ELSEVIER

Pharmacology, Biochemistry and Behavior 73 (2002) 521–528

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Observer-blinded comparison of two nonopioid analgesics for postoperative pain in piglets

L. Reyes[a,b], K.D. Tinworth[a], K.M. Li[b], D.F. Yau[c], K.A. Waters[a,d,*]

[a]*Department of Medicine, The University of Sydney, Room 206, Blackburn Building DO6, Sydney, NSW 2006, Australia*
[b]*Department of Pharmacology, The University of Sydney, Sydney, Australia*
[c]*Department of Biochemistry, Royal Prince Alfred Hospital, Sydney, Australia*
[d]*Department of Paediatrics and Child Health, The University of Sydney, Sydney, Australia*

Received 7 December 2001; received in revised form 13 March 2002; accepted 29 March 2002

Abstract

Piglets are popular for studies of respiratory and cardiovascular function, but opioid analgesics are contraindicated in these studies because of central nervous system depression. We evaluated two nonopioid analgesics for postoperative pain relief following implantation of a central arterial catheter via an inguinal incision. Animals were randomly assigned to paracetamol-treated ($n=8$, rectal suppositories, 100 mg/kg) meloxicam-treated ($n=8$, 1 mg/kg meloxicam via the catheter) or untreated control group ($n=8$, placebo suppositories and normal saline). Additional controls received paracetamol or meloxicam, without pain ($n=6$ for both groups). Behavioral and physiological assessments, and blood sampling were undertaken at nine timed intervals until 24 h after surgery. Multifactorial numerical rating scale (NRS), behavioral and physiological pain scores (PPS) decreased over time for all groups ($P<.001$). On NRS and behavioral criteria, meloxicam was significantly better than paracetamol ($P<.001$), and both were better than control ($p<.001$ for each). Physiological parameters discriminated between the control and analgesia-treated groups, but not between paracetamol and meloxicam. Preliminary pharmacokinetics, determined by isocratic high-performance liquid chromatography (HPLC), revealed no difference in the half-life of paracetamol (2.5 ± 0.3 h) vs. meloxicam (3.4 ± 0.4 h). Paracetamol and meloxicam provided effective postoperative analgesia in piglets, with meloxicam superior to paracetamol on behavioral criteria.

Keywords: Analgesia; Nonopioid; Meloxicam; Paracetamol; Pain

1. Introduction

The use of animals in research is widespread. However, research protocols may cause pain and distress in animals, especially those undergoing experimental surgery. Despite the push for advancement of animal welfare (Association of Veterinary Teachers and Research Workers, Universities Federation for Animal Welfare, 1989; Flecknell, 1994; Morton and Griffiths, 1985), it is still not a routine practice to provide analgesia to animals especially after what is deemed minor surgery (Flecknell et al., 1999). Opioid analgesics are precluded in many physiological studies because they cause central nervous system depression. Nonopioid analgesics are preferred in this situation, but there is a paucity of data regarding their use in the postoperative setting.

Pain assessment in animals is challenging and the use of behavioral and physiological scores can quantify the severity of pain and distress. A numerical rating scale (NRS), for example, uses numbers to measure increasing intensities of pain. A variation of the NRS is the multifactorial NRS (Firth and Haldane, 1999), which uses different behavioral and/or physiological criteria that are independently given a numerical score based on observed changes following the introduction of the pain stimulus. Behavioral parameters that change in animals in response to pain include vocalisation, lameness/mobility, aggression, posture and restlessness (Conzemius et al., 1997; Firth and Haldane, 1999; Flecknell, 1994; Mathews et al., 1999; Morton and Griffiths, 1985; Smith et al., 1996), while physiological parameters include autonomic nervous system responses, particularly changes in cardiovascular and respiratory function (Short, 1999). Heart rate (HR), blood pressure (BP) and respiratory

* Corresponding author. Department of Medicine, The University of Sydney, Room 206, Blackburn Building DO6, Sydney, NSW 2006, Australia. Tel.: +61-2-9351-5165; fax: +61-2-9550-3851.
E-mail address: kaw@mail.med.usyd.edu.au (K.A. Waters).

0091-3057/02/$ – see front matter
PII: S0091-3057(02)00820-1

rate (RR) all increase with pain, while breath efforts become shallow.

Paracetamol is an analgesic and an antipyretic agent with documented efficacy in alleviating postlaparotomy pain in dogs (Mburu et al., 1988). It is said to inhibit pain by activating the spinal serotonergic system. At high concentrations, it may also inhibit the cyclooxygenase (COX) enzyme. Paracetamol is widely used in humans as a postoperative analgesic. However, recommended therapeutic doses in animals range from 12.5 mg/kg in dogs to 200 mg/kg in rats (Dobromylskyj et al., 2000; Liles and Flecknell, 1992). There is no recommended dose for piglets.

