shown in Table 1 were then made, as animals rarely showed any further exploratory ventures during the remainder of the observation period. The most prominent activities during this relatively quiescent period were grooming and twitching. Grooming occurred with animals in a sitting or more open crouched posture, and was subdivided by the three main regions concerned: head, body and wound. Grooming of the head included frontal paw licking and face washing (these most often occurring in sequence) and also head scratching with either the front or hind paws. Body grooming was scored when the animal was observed to lick or scratch any other region excluding the head and ventral abdomen. The latter was scored as wound licking (since ventral scratching was never observed). Body and/or wound licking almost invariably followed face washing. Bouts of such grooming behaviour were separated by periods when the rats again settled, assuming a more orderly crouched or semi-lying posture. Twitching was a transient, apparently involuntary spasm of the dorsal muscles overlaying the lumbar region of the spine that travelled in an anterior-posterior direction. It was rare, or at least rarely detectable during whole body movements such as grooming or walking.
and most frequently occurred during and following styling. These events occurred so regularly following styling periods, or at the conclusion of other activities (such as attentive head movements), that with experience, the observer could often predict their occurrence. A swallowing type movement of the head and neck also occurred during such times. As a similar transient event, this activity was included in the overall frequency of twitching, but was distinct in appearance.

Staggering/falling was characterised by a total loss of balance resulting in the animal falling onto its side (fall), but was more frequently seen as a partial loss of balance (stagger) during walking, grooming or rearing. Writhing usually occurred either immediately prior to, or in conjunction with many of the major body movements such as grooming, walking or rearing. It was a muscular contraction causing a concavity of the abdominal flank, and although comparatively rare, it was also easily recognisable. It was also observed immediately prior to, or following back arching and/or periods of repetitive twitching. Back arching was perhaps the most easily recognisable of all the activities observed and closely resembled feline stretching behaviour upon waking, and frequently accompanied walking or turning round. Partial back arching was also scored when identified, although most such events involved an obvious arching of the back and clear extension of all four limbs. Often two or more instances were observed in succession. Periods of cessation of behaviour excluding minor postural changes or head movements were defined as ‘stop’, and were recorded in the absence of each of the activities described above.

3.3. Visual analogue scoring

Fig. 1 illustrates the results of the VAS scores for each group conducted by the laboratory animal veterinarian following filming. The data indicated a slight, but non-significant trend towards reduced VAS scores as the dose of each analgesic increased, but large variability between the groups' scores meant that no significant group differences were found (p > 0.1). The VAS scores and clinical examination made later (4–5 h post-op.) indicated that two animals in the saline group required additional treatment, and were given a second injection of carprofen (5 mg/kg s.c.). The rats concerned were allocated scores of 9/10 and 8/10.

3.4. Clinical impression

The notes of the laboratory animal veterinarian described the clinical observations that were used to determine the VAS score. Prior to interference, or at least prior to handling, most animals appeared restless and performed exploratory behaviours. Descriptions of this activity included walking, ‘bunny hopping’ while walking, running and ‘jumpy’ attempts to escape from the assessment cage. Irrespective of the analgesic dosage received, all animals were described as alert, with frequent wound licking. Several of the animals in the saline group, however, were described as ‘quieter’ than normal, with eyes partially closed and on one occasion, showing porphyrin staining around one eye. Contrasting with this, two animals also in the saline group were seen feeding and grooming ‘as normal’. All animals struggled to a greater or lesser extent when handled, with several vocalising when the wound was gently palpated. The frequency of vocalising appeared to have no relationship to the treatment received. The most commonly noted difference between animals in the saline group and those in any of the analgesic treated groups was a general disinterest in surroundings, however, usually only prior to handling. Handling seemed to provoke more generalised exploratory movements described as a greater level of ‘alertness’, and although most were noted to have an abnormal gait while walking, no overall postural differences between groups were appreciable from the descriptions of clinical impression that were given. For the animals that received analgesics pre-operatively, it appeared that the gross level of movement, including more active exploratory behaviours such as climbing, was the main factor responsible for the VAS score allocated by the laboratory animal veterinarian. The two rats that were allocated high scores during the second VAS assessment were given intervention therapy on the basis of descriptive remarks such as ‘vocalised during wound palpation’, eyes closed ‘disinterested in surroundings, ‘alert when disturbed’ and ‘quieter than
expected'. The impression obtained by the laboratory animal veterinarian that these individuals required additional therapy at this stage was supported by the subsequently obtained behavioural pain scores of 6 and 7 made by the score system developer.

