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Pain reduction and pain relief in laboratory animals

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Introduction

If animals are to be used for research, then it is important that any pain or suffering that may result is minimised. Although such a statement rarely provokes disagreement, the practical implementation of such a policy may cause considerable difficulties. Minimising pain and suffering requires careful consideration of all aspects of animal husbandry and experimental methodology, and often requires the introduction of specific measures to alleviate pain. Unfortunately, at present we are unable to assess pain and suffering accurately in animals. If we cannot assess pain, then we cannot assess the efficacy of any analgesic therapy and so cannot select the most appropriate treatment regimen. The problems of pain assessment are dealt with elsewhere, this paper aims to highlight the circumstances where pain relief may be required and to discuss the methods which are currently available for providing analgesia.

Pain and experimental procedures

Different experimental procedures may produce different types of pain, for example acute, momentary pain during venepuncture; more long-lasting acute pain following surgical procedures and chronic pain, such as that caused by adjuvant induced arthritis. Different strategies for the reduction and relief of pain are required in these different circumstances. In some instances, pain can be relieved using analgesics. In other circumstances, when analgesic therapy is either inappropriate or contraindicated because of the requirements of the experimental design, attention must be given to methods of reducing the number of animals used, reducing the duration of any pain which they experience, and refining experimental techniques so that the minimum of pain is caused.

Compounds available for pain refief

Opioids

The opioids are the most potent systemically active analgesics, and are the compounds which are most widely used to control post-operative pain. They are also used extensively as components of anaesthetic regimens to provide analgesia during surgery. Opioids are classified according to the receptors at which they act, (μ, k, δ and σ) and whether they are an agonist or an antagonist at these receptors. Morphine, the best known member of this group of analgesics is a μ agonist. Opioids produce good analgesia, but the duration of action of some compounds is too short to allow them to be used to control post-operative pain. If it is practicable to administer analgesics by continuous infusion, then the shorter-acting opioids can be used successfully to provide prolonged periods of pain relief.

Side effects of opioids

Research workers are often reluctant to administer opioids because of a fear of their undesirable side-effects. These concerns generally arise either as a result of discussions with medically qualified colleagues or from reading human anaesthetic texts, or after consulting older veterinary anaesthesia text-books. Much of the information in older text-books concerning the side-effects of opioids in animals is inaccurate, and has often been derived by extrapolation from man. Similarly, uncritical extrapolation, based on the problems which may occur when opioids are administered to man, generally results in an exaggeration of the importance of undesirable side-effects in animals.

Opioids do cause respiratory depression, but the degree of respiratory depression in animals is considerably less than that encountered in man. Although care must still be exercised when administering opioids, respiratory depression is rarely of clinical significance. Severe respiratory depression can be produced following repeated administration of high doses of μ opioids such as morphine and pethidine, or if μ opioids are administered in the immediate post-anaesthetic period following the use of neuroleptanalgesic anaesthetic regimens such as fentanyl/fluanisone ("Hypnorm"). If neuroleptanalgesics are used to provide anaesthesia, or if μ opioids such as fentanyl or alfentanil are used as part of a balanced anaesthetic regimen, then mixed agonist/antagonist opioids such as nalbuphine or buprenorphine should be used to provide post-operative analgesia. These compounds have been shown to reverse any residual respiratory depression caused by the pure μ agonist opioid (e.g. fentanyl) but also to provide analgesia (*De Castro & Viars* 1968, *Robertson & Laing* 1980, *Flecknell et al.* 1989).

Opioids in man may also cause constipation, nausea and urinary retention. The importance of these effects in animals is generally small and very few clinical problems have been encountered by the author over a fourteen year period, during which time a wide range of opioids have been administered to many different species of laboratory animals.

Opioids in man are often withheld in cases of cranial injury. This has led to the assertion that these analgesics should not be administered to animals following cranial surgery. This assertion is incorrect. In man, opioids cause respiratory depression which in turn results in hypercapnia. The hypercapnia produces cerebral vasodilation, an increase in cerebral blood flow, and consequently a rise in intracranial pressure. In addition, the changes in pupil diameter and level of consciousness which can arise following administration of opioids can hinder clinical assessment of patients with head injury (*Alexander & Hill* 1987). In animals, since the degree of respiratory depression produced by most opioids is relatively minor, and little attention is given to clinical assessment of consciousness following cranial surgery, there seems no reason to withhold analgesia following cranial surgery. The author has administered opioids following craniotomy in non-human primates, rabbits, rats and pigs and has not encountered any problems.