Meloxicam is a relatively new, nonsteroidal antiinflammatory drug (NSAID) that inhibits the COX enzyme, and thus the production of prostaglandin and other inflammatory mediators. The prostaglandins sensitise pain receptors, thus, lowering the pain tolerance threshold. Meloxicam is relatively specific for the COX-2 isoform, which is believed to play the major role in inflammation. This avoids adverse side effects due to inhibition of the housekeeping functions of COX-1, such as maintenance of renal and gastric mucosa and regulation of blood flow. The therapeutic doses recommended for meloxicam range from 0.1 mg/kg in cats to 1 mg/kg in rats, again with no recommendations available for piglets.

This randomised study used observer-blinded observation to compare the analgesic effects of paracetamol and meloxicam for the treatment of postoperative pain in piglets. Our hypothesis was that both analgesics would relieve pain relative to an untreated control group, but meloxicam would provide better analgesia because of its longer half-life.

2. Materials and methods

The study was a placebo-controlled, observer-blinded study, utilising a total of 30 piglets. Ethical approval was obtained from the Animal Care and Ethics Committee of the University of Sydney.

2.1. Animals

Mixed-breed miniature piglets were transported from a commercial piggery on day 4.2 ± 1.1 (mean ± S.E.M.) after birth, then housed in an animal facility in groups of up to three, furnished with soft bedding, toys, heat lamps and sow milk substitute ad libitum. The room was maintained at thermoneutral temperature (25–30 °C) and cleaned daily. The animals (16 male, 14 female) were aged between 8 and 20 days and weighed, on average, 1.65 ± 0.08 kg (0.95–2.23 kg) on the day of surgery. All animals underwent the procedures used for behavioral and physiological scoring assessment on a daily basis, for a minimum of 5 days prior to surgery. This provided baseline scores, familiarised the animals with the observer and familiarised the observer with the behavior of untreated animals.

2.2. Surgery

Untreated control, paracetamol- and meloxicam-treated piglets underwent surgery for the implantation of a central arterial catheter. Aseptic surgery was undertaken under general anaesthesia at age 12.7 ± 3.4 days. The piglets breathed spontaneously throughout the anaesthetic and HR was monitored continuously using surface electrodes. Anaesthesia was induced using a face mask delivering 1–3% isoflurane with 30–50% nitrous oxide in O_2, then continued throughout surgery, with anaesthesia adjusted according to the level of spontaneous respiratory efforts and HR. An arterial catheter was placed in the descending aorta via the right femoral artery, tunnelled subcutaneously to exit on the ipsilateral flank, and protected in the pocket of jackets that were worn from the time of surgery. Antibiotic therapy (cephalexin, 15 mg/kg) was commenced intraoperatively and continued daily for 2 days after surgery.

2.3. Analgesia

Analgesia commenced during the anaesthetic. All animals received a suppository, and those with a catheter received an injection via the catheter. Active suppositories contained paracetamol (Panadol, Smith-Kline, Australia; 100 mg/kg rectal suppository), and meloxicam was delivered directly after catheter implantation (Metacam, Boehringer-Ingleheim, Germany; 1 mg/kg via the catheter). A placebo suppository was inserted for all animals in the meloxicam group. A placebo injection of normal saline was given to all animals in the paracetamol group.

The paracetamol dose chosen for this study was 100 mg/kg. This was extrapolated from prior studies cited above, in combination with our own clinical experience using 100-mg/kg paracetamol in the postoperative setting. From the literature, we selected a high dose (1 mg/kg) of meloxicam with the goal of achieving effective analgesia.

The implanted catheter was used for all postoperative blood sample collections. At the end of the study, all animals were killed painlessly with an overdose of pentobarbitone.

2.4. Analgesia (pain free) controls

Six animals were studied to examine the effects of the analgesic drugs, in a crossover design. These animals underwent identical procedures to the study groups including acclimatisation prior to the study day, anaesthesia, random assignment to a drug group and observation for 24 h after the anaesthesia. These animals remained under anaesthesia for 20 min, during which time they received a suppository and a subcutaneous injection, one active and one placebo according to their assigned protocol. However, no skin incision was made, no catheter was implanted, no sutures were inserted and no blood samples were taken in the postoperative period. Each animal was randomly

assigned to receive paracetamol or meloxicam. The placebo injection comprised normal saline. After a 3-day washout period, the same six animals underwent a second study at which time they received the alternative drug. The crossover design was chosen to minimise the number of animals required for this component of the study.

2.5. Pain assessment

A multifactorial NRS was used to provide behavioral and physiological scores, combining observation of behavior and measurement of the physiological responses of the animals. The assessment method used was a modification of previously published methods and recommendations by Firth and Haldane (1999) and Morton and Griffiths (1985). Observations were made at 0.5, 1, 1.5, 2, 3, 4, 5, 10 and 24 h postoperatively. Behavioral parameters included lameness, isolation, posture, vocalisation, aggression, restlessness, agitation and playfulness. Behavior was initially scored during spontaneous activities, and then in response to pressure on the wound as the animals were suspended on a custom-made sling. Physiological measurements were made while the animals were on the sling, and included temperature, HR, RR and BP. Core temperature was measured rectally with a digital thermometer. A pulse oximeter was used to measure HR on a forelimb. Observation of the animal's thoracic movements was used to measure RR, while BP was measured using a sphygmomanometer attached to the arterial catheter. Tables 1 and 2 detail the individual behavioral and physiological criteria, respectively, and their assigned scores, as used in the NRS. These scores were recorded at observation time, as well as a global NRS score based on the observer's overall impression of the animal's pain/distress at the time of assessment.