3.5. Effects of treatment upon behaviour

Table 2 shows the geometric mean frequency of behaviours that gave the clearest indication of the effects of treatment; both in the first 5 min (Table 2A) and over 10 min of observation (Table 2B). The effects upon individual behaviours could be classified simply; those that increased in frequency and those that declined after analgesic treatment. Significant effects upon each activity were restricted to comparisons between animals given only saline and the analgesic treated groups, and no other between treatment differences were apparent. As the table indicates, significant reductions either in the first 5 min or over the entire 10 min included back arching, falling/staggering, writhing and abnormal gait (hopping or with back partially arched). Conversely, rearing (particularly low rearing) and normal walking behaviour tended to increase following analgesic treatment. Effects were less clear concerning twitching behaviour, and although this tended to occur less in animals in groups M1 and M2 this was not apparent following carprofen treatment. Notably, the frequency of back arching, writhing and fall/stagger was roughly proportional with the time period over which calculations were made, occurring approximately twice as often during 10 min of observation (Table 2B) as in the first 5 min (Table 2A).

The possibility that a behaviour score comprising different behavioural elements could be used for greater clarification of the various effects of treatment was evaluated. Analyses indicated that a behaviour 'formula' could be used (the frequency of writhing + back arching - low rearing). It was found, however, that the relative effects of each treatment could be determined equally accurately, and indeed more practically, simply by pooling behaviours that tended to decline following analgesic treatment (back arching, poor gait, writhing and fall/stagger; henceforth referred to as RED), and also those that increased (rearing, normal gait; INC). All further analyses were individual comparisons between groups using these 'composite' (pooled) behaviour scores.

As shown in Table 3 and Fig. 2A, in comparison with saline treatment, all analgesic doses except M0.5 caused a significant reduction in RED. No significant differences were apparent between individual doses of either carprofen or meloxicam. These effects were also prominent in analyses that used only the first 5 min of each observation session as well as with data obtained over 10 min (Figs. 2A and B). Less significant effects were apparent for INC since only animals that received carprofen showed a significant increase in these activities by comparison with those given saline (Table 3 and Fig. 2B). Again, no differences were apparent between individual drug treatments, but the data obtained over both the first 5 and 10 min were effective in distinguishing animals given saline from those treated with each dose of carprofen.

With only a few exceptions, measures of the duration of the different behaviours were highly, and consistently variable. This meant that comparisons between treatment groups showed no significant differences either in the first 5 min or the total 10 min observation period. The duration measures that did indicate positive effects; being increased in magnitude as the analgesic dosage increased, were relatively obscure and thus of little practical value for inclusion in the pain scoring scheme (e.g., the relative duration of body grooming).

4. Discussion

The results of this study confirm that clear post-operative behavioural changes occur in rats. In our previous studies (Roughan and Flecknell, 2000, 2001), assessments were conducted over a period of at least 8 h following surgery, including several hours during darkness (under red light illumination). This would be of little practical value for assessing pain in individual animals. The complexity of the analyses used in our earlier studies would also limit their use for routine scoring of pain. In the present study, a composite behaviour score was developed that comprised the behaviours identified as pain related in our earlier studies. Observations were carried out under normal lighting conditions and could be applied in 5–10 min. The composite measures comprised activities that either declined following analgesic treatment (writhing, back arching, falling/staggering, poor gait (RED)) and of somewhat lesser importance, those that tended to increase (bipedal rearing, improved gait (INC)). Analyses showed that medium or high doses of meloxicam (1 or 2 mg/kg) caused a significant reduction in RED. All doses of carprofen, including the lowest dose given (2.5 mg/kg) were equally effective, but also effected a significant increase in activities comprising INC.

Due to large variability between groups, one previously robust indicator of analgesic effect (writhing) was not included in the overall calculation of RED. Unlike behaviours that either never occurred, or occurred with very low frequency (e.g., writhing), the comparatively high frequency of twitching in all animals following surgery rendered its use in differentiating between groups impossible within the short time allocated for assessment. Another activity that was prominent in our earlier work, but currently rare, was horizontal stretching. It must be appreciated that when major changes from previous
Table 2

The geometric mean frequency of the individual behaviours that were studied (with confidence intervals; LL, lower limit; UL, upper limit) during either the first 5 min (A) and over the entire 10 min of observation (B) in groups of rats given either saline (0.2 ml/100 g s.c. Saline), melaxenic (0.5, 1 or 2 mg/kg s.c; M0.5, M1 and M2, respectively) or carprofen (2.5, 5 or 10 mg/kg s.c; C2.5, C5 and C10, respectively) 1 h prior to surgery for bladder tumour implantation.