Finally, it is often stated that opioids should not be administered to animals which might develop cardiovascular failure. Morphine, administered by rapid i/v injection, causes histamine release, vasodilation, and a fall in blood pressure in the dog. Other opioids have little or no effect on histamine release and have minimal effects on the cardiovascular system (*Pircio et al.* 1976, *Bovill* 1987, *O'Hair et al.* 1988).

Opioids can be administered repeatedly to control pain, but tolerance may develop, usually after several days, resulting in an inadequate degree of analgesia. This limits the use of opioids in the control of long-lasting pain, although recent studies have suggested that continuous administration of buprenorphine to rats in their drinking water can provide pain relief for several weeks (*Kistler* 1988).

Obviously, there will be occasions where opioids cannot be administered because of a specific interference with a research protocol. A commonly encountered example is in studies of some central nervous system receptors, where opioid administration can produce long-lasting changes to receptor responses. In these circumstances other agents should be used to produce analgesia, and these alternatives are discussed below.

Non-steroidal anti-inflammatory drugs (NSAID's)

Non-steroidal anti-inflammatory drugs are generally less potent analgesics than the opioids, but some of the newer agents can

provide quite effective pain relief. A range of NSAID's are available, and these are listed, together with suggested dose rates, in Tables 1 and 2. These dose rates are based on published data concerning the efficacy of these agents in analgesiometric tests. NSAID's also have a range of side effects, the most important of these being the production of gastro-intestinal tract irritation and at high doses, mucosal haemorrhage. NSAID's can also cause bone marrow depression. Their widespread effects on prostaglandins and other mediators of inflammation can limit their use in some types of experimental studies.

Local anaesthetics

Local anaesthetics completely abolish sensation and motor control of a body area. They can be injected locally around a wound site, or can be used to block specific nerve tracts. Short-acting agents such as lignocaine are often used to provide analgesia for surgical procedures. Longer-acting agents such as bupivacaine are more suitable for providing post-operative pain relief. Local anaesthetics can cause a number of side-effects, for example cardiovascular and central nervous system disturbances, if excessive dose rates are administered post-operatively (*Covino* 1987).

Practical problems

Method of administration and duration of action.

The majority of analgesics have a duration of action of less than 4 hours. If prolonged pain relief is required, then this will necessitate repeated administration of analgesics, usually by injection. This can cause practical difficulties in some research units. It is, however, important to recognise the limitations of single injections of analgesics, and develop methods of providing effective analgesia for whatever period is necessary. If compounds must be administered every few hours, then staff should be prepared to attend the animals day and night, in order to provide effective therapy. Alternatives are to administer the agents by continuous infusion, or by administration in food or water. Small, battery operated infusion pumps can be attached to larger animals and these can continuously infuse analgesics either via a previously implanted intravenous catheter, or more simply by inserting a butterfly needle subcutaneously. Small animals require the use of a harness and tether arrangement for analgesic administration, and this may present some practical difficulties if large numbers of animals require treatment. Administration in the food or water is a very attractive option, as it is simple and inexpensive, and can be applied to large numbers of animals. Self administration has been shown to be effective in an experimental arthritis model, where rats drank more water which contained an anti-inflammarory agent (*Colpaert et al.* 1980). It is important to note that rats (and other species), reduce their food and water consumption following surgery (*Flecknell & Liles* 1991 and 1992), and so calculations of dose rates may be inaccurate. It has also been shown that opioids can be administered for long periods in this way (*Kistler* 1988), although no trials in animals which have undergone surgery have been carried out.

Interaction with experiments

When trying to introduce an analgesic regimen as part of a program of refinement of animal experiments, a common problem that is encountered is the concern of research workers that the use of analgesics may interfere with their experimental protocol. In many instances, this concern is completely unfounded. In other circumstances, there will be clear contra-indications to the use of one particular class of analgesics. If this occurs, then other means of providing pain relief should be established. Two additional points should be considered when discussing the use of post-operative analgesics. Following surgical procedures mammals undergo a stress response. The

Table 1. Suggested dose rates of analgesics in laboratory animals. Dose rates are based upon data from analgesiometry and from clinical experience. (*Bjornson et al.* 1988, *Boothe* 1989, *Cominelli et al.* 1990, *Flecknell* 1984, *Flecknell & Liles* 1990, *Jenkins* 1987, *Koch & Dwyer* 1988, *McKellar* 1989, *Otterness & Gans* 1988).

