

## **Chapter 2**

# **Preanesthesia, Anesthesia, Chemical Restraint, and the Recognition and Treatment of Pain and Distress**

The reader is referred to two standard veterinary textbooks for in-depth information about the pharmacodynamics, pharmacokinetics, and practical use of anesthetic and analgesic agents in animals.<sup>1,2</sup> The preanesthetic, anesthetic, chemical restraint, and analgesic regimens cited in this chapter have received approval from an Institutional Animal Care and Use Committee (IACUC) or similar body with the same responsibilities or have been published by board certified veterinary anesthesiologists.

There is increasing pressure, primarily a response of Institutional Animal Care and Use Committees to external pressure, to require that any procedure conducted in animals that could be considered to cause pain or distress to a human be conducted with the benefit of anesthesia or analgesia. This policy can and does result in some anesthetic deaths, stress associated with the anesthetic procedure, and/or confounding drug-induced changes in the animal that may be more severe than the procedure to be conducted. In some instances, proper prior training and acclimation of the animals, particularly of the larger species, to the procedure can result in fewer problems than tranquilizing, sedating, or anesthetizing the animal. It might still be necessary to provide chemical restraint for a variety of reasons including humane considerations. For most circumstances, the same agents used for anesthesia and/or analgesia can be used for chemical restraint.

## **General Principles of Pain Recognition in Animals**

There is an absolute need for anyone conducting animal research to be able to recognize pain and treat the individual animal appropriately. Acute pain is usually accompanied by changes in the autonomic nervous system, does not last beyond the time needed for the injury to heal, and responds to treatment with analgesics. Acute recurrent pain is the term generally used to describe prolonged pain such as that associated with some neoplasms. Chronic pain is classified as long-term pain with no obvious cause or onset in time. Somatic pain is usually localized while visceral pain is not.

The International Association for the Study of Pain (ISAP) defines pain as "...an unpleasant, sensory, emotional experience associated with actual or potential tissue damage or described in terms of such damage..." This definition is open to criticism

since individual animals, including humans, perceive and communicate pain uniquely, as individuals, reacting to the particular circumstance(s) as individuals. There is a well documented body of literature indicating cognitive modulation of pain influenced by attention, distraction, environment, and prior experience.<sup>3</sup> The ISAP guidelines for the effective diagnosis and treatment of pain were specifically developed to provide a formal evaluation process for analgesic agents. The protocol states that the subject should be compared with clinically normal animals of the same species using some quantitative measure of behavioral parameters such as movement, grooming, and sleep, and by physiological parameters such as EEGs, hormone concentrations, and measures of the autonomic nervous system. Whatever parameters used they are then measured again following treatment with an agent being evaluated for analgesic effect.<sup>3</sup>

Pain can be objectively measured by recording increased afferent nerve activity from nociceptors. Changes in the autonomic nervous system in response to pain can be manifest by changes in heart rate, pupillary diameter, skin resistance, and peripheral blood flow. Pain-induced changes in the hypothalamic-pituitary-adrenal axis can be estimated by measuring circulating levels of corticosteroids. Postural changes in response to pain can be voluntary or involuntary. They include hyper-reflexia, the adoption of an immobile stance, abnormal postures during Recumbency and/or abnormal positioning of limbs, head, and/or neck. Pain associated locomotor activity changes include movements such as restlessness, kicking, stamping, rolling, jumping, licking or biting at the site of injury or pain, and excessive tail wagging or “wringing”. Pain is frequently manifested as a lack of appetite and/or thirst, although some animals may “play” with water without drinking it.<sup>4, 5</sup>

Some general signs of animal well-being and absence of pain are common to most species used as animal models for cardiovascular research. Pain-free animals will keep themselves well groomed, have normal movement, eat and drink normally, and demonstrate normal reproduction. They will interact with cage mates and/or handlers and will exhibit curiosity by exploration of their surroundings, particularly when placed in a new, nonthreatening environment. There is an evolving nomenclature associated with the recognition of pain in animals. “Guarding” is any attempt to protect itself or a specific anatomical area. Animals will move away or display aggressive behavior when guarding. “Vocalization” involves crying out when manipulated or when forced to use an affected anatomical area. “Mutilation” involves repetitive licking, biting, scratching, shaking, or rubbing an affected area. “Restlessness” includes relentless pacing, lying down and getting up, or shifting of weight. “Sweating” from the paws in dogs and cats, sweating from the skin in horses, and panting despite cool or comfortable housing conditions for most species can indicate pain. “Recumbency” involves animals lying down for unusual lengths of time for the species. “Depression” is usually manifested as reluctance to move or difficulty in rising. “Postures” including holding the head down, the abdomen tucked up, a hunched over stance, facial distortions, and pallor of mucous membranes are all considered “abnormal appearance”. Signs of pain are often not all present at the same time and those observed at one particular time may not be present the next time the animal is examined. Investigators have the responsibility to become familiar with the normal condition and behavior of the animals they are using and understand that signs of pain involve a complex group of changes that must be considered as a whole.

Recognizing, assessing, and evaluating pain and discomfort in animal models is not as straightforward as some animal rights activists maintain. Beynen et al.<sup>6</sup> created a model of gallstones in mice. They critically evaluated vocalization, magnitude of abdominal muscular contractions, stance, response to abdominal palpation, and at least five other parameters. They found that abdominal palpation was the only parameter routinely effective in differentiating between mice with and without gallstones. Lariviere et al.<sup>7</sup> determined there are heritable aspects of nociception that could indicate genetic sources of variation in individual responses to painful stimuli. Anil et al.<sup>8</sup> claim the assessment of the degree of pain in domestic animals is subjective, not reliable, and has not made much progress since the 1940s.