Adverse drug reactions were evaluated by observation (e.g., skin rashes) and blood testing at 10 h for liver and kidney function tests. A single observer completed the assessments of all animals to avoid interobserver variability.

2.6. Analgesic control groups

The analgesic control groups underwent the same behavioral and physiological assessment protocol as the surgery groups, however, BP could not be recorded due to the absence of the arterial catheter. For comparison of physiological scores between animals with and without catheters, the BP scores were subtracted in those for whom it had been recorded.

2.7. Blood collection

Blood samples of 2 ml each were collected from the catheter at 10 min, 0.5, 1, 2, 3, 5, 10 and 24 h after surgery into 5-ml heparin-containing tubes. The blood was centrifuged at 3500 rpm for 5 min to separate the plasma, which was collected in 2-ml Eppendorff tubes, then stored at − 20 °C until the time of analysis.

2.8. Drug analysis

The paracetamol assay used in this study was a modification of that used for toxicological assessments in the Department of Pharmacology, University of Sydney. Briefly, drug was extracted from plasma using a Waters Oasis HLB extraction cartridge (Waters, Milford, USA) and eluted with methanol (Waters Pharmaceutical Application Notebook, Year 2000, Vol. 1, p. 4). The methanol was then evaporated to dryness and reconstituted in the mobile phase.

Table 1
Multifactorial NRS criteria and scores * (behavioral)

Criteria	Score	Descriptor	Criteria	Score	Descriptor
Lameness	1	slight limping	Aggression	1	quite friendly
	2	moderate limping, slow movements		2	tendency to move away
	3	a lot of limping, small movements		3	biting and screaming when touched
	4	immobile or severe limping		4	biting, screaming without being approached
Restlessness	1	cannot sleep properly	Posture	1	slightly hunched back
	2	poor wake/sleep times, moving often		2	protecting affected limb
	3	frequent pacing, momentary stops		3	kneeling position and hardly moving
	4	continuous pacing around the pen		4	immobile and kneeling position
Vocalisation	1	low volume, occasional cries	Isolation	1	positions away from mates
	2	low volume, continuous cry		2	occasionally moves away from mates
	3	high volume, quite frequent cries		3	keeps moving away from mate
	4	screaming that lasts a long time		4	screams and runs away from mate
Appearance	1	slightly dilated pupils	Sling time (time to settle on sling)	1	doubled over baseline
	2	dilated pupils		2	increased by 5–10 times
	3	dilated pupils with frequent salivation		3	over 10 times increase
Agitation	1	slightly moves away when approached	Posture	1	plays for a while
	2	jumps up and down when approached		2	no interest in toys or mate in the pen
				3	does not play or move much

Adapted from Firth and Haldane (1999) and Morton and Griffiths (1985).

Table 2
Multifactorial NRS criteria and scores (physiological)

Criteria	Score	Descriptor
Temperature	1	any change of >1 °C
RR	1	20–50% increase
	2	51–100% increase
	3	>100% increase
HR	1	20–50% increase
	2	51–100% increase
	3	>100% increase
BP	1	20–50% increase
	2	51–100% increase
	3	>100% increase

A Merck LiChrospher 100 RP-18 (125 × 4 mm, 5-μm particle size) column was used, coupled with its own LiChrCART (4 × 4 mm, 5-μm particle size) precolumn. The isocratic mobile phase consisted of 1.75 mM phosphoric acid (pH 3.0), methanol and acetonitrile in the ratio 88.5:7.5:4.0 (v/v). The flow rate was 1.1 ml/min and UV detection was made at 244 nm under ambient temperature. Paracetamol concentrations were determined using peak area ratio from internal standard theophylline (Sigma Laboratories, Sydney). The relative standard deviation (RSD) for inter- and intraassay variations ($n=6$ for both) were <10% for paracetamol concentrations between 100 ng/ml and 2 μg/ml. The assay recovery rate was 93%.

Meloxicam was assayed using a published reversed-phase HPLC method (Velpandian et al., 2000). Briefly, drug was extracted from the plasma with internal standard, piroxicam (Sigma Laboratories) by the addition of 1 M HCl and chloroform. Chloroform was evaporated and the dry samples were reconstituted with the mobile phase. The analytical column was a steel column (150 × 3.5 mm) packed with Partisil 5 ODS-3 (Whatman). The isocratic mobile phase consisted of 50 mM potassium hydrogen orthophosphate (in water) pH 3.8, methanol and acetonitrile in the ratio 5:4:1 (v/v). The machine was operated at an ambient temperature of 30 °C and the flow rate was 0.5 ml/min. UV detection was at 364 nm. Meloxicam concentrations were determined using peak height ratio from the internal standard. Drug recovery was found to be 88%, with inter- and intraassay variations ($n=6$ for both) of <10% for meloxicam concentrations between 0.65 and 5.2 μg/ml.