	Mouse	Rat	Guinea Pig	Rabbit
Aspirin	120 mg/kg orally 4 hourly	100 mg/kg orally 4 hourly	–	–
Buprenorphine	0.05-0.1 mg/kg s/c 8-12 hourly	0.01-0.05 mg/kg s/c 8-12 hourly	0.05 mg/kg s/c 8-12 hourly	0.01-0.05 mg/kg s/c, i/v 8-12 hourly
Butorphanol	1-5 mg/kg s/c 4 hourly	2.0 mg/kg s/c 4 hourly	–	0.1-0.5 mg/kg i/v 4 hourly
Codeine	60-90 mg/kg orally, 20 mg/kg s/c 4 hourly	60 mg/kg s/c 4 hourly	–	–
Flunixin	2.5 mg/kg s/c, i/m ?12 hourly	1.1 mg/kg s/c, i/m 12 hourly	–	1.1 mg/kg s/c, i/m ?12 hourly
Ibuprofen	7.5 mg/kg orally ?4 hourly	10-30 mg/kg orally ?4 hourly	10 mg/kg i/m ?4 hourly	10-2 mg/kg i/v ?4 hourly
Morphine	2-5 mg/kg s/c 2-4 hourly	2-5 mg/kg s/c 2-4 hourly	2-5 mg/kg s/c, i/m 4 hourly	2-5 mg/kg s/c, i/m 2-4 hourly
Nalbuphine	4-8 mg/kg i/m ?4 hourly	1-2 mg/kg i/m 3 hourly	–	1-2 mg/kg i/v 3-4 hourly
Paracetamol	300 mg/kg orally 4 hourly	100-300 mg/kg orally 4 hourly	–	–
Pentazocine	10 mg/kg s/c 3-4 hourly	10 mg/kg s/c 3-4 hourly	–	5 mg/kg i/v 2-4 hourly
Pethidine	10-20 mg/kg s/c, i/m 2-3 hourly	10-20 mg/kg s/c, i/m 2-3 hourly	10-20 mg/kg s/c, i/m 2-3 hourly	10 mg/kg s/c, i/m 2-3 hourly

metabolic and hormonal changes associated with this response persist for a variable period, ranging from 24–48 hours to several days. It is usually necessary to delay a study in an animal that has undergone surgery to allow this stress response to subside. In these circumstances, the side-effects of analgesics administered immediately post-operatively will also have largely dissipated. In certain circumstances, control of post-operative pain may reduce the surgical stress response. In man, the provision of effective analgesia has been shown to reduce post-operative morbidity and speed recovery (*Kehlet* 1978). Pain itself may have undesirable and unpredictable consequences, and may represent an uncontrolled experimental variable. Controlling pain by administering analgesics may reduce this variability, as well as having clear benefits in terms of animal welfare.

Table 1. (Continued).

	Cat	Dog	Pig	Sheep	Primate
Aspirin	–	10 mg/kg orally 6 hourly	–	–	20 mg/kg orally 6 hourly
Buprenorphine	0.005-0.01 mg/kg s/c, i/v 8-12 hourly	0.01-0.02 mg/kg s/c i/m, i/v 8-12 hourly	0.005-0.01 mg/kg i/m 8-12 hourly	0.005-0.01 mg/kg 4-6 hourly	0.01 mg/kg i/m, i/v 8-12 hourly
Butorphanol	0.4 mg/kg s/c 3-4 hourly	0.4 mg/kg s/c or i/m 3-4 hourly	–	–	–
Codeine	–	0.25-0.5 mg/kg orally, 6 hourly with Paracetamol	–	–	–
Flunixin	1 mg/kg s/c daily for up to 5 days	1 mg/kg orally daily	?1 mg/kg s/c daily	?1 mg/kg s/c daily	–
Ibuprofen	–	5-10 mg/kg orally 24-48 hourly	–	–	–
Morphine	0.1 mg/kg s/c 4 hourly	0.5-5.0 mg/kg s/c, i/m 4 hourly	up to 20 mg total dose i/m 4 hourly	10 mg t.d s/c, i/m 4 hourly	1-2 mg/kg s/c, i/m 4 hourly
Nalbuphine	1.5-3.0 mg/kg i/v 3 hourly	0.5-2.0 mg/kg s/c, i/m 3-8 hourly	–	–	–
Paracetamol	Toxic	10-20 mg/kg orally 6 hourly with Codeine	–	–	–
Pentazocine	8 mg/kg i/p 4-6 hourly	2 mg/kg i/m 4 hourly	2 mg/kg i/m 4 hourly	–	2-5 mg/kg i/m 4 hourly
Pethidine	10 mg/kg s/c, i/m 2-3 hourly	10 mg/kg i/m 2-3 hourly	2 mg/kg i/m 4 hourly	200 mg total dose i/m 4 hourly	2-4 mg/kg i/m 3-4 hourly