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Abnor. gait: walking with abnormal (back arched) gait; Norm. Gait: normal gait for walking. Significant differences between saline and analgesic groups; † (p <= 0.05), ‡ (p <= 0.01).
Table 3
The geometric mean frequency of composite behaviour scores (with confidence intervals; LL: lower limit, UL: upper limit) compiled by pooling activities that either reduced in frequency (RED: back arching, fall/stagger, writhe, abnormal gait) or increased (INC: normal gait, low and high rearing) following analgesic treatment.

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Data were calculated over the first 5 min (A) and over the entire 10 min of observation (B) in groups of rats given either saline (0.2 ml/100 g s.c; Saline), meloxicam (0.5 or 2 mg/kg s.c; M0.5, M1 and M2, respectively) or carprofen (2.5, 5 or 10 mg/kg s.c; C2.5, C5 and C10, respectively) 1 h prior to surgery. Significant differences between saline and analgesic groups; † (p < 0.05), ‡ (p < 0.01).

Fig. 2. The geometric mean frequency of composite behaviour scores for activities that (A) declined (RED: back arching, fall/stagger, writhe, abnormal gait) or (B) increased (INC: normal gait, low and high rearing) following saline or analgesic treatments. Calculations for the composite scores were pooled using data collected during either the first 5 min or the entire 10 min behavioural observation period. Significant differences between saline and analgesic groups are denoted by; † (p < 0.05), ‡ (p < 0.01).

Studies are incorporated, such as the rat age and strain and also the surgical procedure used, it is almost inevitable that changes in behavioural outcomes will occur. Presently the surgical procedure required a smaller abdominal incision over the bladder, followed by manipulation of, and injection into the bladder wall of a tumour cell suspension. It is debatable whether this procedure provoked a greater or lesser degree of pain compared with that resulting from the 4 cm midline incision used in development of the pain scoring scheme, but nevertheless unsurprising that some activities occurred less, and others more often than previously demonstrated.

The visual analogue scores that were based on clinical impression showed a large degree of variation between treatment groups and as such, proved to be a less accurate
pain scoring method than the behavioural technique. This major difficulty with the VAS approach is that it is highly subjective and based upon clinical impression. This impression is itself prone to large variation due to the prior experience of the assessor. In practise, these assessments would be conducted by animal technicians with varying abilities for recognising pain symptoms, and so the VAS approach was of very limited value.

Our previous work provided convincing evidence that NSAIDs (at least ketoprofen and carprofen) have negligible effects upon the normal behaviour of rats and no effect upon the activities of interest here (Roughan and Fiecknell, 1996, 2000, 2001). As far as we are aware there are also no previously published reports of non-specific effects of these drugs on rat behaviours, thus, the most plausible explanation for the changes in behaviour following laparotomy is post-operative pain, which is reduced by analgesic therapy. It is important to note that this does not imply that the animals were not experiencing pain, however; it does support the view that the analgesic treated rats experienced significantly less pain following surgery than those given only saline.

Meloxicam administered at 0.5 mg/kg was not as effective as 1 or 2 mg/kg. This dosage may therefore be at the margin of the minimum effective rate for this procedure in rats. By contrast, meloxicam at 1 and 2 mg/kg was equally effective in reducing RED; implying that 1 mg/kg may be close to an optimal dosage under these circumstances. Since carprofen was administered at a lower dose than we have previously studied (2.5 mg/kg) but produced a similar reduction in RED as meloxicam (1 and 2 mg/kg) and carprofen (5 and 10 mg/kg) and also improved overall mobility (INC), this might be a more effective drug for alleviating this form of abdominal pain.

Withholding analgesic treatment in the saline control group raised serious ethical concerns, and we attempted to minimise post-surgical pain by administering analgesic immediately after completing the initial assessments. The behaviour of the rats was also re-assessed 4.5 h later to determine any need for intervention analgesia. All animals other than those in the saline group received drugs 1 h prior to commencing surgery. No animals in any of these groups were deemed to require additional therapy following the second VAS/behavioural assessment, yet two animals in the saline group required additional analgesia at that time. All of these saline controls received an injection of carprofen (5 mg/kg) when filming was complete, nevertheless, these animals also showed the greatest post-operative weight loss. It was possible, therefore, that the majority of the rats benefited from our adopted practise of pre-emptive analgesic treatment. This has also been demonstrated in rats undergoing ovariohysterectomy, where pre-operative analgesic treatment has been shown to attenuate behavioural signs of pain more effectively than provision of pain relief post-operatively (Gonzalez et al., 2000).