2.9. Data analysis

All data were compiled in Excel 5 (Microsoft). Statistical analyses were performed using Analyse-it for Microsoft Excel, version 1.62. The half-life of paracetamol and meloxicam were calculated using Prism, version 3 (GraphPad Software). The data presented are mean ± S.E.M., unless otherwise specified. All postoperative physiological measurements were normalised to baseline (preoperative) values. Postoperative behavioral and physiological scores were compared using two-way analysis of variance (two-way ANOVA) to assess changes between groups and across time. A P value of <.05 was taken as statistically significant. Post-hoc analyses were performed using least significant difference (LSD).

3. Results

3.1. Behavioral and physiological scores

3.1.1. Global pain score (GPS)

The highest GPS were recorded at 30 min after surgery and scores decreased over time for each treatment group. Differences were significant among all treatment groups [$F(2,23)=16.8$, $P<.001$] and across time [$F(8,71)=16.8$, $P<.001$], without interaction [$F(16,215)=0.5$, $P>.05$]. Post-hoc analysis revealed a significant difference in GPS between control and paracetamol ($P=.03$) despite the apparent convergence in GPS for these two groups from 5-h postsurgery. Significant differences were also present between the control and meloxicam groups ($P<.001$), and between the paracetamol and meloxicam groups ($P<.001$).

If the control groups without pain were included, then differences existed among all groups [$F(4,279)=113.5$, $P<.001$] and across time [$F(8,279)=13.2$, $P<.001$], with interaction [$F(32,323)=2.4$, $P<.001$]. Over the 24-h period, the mean GPS values for the five groups were 24.8 ± 0.8, 20.0 ± 0.8, 14.9 ± 0.8, 0.2 ± 0.9 and 0.2 ± 0.9 for control, paracetamol, meloxicam, no pain paracetamol and no pain meloxicam, respectively.

3.1.2. Behavioral pain score (BPS)

Postoperative scores were significantly different amongst the three treatment groups ($P<.001$) for the sum of the behavioral criteria. BPS also varied with time for the individual behavioral criteria ($P<.001$), except for isolation ($P=.30$).

The sum of the BPS decreased over time (Fig. 1A). ANOVA showed significant differences among all treatment groups and across time [$F(2,23)=27.7$ and $F(8,71)=31.1$, respectively, $P<.0001$ for both], with no interaction [$F(16,215)=0.21$, $P>.05$]. Post-hoc analysis revealed a significantly lower BPS for meloxicam compared to control or paracetamol ($P<.001$ for both) and a significantly lower BPS for paracetamol compared to the control group ($P<.001$). See Fig. 1B.

If the control groups without the pain stimulus were included in this analysis, then differences existed for BPS among all groups [$F(4,279)=181.0$, $P<.001$] and across time [$F(8,279)=25.2$, $P<.001$], with interaction [$F(32,323)=3.9$, $P<.001$].

Factorial analysis revealed that all criteria contributed independently to the total BPS. Lameness, restlessness and vocalisation were the major contributors to the BPS, accounting for 85% of the variance, while isolation contributed least.