Recommendations

Acute, transient pain

The pain associated with procedures such as venepuncture or intramuscular injection can be reduced by thorough training of the personnel involved. Expert handling and restraint reduces fear and anxiety and may consequently reduce the degree of pain perceived by the animal. The pain associated with venepuncture can be eliminated by prior application of local anaesthetic cream (EMLA), to the skin over the blood vessel (*Flecknell et al.* 1990). Infiltration of local anaesthetic can also allow procedures to be carried out without causing pain. If there is any doubt as to the degree of pain that may be caused, then general anaesthesia should be used to completely abolish pain sensation. For example, the procedure of inoculation of material into the foot-pad is both technically easier to undertake and much less stressful to the animal, if carried out under general anaesthesia.

Table 2. Availability of analgesics in Scandinavia.

Country	Approved Name	Trade Name	Manufacturer
Acetaminophen (UK)			
S	paracetamol	Alvedon	Astra
		Lemsip	Reckitt & Colman/Meda
		Panodil	Sterling-Winthrop
		Reliv	ACO
DK	paracetamol	Pamol	DAK
		Panodil	Winthrop
		Pinex	A.L.
		Setamol	Pharmacia
N	paracetamol	Panodil	Winthrop
		Paracet	WIFA
		Paracetamol	Hydro Pharma
		Pinex	A.L.
SF	–	–	–
Aspirin (UK)			
S	acetylsalicylsyra	Albyl	Leo
		Aspirin	Bayer
		Bamyl	Hässle
		Dispril	Reckitt & Colman/Meda
		Magnecyl	ACO
DK	acetylsalicylsyre	Acetard	Benzon Pharma
		Acetylsalicylsyre	DAK
		Albyl	Leo
		Aspirin	Bayer
N	acetylsalicylsyra	Acetylsalicylsyra	Hydro Pharma
		Albyl	Nicomed Pharma
		Dispril	Reckitt & Colman
		Globentyl	Nicomed Pharma
		Globoid	Nicomed Pharma
		Magnyl	Hydro Pharma
		Novid	Nicomed Pharma
SF	Asetyyli-salisyylihappo	Acetard	Benzon Pharma
		Acetylsalic.	Leiras
		Alka-Seltzer	Miles
		Asapor	Orion
		Aspirin	Bayer
		Disperin	Orion
		Medisyl	Leiras
		Primaspan	Lääkefarmos
Buprenorphine (UK)			
S	buprenorfin	Temgesic	Reckitt & Colman
DK	buprenorfin	Temgesic	Reckitt & Colman
		Anorfin	GEA
N	buprenorfin	Temgesic	Reckitt & Colman
SF	buprenorfiini	Temgesic	Reckitt & Colman
Butorphanol (UK)			
Not available	"Torbutrol"available in UK from C-Vet.		

Table 2. (Continued).