The fact that the recognition and assessment of pain in animals used for research is difficult must not deter us from making those evaluations. No small part of the problem comes because of the regulatory view, based on pure anthropomorphic thought, that any procedure or condition likely to cause pain in humans will do the same in animals. Flecknell suggests the use of a “critical anthropomorphic approach,” an approach that considers differences in anatomy, posture, and behavior in the framework of a pain assessment scheme.<sup>9, 10</sup> To make matters more complicated distinction between distress, suffering, and stress in animals tend to be blurred and the terms are frequently used synonymously. It would be very helpful to develop species-specific pain scoring systems to facilitate the evaluation of pain and its rationale treatment. This is extremely important in cardiovascular studies since, as will be discussed in Chap. 7, almost all drugs used for chemical restraint or for analgesia in research animals have significant cardiovascular effects.<sup>11</sup>

There are three pain-scoring systems commonly used for humans and animals: the simple descriptive scale (SDS), the numeric rating scale (NRS), and the visual analogue scale (VAS). All three of these scales were developed for use by human patients to record the intensity of their own pain. Physicians, parents, and nurses interacting with pediatric patients use the same scoring systems. McGrath and colleagues have studied pain recognition in pediatric patients. They describe three aspects of pain, cognitive or phenomenological, behavioral, and physiological. Each of these aspects may require a different method of measurement. They developed the Children’s Hospital of Eastern Ontario Pain Scale (CHEOPS), a NRS that assigns a score to various behaviors for pediatric patients. A study conducted after major surgery in 3 to 7-year-old patients found that two different self-report scales used were strongly and significantly correlated but there was little relationship between the scores for the self-reports and the behavioral measures. Many of these patients who reported severe pain manifested few of the behavioral indicators used by CHEOPS.<sup>12</sup> Another study by the same group found that parents tended to overestimate their child’s pain whereas nurses were less consistent in their scoring and tended to underestimate.<sup>13</sup> Another scoring system, the Non-Communicating Children’s Pain Checklist, was used by caregivers to discriminate between pain and distress in children with cognitive impairments. Seven of the items in this checklist: “Cranky, Seeking Comfort, Change in the Eyes, Less Active, Gesture to Part That Hurts, Tears, and Gasping” significantly predicted numerical pain ratings by caregivers.<sup>14</sup> Studies have also demonstrated a relationship between maternal behavior and infant pain during immunization in human patients tested at 6 months

and again at 18 months of age comparing measured vagal tone and “infant difficultness.” At 6 months, 44% of the variability between biologically based infant variables (measured vagal tone and infant difficultness) and maternal contextual variables (maternal behavior during pain to the infant and maternal sensitivity) was predicted by infant difficultness and mothers’ vocalizations during immunization.<sup>15</sup>

The advent of patient-controlled analgesia (PCA) has enabled many studies that all emphasize the psychological aspects of pain perception in human patients. This technique gives control of the frequency of analgesic administration to the patient. Patients with higher anxiety levels and less social support use more PCA. Older patients usually report less pain but use the same amount of analgesic as younger patients. Music decreased the amount of PCA in one group of patients. Females use significantly less PCA than males but the state of preoperative anxiety in women receiving abdominal hysterectomy correlated with increased PCA use.<sup>3</sup>

Even objective tests for the relief of pain are sometimes less than reliable. Changes in motor reflexes, autonomic reflexes, and neuroendocrine responses that mimic pain and severe distress can be induced just by approaching and handling animals that are not well acclimated to some level of human interaction. The use of parameters such as heart rate, respiratory rate, body temperature, and salivation will be unreliable as measures of postoperative pain unless considerable time and effort is expended to tame, handle, and train each animal preoperatively. The Bispectral Index Score (BIS) is a software program used to quantitate electroencephalographic data for the purpose of evaluating the hypnotic state during anesthesia. A recent study determined the relationship between BIS values and the minimum alveolar concentration (MAC), using isoflurane in cats and concluded that the BIS endpoints used to titrate anesthetic agents in humans may not be applicable to cats.<sup>16</sup>

Pain is a natural phenomenon that results in injured anatomical sites being protected and allowed to heal. Following surgery it might be beneficial for an animal, or human, to not move about normally and thus to protect the incision site. There is increasing evidence that performance animals particularly racehorses, routinely treated with Nonsteroidal anti-inflammatory drugs (NSAIDs) such as phenylbutazone, for supposedly minor injuries suffer more catastrophic injuries while performing. It is also true that excessive pain can be detrimental and even life threatening, particularly in animals considered as prey species, such as rabbits. Excessive pain prolongs recovery from illness or injury. Excessive pain will stop an animal from eating and may lead to GI shut down and even death. Some species, particularly rabbits and sheep, can go into shock from excessive pain and die, even though the illness or injury might not have been life-threatening. Decisions regarding the administration of analgesia must involve clinical judgment.

Anyone who works with or lives with a variety of individual animals or animal species on a regular basis realizes that individual animals have different personalities. These differences extend to the demonstration and even perception of pain. Some individuals are stoic while others are crybabies, and the response to pain can vary with the circumstances in any one individual. Although there are definite species differences in pain demonstration, individual variations within a species are sometimes greater than between species differences. There is clear evidence that the perceived intensity and tolerance of pain varies among individuals. There are also significant

differences between quadrupeds and bipeds related to postoperative pain. Abdominal surgery is apparently less painful in quadrupeds than in bipeds since the latter use their abdominal muscles to a greater extent to maintain posture and while ambulating. A median sternotomy produces low to moderate pain in humans but significant pain in animals because quadrupeds use their forelimbs for walking. A lateral thoracotomy is less painful in quadrupeds since they rely more on abdominal respiration and bipeds more on thoracic respiration.<sup>5</sup>

Female subjects apparently experience greater analgesia from  $\kappa$ -opioid analgesics such as nalbuphine and butorphanol than do male subjects.<sup>17</sup> The same research group conducted a double-blind, placebo-controlled study to evaluate the analgesic efficacy of the combination of a  $\mu$ -opioidergic analgesic (morphine) and pentazocine (a  $\kappa$ -opioidergic agent) and found a level of analgesia significantly greater than could be accounted for by the addition of the analgesic effects of each opioid alone.<sup>18</sup> The effects of gonadal hormones on persistent pain has also been demonstrated in rats.<sup>19</sup>

The use of the tricyclic antidepressants, anticonvulsants, *N*-methyl-D-aspartic acid receptor antagonists, and low-dose intravenous local anesthetics for analgesia is increasing in veterinary and laboratory animal medicine. These agents have proved to be efficacious in relieving certain types of pain, particularly neuropathic and cancer pain in humans, but their effectiveness in laboratory animals has not been totally evaluated.