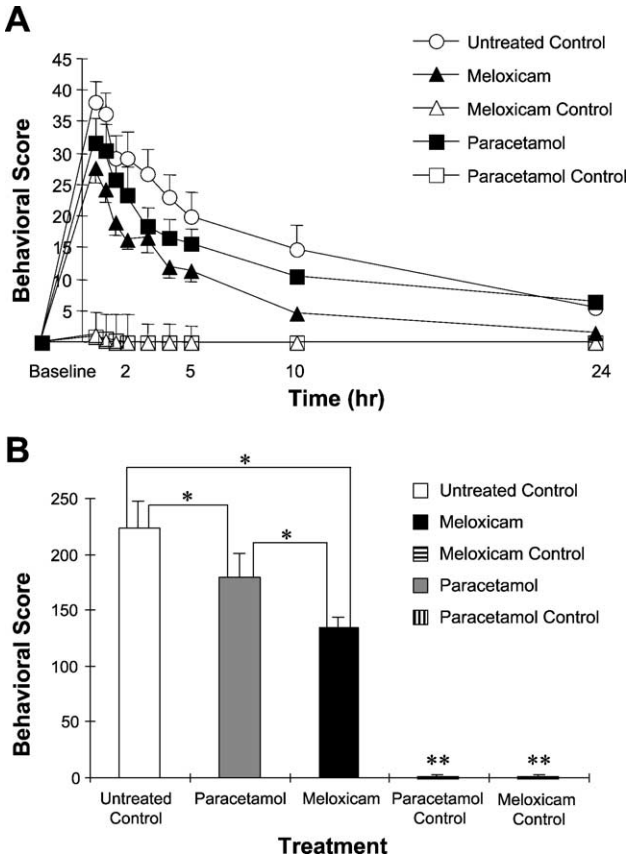

Fig. 1. BPS. (A) BPS over time. Baseline (preoperative) values are to the left of the *y*-axis and were zero for all groups. Observations commenced 30 min after surgery and observation times are marked. (B) Sum of all behavioral pain scores for 24-h. Mean values for untreated controls, paracetamol and meloxicam-treated groups were 223.4 ± 24.3, 179.6 ± 21.4 and 134 ± 9.7, respectively. Behavioral pain scores for the paracetamol and meloxicam control groups without pain were 1.7 ± 0.5 and 1.8 ± 0.9, respectively. Significant differences in the BPS were found between all the surgery groups and between the surgery and analgesic control groups (*) $P < .001$. ** $P < .001$ compared to all three groups that underwent surgery. Values are mean ± S.E.M.

3.1.3. Physiological pain score (PPS)

Temperature, HR, RR and BP were used as our physiological assessment parameters. Fig. 2A,B shows the sum of the PPS over time and for the 24 h of observation, respectively. ANOVA confirmed a significant difference in the PPS between groups [$F(2,23) = 12.7$, $P < .001$] and across time [$F(8,71) = 4.8$, $P < .001$], without interaction [$F(16,215) = 0.21$, $P > .05$]. Post-hoc analysis showed a significant difference between control and paracetamol, and control and meloxicam ($P < .001$ for both post-hoc analysis), but no difference between paracetamol and meloxicam groups ($P = .46$).

If the control groups without the pain stimulus were included in this analysis (without BP in those animals who had a catheter), then differences existed for PPS among all groups [$F(4,279) = 32.2$, $P < .001$] and across time [$F(8,279) = 14.5$, $P = .001$], but without interaction [$F(4,208) = 1.2$, $P = .25$]. The mean PPS values for the five groups without including BP were 1.6 ± 0.09, 0.90 ± 0.09, 1.0 ± 0.09, 0.3 ± 0.10 and 0.3 ± 0.10 for control, paracetamol, meloxicam, no pain paracetamol and no pain meloxicam, respectively.

3.2. Analgesic control groups

Both the paracetamol and meloxicam control groups had significantly lower BPS across time and for the 24-h observation compared to the surgery groups (see Fig. 1A and B). Similarly, the PPS and GPS of the analgesic control groups were significantly lower than that of the surgery groups across the 24-h period. None of the analgesic control animals showed significant changes in behavior except for some mild, initial, agitation that lasted for up to 1.5 h after the anaesthesia.

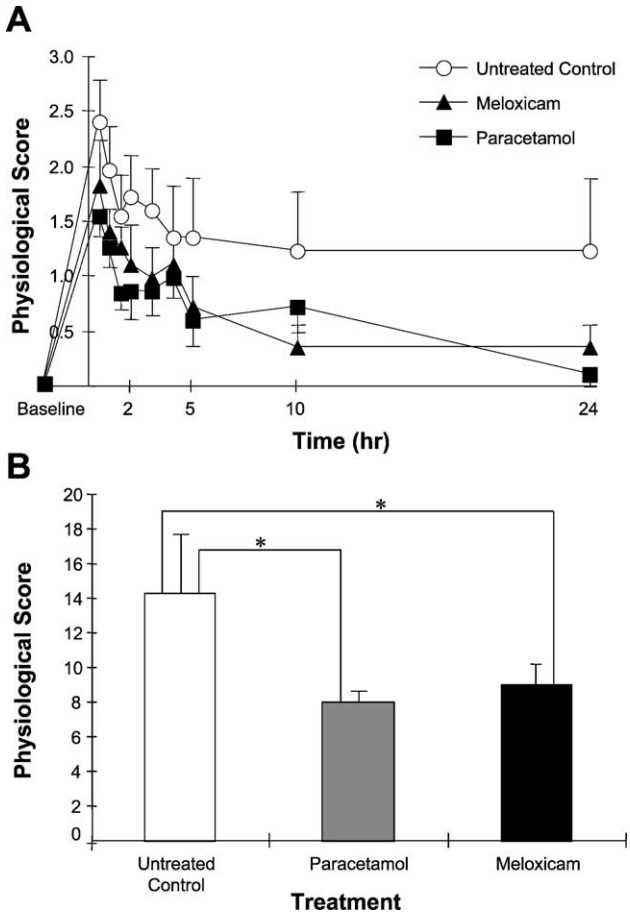

Fig. 2. PPS. (A) PPS over time. Baseline (preoperative) values are to the left of the *y*-axis and, by definition, were zero for all groups. Observations commenced 30 min after surgery. (B) Sum of all PPS for 24 h. Mean values for untreated controls, paracetamol and meloxicam-treated groups were 14.5 ± 3.2, 8.1 ± 0.7 and 9.1 ± 1.1, respectively. Significant differences in the pain scores were found between the control and analgesic-treated groups. * $P < .001$. Values are mean ± S.E.M.