Country	Approved Name	Trade Name	Manufacturer
Codeine (UK)			
S	kodein	Kodein	Kabi Pharmacia
DK	codein	Kodein	DAK
N	–	–	–
SF	–	–	–
Morphine (UK)			
S	morfin (-hydro-klorid	Morfin Morfin Special	Kabi Pharmacia Karo Bio Medica
DK	morphin	Contalgin Morfin	Pharmacia DAK
N	morfin	Dolcontin Epimor Morfin Morfin Epidural	Pharmacia Astra Hydro Pharma Hydro Pharma
SF	morfiinihydro-kloriidi morfiinisulfaatti	Morphin Dolcontin	Leiras Kabi Pharmacia
Nalbuphine (UK)			
Not available	"Nubain" available in UK from DuPont		
Pentazocine (UK)			
S	pentazocin	Fortalgesic	Sterling-Winthrop
DK	pentazocin	Fortral	Winthrop
N	pentazocin	Fortralin	Winthrop
SF	pentasosiini	Fortralin	Medipolar
Pethidine (Meperidine) (UK)			
S	petidin (-hydro-klorid)	Petidin	Kabi Pharmacia
DK	pethidin	Petidin	DAK
N	petidin	Petidin	Hydro Pharma
SF	petidiinihydro-kloridi	Petidin	Leiras

Acute, longer-lasting pain

Post-operative pain is the major cause of longer periods of acute pain, although pain may also arise because of other types of tissue trauma, for example injection of irritant material into body tissues or body cavities. Whenever possible, pain should be controlled by the administration of opioids. For post-operative pain relief, opioids should be administered while the animal is still anaesthetised, so that the analgesic is acting effectively before pain is perceived. It has been demonstrated in man that this reduces the degree of pain and reduces the requirement for analgesics (*McQuay et al.* 1988).

Generally speaking, opioids should be administered for 24–48 hours, but the period of treatment should be adjusted depending upon the severity of the procedures and the animals' response to treatment. Care must be taken when interpreting the animal's responses, since recent studies have shown that administration of high doses of buprenorphine to normal rats can produce a reduction in food intake (*Flecknell & Liles* 1992). Post-operative inappetence could

therefore result either from pain, or because opioids were administered to an animal which was no longer experiencing pain.
Because it has a prolonged duration of action, buprenorphine is recommended for routine use, administered intraoperatively and then at 8 hour intervals. Buprenorphine may, on occasion, fail to control very severe pain, and in these circumstances a pure μ agonist such as morphine should be administered. Slow release preparations of morphine are available, but no controlled trials of their use in animals appear to have been published. If opioids are contra-indicated then the surgical incision should be infiltrated with bupivacaine. The local anaesthetic should be infiltrated along the muscle layers and under the skin, so that all of the sensory innervation to the wound is blocked. If possible, a non-steroidal anti-inflammatory drug should be administered about 6 hours post-operatively to provide pain relief when the bupivacaine nerve block is no longer effective.

Chronic pain

Chronic pain in experimental animals is difficult to control. If the experimental design permits it, then repeated administration of NSAID's can be used to alleviate pain. Prolonged administration of NSAID's can result in undesirable side effects, but providing that low doses are used, these should not be clinically significant. The side effects may, however, interfere with the progress of the experiment. It is most convenient to administer NSAID's in the drinking water, and by monitoring water intake, an appropriate dose can be calculated. Opioids can be used, and although tolerance may develop, it has been demonstrated that a prolonged analgesic effect can be achieved using buprenorphine administered in drinking water (*Kistler* 1988).
Since longer term administration of analgesics may interfere with an experimental protocol, it is important to monitor carefully animals that may be experiencing chronic pain. If the degree of pain varies, it may be possible to control periods of acute pain by intermittent administration of analgesics. Careful selection of end-points for the study, reduction of the length of the study to the minimum possible period, and reduction of the number of animals used will also reduce the overall amount of pain suffered.

Conclusions

There is currently considerable interest throughout the research community in methods of assessing and alleviating pain in laboratory animals. Our understanding of pain in animals is developing rapidly, and it is hoped that further research will lead to improvements in our ability to alleviate pain. One area of investigation that urgently requires additional efforts is the establishment of controlled clinical trials of different analgesic regimens. In man, a wide range of analgesics have been evaluated following virtually every surgical procedure that is undertaken. Comparable trials in animals are more difficult to complete because of the uncertainties of pain assessment in species other than man, but there is considerable scope for a concerted effort in this field. The improved morbidity and reduced periods of hospitalisation which have been reported in man following advances in post-operative analgesia, suggest that better pain relief for animals would result both in improvements in animal welfare and more defined and reliable research data.

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