## The Use of Anti-Cholinergic Drugs for Preanesthesia

Atropine sulfate has a long history of veterinary use as a routine adjunct to general anesthesia, particularly with the use of inhalant anesthetic agents. Because ether and other early inhalant anesthetic agents were very irritating to mucous membranes, atropine was useful for controlling salivary and respiratory tract secretions. Atropine also blocks the so-called “laryngeal reflex,” purported to result in cardiac arrest. Modern inhalant anesthetic agents produce minimal respiratory tract irritation and secretions.

Atropine does have significant effects on the cardiovascular system. The usual doses recommended for preanesthesia do not markedly affect blood pressure but do cause tachycardia. Individual animals will have varying degrees of tachycardia depending upon the normal degree of vagal tone in that individual. As a result of the tachycardia, cardiac output tends to increase. The cardiac vagal efferent nerves are blocked so atropine interferes with the response to any vagally-mediated perturbation. The pressor effects of catecholamines are accentuated. Large doses of atropine can act as direct cardiac depressants.<sup>20</sup>

Atropine has other effects of possible concern in animals being surgically prepared for follow-up studies. It can cause inhibition of GI smooth muscle motility resulting in postoperative GI stasis. This is of particular concern with ruminants. GI secretions are also blocked by atropine, and this can add to postoperative GI problems, particularly in ruminants where salivary secretions high in bicarbonate are important to normal rumen pH and function. Atropine decreases bronchial and tracheal secretions, dilates bronchioles, and changes the viscosity of bronchial and tracheal secretions and the muco-ciliary blanket resulting in prolonged muco-ciliary clearance.

The respiratory effects can lead to atelectasis. Atropine can also lead to urinary retention, and there is a definite anhydrotic effect. There seems to be more reasons not to use atropine as a preanesthetic agent than reasons to do so.

## General Comments on Preanesthetic Agents

The psychotropic agents have been used extensively in veterinary medicine since the 1950s when reserpine and the phenothiazine derivatives were first widely accepted for use. These agents are valuable in quieting and calming animals but are most effective when used in animals that are reasonably calm at the time the agents are administered. If the animal is very agitated before the agent is given, the beneficial effects are sometimes mitigated. The major advantage of these agents as preanesthetics is to make induction of anesthesia easier, smoother, and to reduce the total dose of anesthetic agent needed. Drug interactions can occur and if the cardiovascular studies are being conducted while the animal is anesthetized, it becomes difficult to separate drug effects from physiological responses to the perturbations introduced. Many of the tranquilizers used today are  $\alpha$ -adrenergic blocking agents, and therefore have a direct effect on blood pressure and, in some cases, heart rate. When used in combinations with other agents, it is difficult to identify which drugs are responsible for the cardiovascular responses observed.

## Preanesthesia and Anesthesia in Rats and Mice

The following agents are used and recommended for anesthesia in rats and mice:

Buprenorphine (0.05 mg/kg) administered 1 h prior to administration of Ketamine (45 mg/kg) and medetomidine (0.3 mg/kg), IP. This combination resulted in significantly longer duration of anesthesia than ketamine/medetomidine alone, significant respiratory depression, and two anesthetic deaths.<sup>21</sup>

Chloral hydrate (300 mg/kg) IP: This mixture should be diluted since concentrations above 2% can result in peritonitis.

ChloroPentR (3.0 mL/kg) IP: This is a mixture of chloral hydrate (42.5 mg/mL), sodium pentobarbital (8.86 mg/mL) and  $\text{MgSO}_4$  (21.2 mg/mL) (Very similar to the old Equithesin sold in the 1950s and 1960s, ouch!)

Diethyl-ether (Avertin) (200–300 mg/kg) IP: Must be stored in a lightproof container under refrigeration. Induction with Avertin in rats combined with orbital puncture for obtaining 0.5 mL of blood caused more distress than did tail vein puncture under nitrous oxide/halothane anesthesia or saphenous vein puncture in untreated rats.<sup>22</sup>

Halothane, same as Isoflurane, but does not seem to be as effective and is more dangerous to laboratory personnel over long periods of use.

Isoflurane induce in a chamber or with a mask using 5 vol% then reduce and maintain in a surgical plane with 1.25–2.5 vol% to effect.

Ketamine (40–80 mg/kg) + Xylazine (5–10 mg/kg) IP

Ketamine (40–80 mg/kg) + ValiumR (5–10 mg/kg) IP

Ketamine (31.25 mg/kg) + Xylazine (6.25 mg/kg) + Acepromazine (1.25 mg/kg), SQ<sup>23</sup>

Ketamine (60 mg/kg) medetomidine (0.4 mg/kg) IP<sup>21</sup>: A gender based difference in this combination when used for short-term chemical restraint was noted. Male mice required a dose of ketamine (50 mg/kg)/medetomidine (10 mg/kg), IP, while female mice needed 75 mg/kg of ketamine to produce the same level of restraint and anesthesia. Atipamezole (1–2.5 mg/kg, IP) effectively reversed the anesthesia by ketamine/medetomidine with males recovering more rapidly than females.<sup>24</sup>

Oxygen + nitrous oxide + halothane, induction with high concentrations of halothane, then reduce to maintain in a surgical plane.