3.3. Pharmacokinetic modelling

Drug concentration versus time curves were constructed for individual animals, then summarised for the group (Fig. 3). Plasma concentration peaked for meloxicam and paracetamol at the first sample, and decreased over time. Both drugs were undetectable by 24 h after surgery. By inspection of the individual and group curves, and calculation using a one-phase exponential decay model, the mean half-life of paracetamol and meloxicam in piglets were found to be 2.5 ± 0.3 and 3.4 ± 0.4 hr, respectively (two-tailed P=.13).

3.4. Renal and hepatic effects

Plasma samples collected for study of renal and hepatic side effects of the drugs were analysed in the biochemistry laboratory of the Royal Prince Alfred Hospital, Sydney, using routine, automated analysis (Hitachi 917). There was no significant difference in kidney and liver function among the three surgery groups.

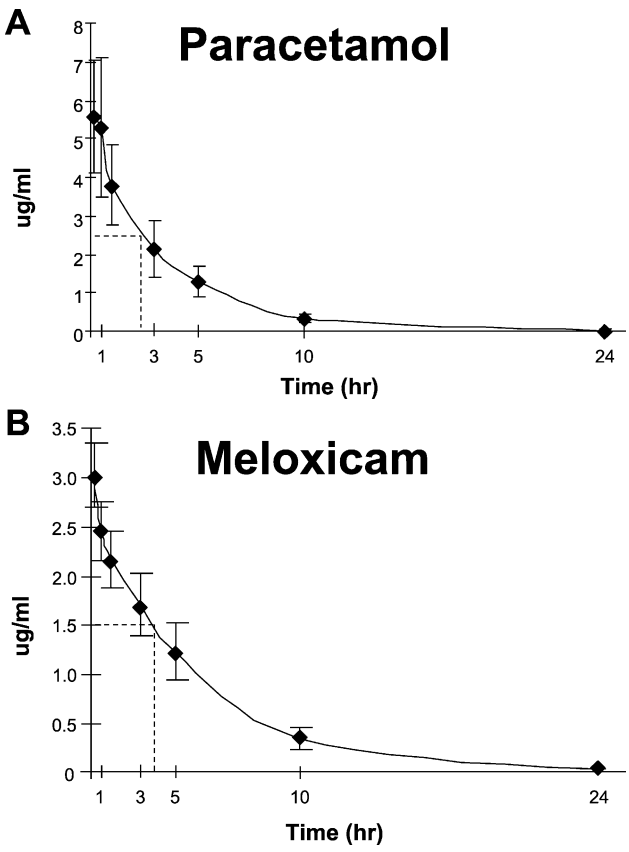

Fig. 3. Concentration against time curves for (A) paracetamol and (B) meloxicam in piglet plasma. The first sample was collected 10 min after surgery, the final sample 24-h and 48-h postsurgery for paracetamol and meloxicam, respectively. Plasma was separated from the whole blood and the drug was extracted from the plasma and quantified using HPLC. Values are mean ± S.E.M. Broken lines indicate the half-life (time) and 50% plasma concentration.

4. Discussion

We have demonstrated that paracetamol and meloxicam, both nonopioid analgesics, provide effective postoperative analgesia in piglets compared to untreated controls. Multifactorial NRS pain scores were lower for both analgesia-treated groups compared to the untreated control group, suggesting that the treated animals suffered less pain. Meloxicam was superior to paracetamol on behavioral criteria, whereas physiological parameters did not distinguish between the two drugs. Neither paracetamol nor meloxicam caused any behavioral or physiological effects in animals without the pain stimulus. Finally, the half-lives of the two drugs were not different, in contrast to previous reports.

Paracetamol is a commonly used postoperative analgesic in human adults, but reports of its use in animals are limited. In this study, the paracetamol-treated animals had significantly lower pain scores, both behavioral and physiological, than the controls, supporting the findings of Mburu et al. (1988) that paracetamol provides effective postoperative analgesia in animals. We also provide a pharmacokinetic profile for paracetamol in piglets, because this information was not previously available. A dose of 100 mg/kg proved effective for postoperative analgesia in piglets, with no adverse effects detected in these young animals.

Meloxicam, although relatively new in the market, has been assessed as a postoperative analgesic in other species. It has been shown to have similar analgesic effects to the other NSAIDs ketoprofen and tolfenamic acid for postoperative pain in cats (Slingsby and Waterman-Pearson, 2000). Meloxicam has also been studied for the treatment of postlaparotomy pain in dogs (Mathews et al., 1999), suggesting reduced pain relative to controls on behavioral and physiological criteria. Our study showed that meloxicam provided more effective analgesia than paracetamol on behavioral criteria, including a return of the overall pain scores to baseline values by 24 h postoperatively. Again, the pharmacokinetic profile that we provide is new information. Our evaluations of meloxicam include behavioral and physiological assessments, and renal and hepatic studies. The results show no adverse effects in piglets at a dose of 1 mg/kg.