Since it was possible to distinguish the behaviour of saline from drug treated groups within just 10 min, or in many instances within 5 min, this quantitative approach to pain assessment may be a practical and accurate approach where time constraints apply, or where large numbers of animals are involved. The fact that no individual behaviour was found to be singularly effective in predicting analgesic dosage (and therefore pain severity) might be seen as a practical limitation. However, considering the complexity of rat behaviour and the time period over which analyses were conducted, this was not surprising. This potential limitation is also offset by the fact that since the behaviours were easily recognisable, computer based data acquisition and analysis systems (e.g., The Observer) are not pre-requisites for implementing assessments. This system was used merely to ease data collection and analysis. These computer systems are not suited nor intended for 'on-the-spot' or large numbers of assessments such as in a laboratory animal facility. In such circumstances it would be more appropriate to use one of the many software compatible hand held data acquisition units currently available.

This study has demonstrated that relatively simple to identify components of post-laparotomy behaviour of rats may be used to assess pain. The strain and age of rat and the surgery undertaken differed from that in our previous investigations. Back-arching and writhing seem to be particularly important, and are very similar to postures shown to be prevalent in Sprague–Dawley rats subjected to visceral pain caused by artificial ureteral calculus (Giamberardino et al., 1995) and ovariohysterectomy (Gonzalez et al., 2000). These data therefore encourage further similar studies of the use of these behaviour criteria for assessing abdominal/visceral pain following a range of different types of surgery and in different strains of rat. It is also important to validate the practical application of this pain scoring technique using inexperienced 'blinded' observers. Despite these qualifications, our results suggest that pain scoring can be used to determine analgesic requirements following experimental surgery, and this could have significant effects on the welfare of large numbers of laboratory animals.

Acknowledgements

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References


Prophylactic tolperisone for post-exercise muscle soreness causes reduced isometric force – a double-blind randomized crossover control study

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Abstract

The role of tolperisone hydrochloride, a centrally acting muscle relaxant in relieving painful muscle spasm is recently being discussed. The present study hypothesizes that the prophylactic use of tolperisone hydrochloride may effectively relieve post-exercise muscle soreness, based on the spasm theory of exercise pain. Twenty male volunteers, aged 25.2 ± 0.82 years (mean ± SEM) participated in 10 sessions in which they received oral treatment with placebo or the centrally acting muscle relaxant tolperisone hydrochloride (150 mg) three times daily for 8 days, in randomized crossover double-blind design. Time course assessments were made for pressure pain threshold, Likert's pain score (0–5), pain areas, range of abduction, isometric force, and electromyography (EMG) root mean square (RMS) during maximum voluntary isometric force on day 1 and 6, immediately after an eccentric exercise of first dorsal interosseous muscle, and 24 and 48 h after the exercise. Treatment with placebo or tolperisone hydrochloride was initiated immediately after the assessments on the first day baseline assessments. On the sixth day baseline investigations were repeated and then the subjects performed six bouts of standardized intense eccentric exercise of first dorsal interosseous muscle for provocation of post-exercise muscle soreness (PEMS). Perceived intensity of warmth, tiredness, soreness and pain during the exercise bouts were recorded on a 10 cm visual analogue pain scale. VAS scores and pressure pain thresholds did not differ between tolperisone and placebo treatment. All VAS scores increased during the exercise bouts 2, 3, 4, 5 and 6 as compared to bout 1. Increased pain scores and pain areas were reported immediately after, 24 and 48 h after exercise. Pressure pain thresholds were reduced at 24 and 48 h after the exercise in the exercised hand. Range of abduction of the index finger was reduced immediately after the exercise and was still reduced at 24 h as compared to the non-exercised hand. The EMG RMS amplitude was also reduced immediately after the exercise, but was increased at 24 and 48 h. Isometric force was reduced immediately after the exercise as compared to days 1, 6, and the 24 and 48 h post-exercise assessments with a greater reduction following the tolperisone hydrochloride treatment and the reduction was more in tolperisone group as compared to the placebo group. The results suggest, that the prophylactic intake of tolperisone hydrochloride provides no relief to pain in course of post-exercise muscle soreness but results in reduction in isometric force.

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Keywords: Central muscle relaxant; Randomized clinical trial; Post-exercise muscle soreness; Experimental muscle pain; Isometric force; EMG

1. Introduction

Muscular pains are the most common source of pain encountered in humans (Brattberg et al., 1989), and often tend to become chronic, therefore early treatment and pain management are essential. Intense eccentric exercise is followed by post-exercise muscle soreness (PEMS) and muscle weakness that may mimic the pain and weakness of muscle-damage in disease (Abraham, 1977). Early studies showed that electromyography (EMG) root mean squared amplitude (RMS) increased after the exercise induced muscle pain and these changes reverse on giving stretching treatment (de Vries, 1960, 1990-3801/S30 © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved. doi:10.1016/S1090-3801(02)00145-3