Sodium pentobarbital (35–45 mg/kg) IP or IV

Sufentanil/medetomidine at 0.04/0.15 mg/kg, or 0.50/0.15 mg/kg, IP or 0.8/0.3 mg/kg, SQ all produced a surgical plane of anesthesia. All three combinations also resulted in marked respiratory depression. The SQ method was recommended since it resulted in a more reliable and more rapid induction. The administration of butorphanol and atipamezole (0.2/0.5 mg/kg) caused rapid reversal of anesthesia.<sup>25</sup>

## Chemical Restraint (Sedation) in Rats and Mice

All of the above agents and combinations can be used for chemical restraint as well as the following agents:

Acetylpromazine (Acepromazine): 1.0–5.0 mg/kg, SQ, IM, IP, bid.

Diazepam: 5.0–15.0 mg/kg, SQ, IM, IP, bid. Only adequate sedation for minor procedures.<sup>26</sup>

Droperidol: 0.5–2.0 mg/kg, SQ. Doses above 0.5 mg/kg cause subcutaneous inflammation. Allows easier manipulation of the animal for minor procedures but not sufficient sedation for tail-vein or orbital bleeding.<sup>26</sup>

Methimazole: 10–100 mg/kg, IP.

Methohexitone sodium: 44 mg/kg, IP provided < 5 min of immobilization in female C3H/Neu mice. Complete recovery was achieved in 10–15 min.<sup>27</sup>

## Pain and Distress Recognition in Rats and Mice

Rats and mice pose some special problems regarding the recognition of pain. Mice, as prey animals, have a genetic predisposition not to display pain behavior since this will signal them out to predators. They are less likely to limp or display other obvious signs of pain than other species. Rats are genetically predisposed to aggressive behavior against injured individuals of their own species, so they also tend to hide injuries.

The detection and appropriate treatment of postoperative pain in rats and mice presents a common problem for cardiovascular researchers. Investigators should devise, adopt, or adapt a pain scale appropriate to their situation. When the experimental



protocol requires surgery, the animals should be observed and scored in their normal environment, when first brought to the laboratory or surgery room, again postoperatively on a regular and ongoing schedule for a period of time depending upon the severity of the insult, until they recovered fully. When the total postoperative score is greater than the preoperative score, animals should be treated with appropriate analgesics. This approach does not exclude preemptive, presurgical use of analgesics in a standardized protocol. Preemptive use is an effective strategy particularly when the drug(s) and dose are predetermined to be effective and safe for the particular procedure and will not interfere with the measurements to be obtained. Martini et al.<sup>28</sup> describe a system that includes code values for observed changes in such parameters as body weight, food consumption, water consumption, body temperature, level of hydration, heart rate, respiratory rate, urine output, feces output, behavior, body positioning, piloerection, ataxia, hyper reactivity, vocalization, and teeth grinding. When rodents demonstrate pain with rapid and shallow respiration, it can be accompanied by grunting or chattering on expiration. Tearing can occur and, in albinos, porphyrin secretion or “red tears” can be observed. Vocalization in rats and mice in acute pain can be at very high frequencies, above human perception. Studies using high frequency recordings have demonstrated this in the absence of other signs. Abnormal feeding behaviors, such as eating their bedding or cannibalism of offspring, can sometimes be observed. If housed with other animals, individuals might separate themselves from the rest of the animals in the cage or attempt to hide.<sup>5</sup>

Distress identification is very difficult. Studies have shown that the area under the corticosterone concentration vs. time curve can be used to model and predict the effects of restraint stress and chemical stressors.<sup>29</sup> Unfortunately, obtaining blood from rats and mice to generate these curves is highly stressful.

Behavioral psychologists have used a wide range of maze testing, learned behavior, and observational studies to characterize anxiety, stress, and distress-related behaviors in rats and mice. Prolonged exposure of female mice to psycho emotional conditions, such as housing aggressive males in proximity separated only by a perforated partition, causes marked anxiety in the females with inhibition of both motor and investigative activity.<sup>30</sup> Male mice exposed to repeated aggression by other male mice demonstrate signs of anxiety determined by various methods of psychological testing, primarily learning, risk avoidance, and problem solving behaviors. The level of anxiety and its behavioral manifestation depends upon the duration of aggression exposure and the genetic strain of the mice.<sup>31, 32</sup> Male mice of two different strains were separated at 4 weeks of age and kept in individual cages for 7 weeks. All mice exhibited signs of chronic anxiety as determined by various psychological tests but there were strong strain and test-specific effects on emotional behavior and memory in these animals.<sup>33</sup>

The following system for evaluating pain and related stress in rats and mice was approved by the IACUC at the University of Illinois and has been used successfully in our lab for the past few years. It is not perfect. Many other schemes have been devised that work just as well or better. The strength of this system is that it became routine for our lab. Laboratory personnel became familiar with it and comfortable using it so it served its purpose. It works best if the animals are scored prior to being moved from the animal care facility, again shortly after arriving at the laboratory or surgery room, after recovery from anesthesia and at regular intervals thereafter until the animals recover and are pain free.



Animal # \_\_\_\_\_ Treatment: \_\_\_\_\_ Date: \_\_\_\_\_

Circle the appropriate score

Parameter	Descriptors	Score
Comfort when placed in a new, clean cage	Normal investigation and movement during introduction to new surroundings, interested in surroundings, normal grooming, face washing, asleep or calm, resting, moving about normally	1
	Relatively uninterested in surroundings, reluctant to move about, more than normal grooming, chewing, awake but depressed	2
	Uninterested in new surroundings, apparently agitated and restless, incessant grooming	3
Movement once acclimated to new surroundings	Normal	1
	Restless, pacing continuously, getting up and down repeatedly	2
	Face twitching, large muscle twitching	3
	Rolling, thrashing, whole body twitching, losing balance, falling over	4
Appearance or posture	Normal (on sternum or curled up)	1
	Eyelids partially closed, ears flattened or carried abnormally, twitching	2
	Abnormal posture, prayer position, back arching and/or stretching, abnormal facial expression, abnormal leg positioning, grunting, teeth grinding, piloerection, uncontrollable twitching	3-4
Physiological	Normal pupils	1
	Abnormally dilated pupils	2
	No visible salivation	1
	Abnormal salivation	2
8 + h evaluations	Not eating	3
	Eating less than normal	2
	Eating normally	1
	No water intake	3
	Less than normal water intake	2
	Normal water intake	1
	Normal feces	1
	Abnormal feces	2
	Normal urination	1
	no sign of urination	3
Mental status	Same as preop	1
	Submissive or wary compared to preop	2
	Aggressive	3
Vocalization	None	1
	Vocalizes only when touched	2
	Intermittent vocalization	3
	Continuous vocalization	4
Response to palpation of incision site	No change from preop	1
	Pulls away when touched, looking at incision site when moving about	2
	Vocalizes when incision touches, reluctant to move unless prodded	3
	Violent reaction to palpation, vocalizes without wound being touched, snapping or hissing when trying to handle	4
	Extremely restless and violent or aggressive when trying to handle, freezes when palpated	5
Total score:		