Although paracetamol and meloxicam inhibited postoperative pain in piglets, meloxicam did provide better analgesia on behavioral criteria. This difference may be explainable on the basis of the pharmacological activity of the two drugs, either with regard to inhibition of the COX enzyme or their actions on other central and peripheral pathways. Meloxicam's antinociceptive effect is mainly by inhibition of the COX enzyme, while paracetamol can only inhibit the enzyme at very high drug concentrations (Ali et al., 1996; Bovill, 1997; Brune, 1988). However, paracetamol and meloxicam are thought to have other analgesic mechanisms. Paracetamol activates the spinal serotonergic system (Tjolsen et al., 1991) and possibly other monoami-

nergic systems, also in the spinal cord (Courade et al., 2001). Meloxicam may also inhibit pain at the level of the spinal cord via mechanisms other than COX inhibition, although this is less well characterised than paracetamol (Lopez-Garcia and Laird, 1998). Other mechanisms of action that have been postulated for meloxicam include inhibition of the actions of cyclic AMP (adenosine monophosphate) and nitric oxide (Aguirre-Banuelos and Granados-Soto, 2000).

Meloxicam was expected to have a much longer plasma half-life than paracetamol, which would have conferred additional practical benefits. Previous reports indicated half-lives of 62 min for paracetamol (Bailie et al., 1987) and 8 h for meloxicam (Busch et al., 1998). In our animals, the half-lives were not different for the two drugs (half-lives of 2.5 and 3.4 h, for paracetamol and meloxicam, respectively). This substantial difference in the half-life of the drugs as compared to previous studies may be due to methodological or subject differences. The route of administration was different in both cases (George, 1996). For paracetamol, we used the rectal rather than intravenous route (Bailie et al., 1987) and, for meloxicam, we delivered the drug through a central catheter, not orally (Busch et al., 1998). The animals were much younger in this study compared to the previous studies, where adult pigs were utilised. Effects of age can be significant with regard to drug pharmacokinetics (Busch et al., 1998). Paracetamol and meloxicam are metabolised in the liver enzymatically (Busch et al., 1998; Gogny, 1999; Grahame-Smith and Aronson, 1992), and the longer half-life of paracetamol that we found may be accounted for by the immaturity of drug metabolism systems. The half-life of meloxicam reported by Busch may have been artificially prolonged by their use of a radiographic drug detection method that was not specific to the parent drug alone. Since the metabolites of meloxicam are biologically inactive (Engelhardt, 1996), the half-life that we found for meloxicam may be a more accurate reflection of the half-life for its biological activity in piglets. To our knowledge, there are no previous studies of the pharmacokinetics of either drug in piglets.

No adverse effects on the kidney and hepatic function of the animals were observed. It was recently discovered that COX enzymes are present in the kidneys under normal conditions and inhibition of the enzyme by the NSAIDs may cause kidney damage (Harris et al., 1994). However, there has been no evidence that meloxicam or paracetamol cause kidney or liver damage at therapeutic doses. Only one dose of each drug was used in the study. It was beyond the scope of the study to construct dose–response curves for paracetamol and meloxicam in piglets but future studies should be directed towards the provision of additional information, and may reveal dosages where equivalent analgesic effects are achieved for the two drugs in all parameters.

Neither paracetamol nor meloxicam caused changes to the behavior of animals that did not receive pain. Mild behavioral agitation was observed in some of the "no pain" control piglets immediately after the anaesthetic. This may have been an early effect of the analgesics, a behavioral response to the jacket that was applied during the anaesthetic, or in response to the anaesthetic itself. We are not able to distinguish which of the three factors was responsible in the current study, but the effect was not statistically significant and does not affect our conclusion that the administration of our protocol without pain caused no alteration in BPS or PPS.

This study has provided new information about paracetamol and meloxicam for postoperative analgesia in piglets, including new data on the pharmacokinetics of the two drugs. These two nonopioid analgesics provide similar postoperative analgesia in piglets compared to untreated controls, with multifactorial NRS pain scores being lower for both analgesia-treated groups compared to a control group. BPS were better for meloxicam than paracetamol, but physiological scores were not different, and meloxicam did not have the markedly longer half-life that we anticipated, in piglets.

Acknowledgments

We gratefully acknowledge the kind donation of Panadol by Smith-Kline, Australia and Metacam by Boehringer-Ingleheim, Germany.

References

Aguirre-Banuelos P, Granados-Soto V. Evidence for the participation of the nitric oxide-cyclic GMP pathway in the antinociceptive action of meloxicam in the formalin test. Eur J Pharmacol 2000;395(1):9–13.

Ali BH, Cheng Z, el Hadrami G, Bashir AK, McKellar QA. Comparative pharmacokinetics of paracetamol (acetaminophen) and its sulphate and glucuronide metabolites in desert camels and goats. J Vet Pharmacol Ther 1996;19(3):238–44.

Association of Veterinary Teachers and Research Workers, Universities Federation for Animal Welfare, 1989. Guidelines for the recognition and assessment of pain in animals. South Mimms, Potters Bar, Herts.