## Treatment of Pain in Rats and Mice

The following drugs and range of doses are recommended by several IACUC Websites, the NIH Website, and journal articles:

### *Local Anesthetic Agents*

Bupivacaine: Local infiltration along the surgery site during closure

Lidocaine: Local infiltration, short duration anesthesia for minor procedures such as skin biopsies.

### *Nonsteroidal Anti-Inflammatory Drugs*

NSAIDs, particularly the derivatives of propionic acid, have been shown to provide postsurgical pain relief at least equivalent to the opioids for certain surgical models in mice.<sup>34</sup> The same conclusions have been made using colorectal distension models in rats.<sup>35-37</sup> The NSAIDs can, however, result in gastrointestinal bleeding and other signs of GI toxicosis, some at therapeutic doses in rodents.<sup>36, 37</sup>

Acetaminophen (Tylenol Pediatric Suspension): No longer recommended since latest data indicate it is not effective in rats and mice.

Aspirin: 100–400 mg/kg, PO, once or twice daily

Carprofen: 5–15 mg/kg, SQ or IM, q 4–5 h, 5–10 mg/kg in water or jello, once daily. (Nonsteroidal anti-inflammatory agent, NSAID), analgesia lasted 4–5 h at 5 mg/kg dose<sup>38</sup>

Ibuprofen: Mice, 30 mg/kg, PO, (NSAID), once daily; Rats, 15 mg/kg, PO, once daily<sup>39</sup>

Flunixin-meglumine (Banamine): 2.5 mg/kg, SQ or IM, bid

Ketoprofen: 5–15 mg/kg, SQ or PO, q 4–5 h (NSAID), analgesia 4–5 h at 5 mg/kg dose<sup>38</sup>

Ketorolac: 5 mg/kg, IM (NSAID)<sup>23</sup>

Meloxicam: 1.0 mg/kg, SQ or PO (NSAID), once daily

### *Narcotics*

Studies conducted on F344, Sprague–Dawley, Long–Evans, and Lewis rats using tail withdrawal from 50, 52, and 55°C water concluded that there is a hierarchy of antinociceptive effects of  $\mu$ -opioids in rats with morphine and levorphanol demonstrating high potency, buprenorphine intermediate potency, and butorphanol and

nalbuphine low potencies. There were also differences in species sensitivity to these drugs. Morphine and levorphanol were most potent in F344 and least potent in Lewis rats. Butorphanol produced maximal effects in F344 and Sprague-Dawley at relatively low doses and half-maximal effects in Long-Evans at very high doses, but no effect in Lewis rats. Nalbuphine administration elicited near maximal effects in F344 and Sprague-Dawley and no effects in Long-Evans or Lewis strains. Similar effects were found with intermediate doses for these agents. These studies indicate a rank order of intrinsic efficacy in rats as: levorphanol > morphine > dezocine > buprenorphine > butorphanol > nalbuphine. Each of these drugs were found to have significant affinity for other types of opioid receptors, such as  $\kappa$ -receptors, but the antinociceptive effects, in these studies, was mediated by action at the  $\mu$ -opioid receptor. Because these drugs differ in intrinsic efficacy, they are variously called agonists, partial agonists, to agonist/antagonists.<sup>40, 41</sup>

Buprenorphine continues to be recommended as the analgesic of choice for laboratory rodents at many institutions. A rat model of visceral pain induced by laparotomy and intestinal resection was used to evaluate treatment with buprenorphine (0.5 mg/kg, q 6 h, SQ). The animals exhibited behavior and appearance consistent with pain and distress for as long as 32 h postop. Animals in the same study treated with oxymorphone (0.03 mg/kg/h by continuous IV infusion) showed no signs of pain or distress.<sup>42</sup> Our experience with buprenorphine administered prior to surgery, or just prior to closure of thoracotomy incisions for control of postoperative pain, has not been good. We used recommended doses of buprenorphine in a mouse model of cardiac arrest and resuscitation and in a rat model of coronary ligation. We recorded significant increases in time to recovery and mortality in both models compared with animals treated with local anesthesia of the surgical site and NSAIDs.<sup>43</sup> This agrees with the high mortality rates previously reported on the use of buprenorphine in conjunction with ketamine/medetomidine anesthesia.<sup>21, 44</sup>

There are substantial differences in reports documenting the affects of opioids on both locomotor activity and food and water consumption in laboratory rodents. Morphine significantly decreases gastric emptying times in mice.<sup>45</sup> Because butorphanol and buprenorphine resulted in reduced food intake in rats, it has been concluded that water consumption was a more reliable parameter than food intake for evaluating postoperative pain.<sup>46, 47</sup> However, it has also been reported that butorphanol administered to normal rats results in significant increases in food intake via direct stimulation of the CNS.<sup>45</sup> Recommended drugs are:

Buprenorphine (Buprenex): 0.01–0.5 mg/kg, SQ, IM, or IP bid tid or q 6–12 h depending upon the extent and location of the procedure (0.1–0.25 mg/kg, PO, bid or tid, 0.01–0.02 mg/mL in drinking water, 0.5 mg/kg in jello).

Butorphanol (Torbugesic): 1.0–2.0 mg/kg, SQ, only provides 1–2 h of analgesia in both rats and mice.<sup>48</sup>

Dezocine: 1.0–5.0 mg/kg, PO, high concentrations detected in 15 min after dosing, concentrations in the brain significantly higher than those in the plasma.<sup>49, 41</sup>

Etorphine: 0.05–0.5 mg/kg, IP or Intrathecal<sup>50</sup>

Fentanyl: 0.01–0.3 mg/kg, SQ, provides 2–4 h of analgesia

Levorphanol: 0.5–5.0 mg/kg, IP<sup>41</sup>

Meperidine (Demerol): 2–4 mg/kg, bid

Morphine: 5.0–10.0 mg/kg, SQ or intrathecal, provides 2–3 h of analgesia but the level of analgesic effect is greater than that provided by buprenorphine or butorphanol<sup>48, 51</sup>

Nalbuphine: 2.5, 25, and 250  $\mu$ mol/kg, IP resulted in 1.5, 2, and 4 h of analgesia, respectively

Naloxone: 0.1–10 mg/kg, SQ, provides 2–4 h of analgesia.<sup>52</sup> Potentiates pentazocine, fentanyl, methadone, and levorphanol analgesia but attenuates morphine, etorphine, propoxyphene analgesia<sup>18</sup>

Oxymorphone: 0.03 mg/kg, Alzet mini-pump, bolus IV injection or continuous IV infusion<sup>42</sup>

Pentazocine: 2 mg/kg, IV

Propoxyphene: 100 mg/kg/day, PO<sup>53</sup>

There is good evidence for antinociceptive synergy between opioid agonists and local anesthetics,<sup>54</sup> and institutional veterinarians and veterinary anesthesiologists are now recommending these combinations for use more frequently. Newer agents including 5-hydroxytryptamine receptor antagonists<sup>55</sup> and specific blockers of pain perception such as capsaicin and serotonin antagonists, as well as other antagonists of peripheral sensitization are being discussed and new agents are being developed.<sup>56</sup> Cyclooxygenase-2 inhibitors and *N*-methyl-D-aspartate receptor antagonists are coming to the market for use in laboratory animals and will require critical review for use in this setting. Agents that selectively block ectopic discharge are also being developed.<sup>56</sup>

## Preanesthesia and Anesthesia in Rabbits

The following agents are recommended for use in rabbits:

Fentanyl (0.4 mg/mL) + Droperidol (20 mg/mL) administered at 0.3–0.5 mL/kg, IM will provide a surgical plane of anesthesia. Dosage of 0.125 mL/kg of this mixture will provide sedation and also results in vasodilation and easy blood collection from the central ear artery.

Isoflurane (1.25–2.5 vol%, to effect) following Ketamine/Xylazine or Ketamine/ValiumR will provide a good plane of surgical anesthesia for more prolonged procedures. A mask can be used for isoflurane delivery but intubation of the trachea is preferred. When used exclusively masking with isoflurane for induction results in severe apnea and struggling, hypercapnia, acidosis, and bradycardia. Induction with isoflurane is not recommended.<sup>57</sup>

Ketamine (35 mg/kg) + ValiumR (5–10 mg/kg), IM

Ketamine (44 mg/kg) + Xylazine (5 mg/kg), IM

Pentobarbital sodium (35–45 mg/kg), IV, the barbiturates should always be administered with half the dose given rapidly and the rest of the calculated dose given slowly to effect. Apnea is common with pentobarbital.

Servoflurane can be used as an inhalant anesthetic agent but as with isoflurane animals should not be induced using this agent.<sup>57</sup>

## **Chemical Restraint (Sedation) in Rabbits**

Acepromazine: 1.0 mg/kg, SQ, IM, IV, bid

Diazepam: 2.0 mg/kg, IM, IV, bid

Telazol (combination of tiletamine and zolazepam) was found to be nephrotoxic at doses of 32 or 64 mg/kg and produced no analgesia at those doses. Its use is contraindicated in rabbits.<sup>58, 59</sup>

## **Pain Recognition in Rabbits**

Normal rabbits are bright, alert, active, inquisitive, have a smooth hair coat and a good body condition. Pain in rabbits can be evidenced by limping or a change in gait, the withdrawal or protection of an injured part, awkward or abnormal postures, or by licking, rubbing, or scratching the area of injury. Decreased eating and drinking often accompanies chronic pain in rabbits. Rabbits can demonstrate pain by an anxious or apprehensive appearance, inactivity, and a hunched appearance. They sometimes attempt to hide and/or to vocalize. Some individuals might demonstrate aggressive behavior with increased activity, excessive scratching and/or licking. Reactions to being handled might become exaggerated and result in “screaming.” Some rabbits will grind their teeth and salivate excessively when experiencing abdominal pain. Respiratory rates can increase. Anxious rabbits, or rabbits in distress, will sometimes cannibalize their young. Severe distress and pain can result in the tonic immobility reflex (playing dead). This phenomenon is thought to block pain in prey species.<sup>5</sup>

## **Treatment of Pain in Rabbits**

### ***Local Anesthetics***

Bupivacaine: Longer acting local anesthetic. This agent is very useful for infusion along an incision site to provide postoperative analgesia.

Lidocaine: 2% for local infusion. Provides short-term anesthesia adequate for biopsies or minor procedures.

### ***Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)***

Aspirin: Usually use liquid baby aspirin, 100–400 mg/kg, PO

Carprofen: 1–5 mg/kg, PO, bid

Flunixin: 1–2 mg/kg, SQ or IM, bid

Ketoprofen: 1–3 mg/kg, IM

There is no real reason that other NSAIDs cannot be used, but dosages need to be established.