Bailie MB, Federowicz DA, Dolce K, Kahn C, Mico BA, Landi MS. Pharmacokinetics of acetaminophen, vancomycin, and antipyrine in the Hanford miniature swine. Drug Metab Dispos 1987;15(5):729–30.

Bovill JG. Mechanisms of actions of opioids and non-steroidal anti-inflammatory drugs. Eur J Anaesthesiol Suppl 1997;15:9–15.

Brune K. The pharmacological profile of non-opioid (OTC) analgesics: aspirin, paracetamol (acetaminophen), ibuprofen, and phenazones. Agents Actions Suppl 1988;25:9–19.

Busch U, Schmid J, Heinzel G, Schmaus H, Baierl J, Huber C, Roth W. Pharmacokinetics of meloxicam in animals and the relevance to humans. Drug Metab Dispos 1998;26(6):576–84.

Courade JP, Caussade F, Martin K, Besse D, Delchambre C, Hanoun M, Hamon N, Eschalier A, Cloarec A. Effects of acetaminophen on monoaminergic systems in the rat central nervous system. Naunyn-Schiedeberg's Arch Pharmacol 2001;364(6):534–7.

Conzemius MG, Hill CM, Sammarco JL, Perkowski SZ. Correlation between subjective and objective measures used to determine severity of postoperative pain in dogs. J Am Vet Med Assoc 1997;210(11):1619–22.

Dobromylskyj P, Flecknell PA, Lascelles BD, Pascoe PJ, Taylor P, Waterman-Pearson A. Management of post-operative and other acute pain. In: Flecknell PA, Waterman-Pearson A, editors. Pain management in animals. London: W.B. Saunders, 2000. p. 81–145.

Engelhardt G. Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2. Br J Rheumatol 1996;35(Suppl. 1):4–12.

Firth AM, Haldane SL. Development of a scale to evaluate postoperative pain in dogs. J Am Vet Med Assoc 1999;214(5):651–9.

Flecknell PA. Refinement of animal use-assessment and alleviation of pain and distress. Lab Anim 1994;28(3):222–31.

Flecknell PA, Orr HE, Roughan JV, Stewart R. Comparison of the effects of oral or subcutaneous carprofen or ketoprofen in rats undergoing laparotomy. Vet Rec 1999;144(3):65–7.

George CF. Pharmacokinetics. QJM 1996;89(2):91–3.

Gogny M. Pharmacological profile and therapeutic value of meloxicam. Recent advances in non-steroidal anti-inflammatory therapy in small animals, 1999 (Paris).

Grahame-Smith DG, Aronson JK. Oxford textbook of clinical pharmacology and drug therapy. Oxford: Oxford Univ. Press, 1992.

Harris RC, McKanna JA, Akai Y, Jacobson HR, Dubois RN, Breyer MD. Cyclooxygenase-2 is associated with the macula densa of rat kidney and increases with salt restriction. J Clin Invest 1994;94(6):2504–10.

Liles JH, Flecknell PA. The use of non-steroidal anti-inflammatory drugs for the relief of pain in laboratory rodents and rabbits. Lab Anim 1992; 26(4):241–55.

Lopez-Garcia JA, Laird JM. Central antinociceptive effects of meloxicam on rat spinal cord in vitro. NeuroReport 1998;9(4):647–51.

Mathews K, Pettifer G, Foster R, McDonell W. A comparison of the safety and efficacy of meloxicam to ketoprofen and butorpphanol for control of post-operative pain associated with soft tissue surgery in dogs. Recent advances in NSAID therapy in small animals, Metacam Pain Management Meeting, Borhringer Ingelheim, Paris. 1999;679.

Mburu DN, Mbugua SW, Skoglund LA, Lokken P. Effects of paracetamol and acetylsalicylic acid on the post-operative course after experimental orthopaedic surgery in dogs. J Vet Pharmacol Ther 1988;11(2):163–70.

Morton DB, Griffiths PH. Guidelines on the recognition of pain, distress and discomfort in experimental animals and an hypothesis for assessment. Vet Rec 1985;116(16):431–6.

Short CE. Animal pain. Textbook of pain. Edinburgh: Churchill Livingstone, 1999. p. 1588 (p. xii).

Slingsby LS, Waterman-Pearson AE. Postoperative analgesia in the cat after ovariohysterectomy by use of carprofen, ketoprofen, meloxicam or tolfenamic acid. J Small Anim Prac 2000;41(10):447–50.

Smith JD, Allen SW, Quandt JE, Tackett RL. Indicators of postoperative pain in cats and correlation with clinical criteria. Am J Vet Res 1996; 57(11):1674–8.

Tjolsen A, Lund A, Hole K. Antinociceptive effect of paracetamol in rats is partly dependent on spinal serotonergic systems. Eur J Pharmacol 1991; 193(2):193–201.

Velpandian T, Jaiswal J, Bhardwaj RK, Gupta SK. Development and validation of a new high-performance liquid chromatographic estimation method of meloxicam in biological samples. J Chromatogr, B: Biomed Sci Appl 2000;738(2):431–6.