### ***Narcotics***

Buprenorphine: 0.01–0.1 mg/kg, SQ or IM, q 6–12 h

Butorphanol: 0.1–0.5 mg/kg, SQ, IV, IM, q 2–4 h

### ***Alpha-Agonists***

Xylazine: 20 mg/kg, IM

These agents are powerful analgesics, particularly for abdominal organ pain, but also produce significant sedation, bradycardia, and hypotension and are therefore rarely used as analgesics.

## **Preanesthesia and Anesthesia in Dogs**

Entering “general anesthesia, dog” into PubMed yielded 2,373 references. Many different techniques and agents for anesthesia in dogs are available. Board certified veterinary anesthesiologists are working hard to refine and develop techniques for safe and effective anesthesia and analgesia in dogs to cope with a wide variety of health status issues. Anesthesia of the critically ill or injured animal is especially problematic. Veterinary anesthesiologists have taken the same tack as human anesthesiologists using a variety of different agents in combination to achieve

balanced anesthesia with minimal adverse effects. For cardiovascular researchers, the most important aspect relating to the choice of anesthetic regimen to use is to have great familiarity and maximum comfort level with the choice. The following anesthetic protocols all provide reasonable results in dogs:

\*Acepromazine (0.2 mg/kg) + Butorphanol (0.4 mg/kg), IM followed by inhalation anesthesia.

\*Acepromazine (0.05 mg/kg), IM + Oxymorphone (0.05–0.2 mg/kg) IV for induction, followed by inhalation anesthesia (Isoflurane, Halothane, Sevoflurane, or Desflurane)

Acepromazine (0.025 mg/kg) + Pethidine (Meperidine) (3.5 mg/kg), IM + thiopental (10 mg/kg), effects of varying the rate of infusion of thiopental were studied. It was found that a slow rate of thiopental infusion (0.1 mL/kg/min) reduced the induction dose of thiopental required but the quality of induction was inferior to a faster rate of thiopental infusion (0.4 mL/kg/min).<sup>60</sup>

\*Acepromazine (0.05 mg/kg), IM followed by Propofol (4–6 mg/kg), IV

\*Acepromazine (0.05 mg/kg), IM followed by thiopental (8–20 mg/kg), IV for induction, followed by inhalation anesthesia

Aflaxan (steroid anesthetic agent) (2.0–10.0 mg/kg), IV. The duration of anesthesia was dose dependent. It was found that the agent provided rapid and smooth induction with satisfactory conditions for endotracheal intubation and a short duration of anesthesia,  $26.2 \pm 7.5$  min.<sup>61</sup>

Chloralose (60 mg/kg) + Urethane (200 mg/kg): IV is the classical anesthesia used to maintain autonomic control during acute cardiovascular experiments. Dogs do not recover well from this regimen.

Chlorpromazine (0.5 mg/kg), IV + Ketamine (2 mg/kg), IV + Midazolam (0.5 mg/kg), IV

Chlorpromazine (0.5 mg/kg), IV + Propofol (5 mg/kg), IV

Chlorpromazine (0.5 mg/kg), IV + Thiopental (8 mg/kg), IV

Desmedetomidine ( $\alpha$ -2-adrenoceptor agonist, active enantiomer of medetomidine) (1.0–2.0  $\mu$ g/kg) IV, followed by propofol induction (2.3–3.3 mg/kg), IV, followed by desflurane, to effect. Determined to be effective and safe for induction and maintenance of general anesthesia in healthy dogs.<sup>62</sup>

Fentanyl (5.0–10.0  $\mu$ g/kg/h) + isoflurane or sevoflurane

Fentanyl (10.0  $\mu$ g/kg), IV bolus + fentanyl (10.0  $\mu$ g/kg/h) continuous infusion, resulted in sedation but no anesthesia.<sup>63</sup>

Hydromorphone (0.1 mg/kg) + Diazepam (0.2 mg/kg), IV, followed by inhalation anesthetic

\*Ketamine (4–8 mg/kg) + Diazepam (0.2–0.4 mg/kg), IV

Oxymorphone (0.05 mg/kg) + Diazepam (0.2 mg/kg), IM, followed by inhalation anesthetic

Pentobarbital sodium (20–30 mg/kg): IV, half the calculated dose is administered and the remainder to effect

Propofol (6–8 mg/kg), IV for induction, maintained at 24 mg/kg/h constant infusion



Propofol (24 mg/kg/h) + Fentanyl (5.0 µg/kg/h) continuous infusion, IV  
 Romifidine (0.04–0.08 mg/kg) + propofol (6–8 mg/kg), IV for induction followed by isoflurane to effect. This regimen was determined to be effective for induction and maintenance of general anesthesia in healthy dogs.<sup>64</sup>

Telazol (tiletamine/zolazepam) (6–20 mg/kg), IV<sup>65, 66</sup>

Telazol (10 mg/kg) + Etomidate (0.3 mg/kg), IV<sup>67</sup>

Telazol (10 mg/kg), IV + Medetomidine (30 µg/kg), IM<sup>65</sup>

Telazol (10 mg/kg), IV + Xylazine (1.1 mg/kg), IM<sup>65</sup>

\*Thiopental (8–20 mg/kg): IV, half the calculated dose then to effect. Thiopental is usually used for induction followed by intubation of the trachea and then maintenance with inhalation anesthetic.

The seven protocols marked with an asterisk (\*) were compared for arytenoid cartilage motion immediately after induction and no differences were found.<sup>68</sup> It is common to add N<sub>2</sub>O (nitrous oxide) to halothane, isoflurane, and sevoflurane. The use of N<sub>2</sub>O reduces the requirements for the inhalation anesthetics, i.e., less concentration required to maintain the same plane of anesthesia in dogs. N<sub>2</sub>O with isoflurane caused increases in heart rate and arterial blood pressure, less of this reaction with sevoflurane and was not observed with halothane.<sup>69</sup> Combinations of acepromazine with butorphanol and induction with thiopental or propofol were compared with premedication with medetomidine and butorphanol and induction with ketamine and diazepam. In all cases, anesthesia was maintained with halothane. It was found that the use of medetomidine, diazepam, and ketamine produced increased splenic volumes.<sup>70</sup> Combinations of hydromorphone + diazepam and oxymorphone + diazepam were found to be safe in hypovolemic dogs.<sup>71</sup>

Chlorpromazine + thiopental, chlorpromazine + ketamine + midazolam, and chlorpromazine + propofol were compared in an evaluation of neurological reflexes in puppies taken by caesarian section. The neurological reflexes in the puppies were most depressed with chlorpromazine + ketamine/midazolam, next most depressed with chlorpromazine + thiopental and least depressed with chlorpromazine + propofol. The absolute least amount of neurological depression was seen in puppies taken from dams with epidural anesthesia.<sup>72</sup>

Skarda et al.<sup>73</sup> published a retrospective report on 137 dogs and 13 cats with congenital or acquired cardiac disease that were anesthetized for diagnostic, therapeutic, or surgical interventions. The most commonly used drugs were a combination of midazolam + oxymorphone for premedication, thiopental or etomidate (remifentanyl HCl, a µ-opioid agonist with rapid onset and short duration of action) for induction, and isoflurane for maintenance of anesthesia.

## Chemical Restraint (Sedation) in Dogs

Any of the drugs and drug combinations used as preanesthetic regimens listed previously can and are used for chemical restraint in dogs. Some of the most often mentioned agents are:

Acepromazine (0.05–0.2 mg/kg), IM

Acepromazine (0.05 mg/kg) + Butorphanol (0.2 mg/kg), IM

Acepromazine (0.05 mg/kg) + Oxymorphone (0.2 mg/kg), IM

Innovar vet (mixture of Fentanyl + Droperidol) (0.05–0.2 mL/kg), IM

Medetomidine (20 µg/kg), IM

Medetomidine (20 µg/kg) + Butorphanol (0.2 mg/kg), IM

Medetomidine (20 µg/kg) + Hydromorphone (0.1 mg/kg), IM

Medetomidine + hydromorphone and medetomidine + butorphanol provided a longer duration of sedation and better quality of analgesia than medetomidine alone.<sup>74</sup> The combination of acepromazine with butorphanol resulted in a lower incidence of temporary excitement and less panting in dogs after injection compared with the acepromazine oxymorphone combination. There were no significant differences in the degree of sedation, response to noise or manipulation, vocalization, or defecation between the two.<sup>75</sup> When three different sedation protocols were compared for their ability to restrain dogs well enough to make a correct diagnosis of hip dysplasia, it was found that medetomidine and butorphanol were significantly better for this purpose than acepromazine.<sup>76</sup> The combination of medetomidine + butorphanol increased total GFR in healthy dogs but the effect was blocked by the concomitant administration of atropine.<sup>77</sup>

Fentanyl + droperidol (the mixture marketed as Innovar-vet) (0.05 and 0.1 mL/kg), IM were compared with two different doses of medetomidine (0.75 and 1.0 mg/kg). Excellent chemical restraint was achieved with all four regimens. The medetomidine-treated dogs had lower respiratory rates, longer durations of the analgesic effects, but an increased incidence of bradycardia, vomiting, and twitching. Medetomidine-treated dogs shivered less and were less responsive to noisy stimuli than the Innovar-treatment groups. There was also an increased incidence of second-degree heart block in the low dose medetomidine group.<sup>78</sup>

The cardiopulmonary effects of medetomidine (20 µg/kg) + midazolam (0.3 mg/kg) were compared with medetomidine alone (80 µg/kg), both administered IM, in another study. Both protocols caused bradycardia and a transient pressor response but the combination of medetomidine + midazolam provided changes that were less intense than those resulting from the medetomidine alone.<sup>79</sup> Acepromazine (0.1 mg/kg), IM did not have any effect on intravenous glucose tolerance testing in dogs.<sup>80</sup>

## Pain Recognition in Dogs

The behavior of dogs with other dogs and with humans can be unique to the type of pain the animal is experiencing. The personality of the individual animal and the intensity of the pain also play a role. Postural changes can include a hunched back, guarding or protecting the painful area, assuming a “praying” position, sitting or lying down in abnormal ways, or head hanging. Movement changes can include

stiffness, not bearing weight on an affected limb, limping, restless thrashing, trembling or shaking, less than normal tail wagging or carrying the tail abnormally low, reluctance to move about when awake, and being slow to rise. Vocalization signs of pain can include screaming, whining, crying, barking, howling or growling, or a lack of expected vocalization in an animal that is normally vocal. Other behavior keys can be abnormal agitation, poor or no self-grooming, a decrease or complete lack of appetite, a dull attitude, inappropriate urination or defecation or not moving away from it, licking or biting of the affected area, or behavior out of character such as a normally gentle dog becoming aggressive.

Hudson et al.<sup>81</sup> assessed the repeatability and validity of using a VAS to evaluate pain and lameness in dogs. The results were compared with objective measures of lameness made using a force-plate. A rather sophisticated statistical analysis enabled them to conclude that a number of behavioral observations were highly and rather easily correlated with a presumption of pain and/or lameness validating their VAS.

## **Treatment of Pain in Dogs**

### ***Local Anesthetics***

Infusion of local anesthetics, particularly bupivacaine, in surgical incision sites, particularly when combined with NSAIDs or narcotics can be particularly effective for pain relief in dogs.

### ***NSAIDs***

Carprofen: 1–5 mg/kg, PO, bid

Flunixin meglumine: (1 mg/kg), IV or IM qid, do not treat for more than 5 days

Ketoprofen: (1.0 mg/kg), IM, bid

Other NSAIDs such as aspirin, ibuprofen, and acetaminophen seem to have more limited effects in dogs.

### ***Narcotics***

Buprenorphine: (0.01–0.04 mg/kg), SQ every 8–12 h

Butorphanol: (0.2–0.4 mg/kg), SQ, IM, or IV every 2–5 h

Fentanyl patch: (25, 50, 75, or 100 µg/h sizes, depending upon the size of the dog, <10 kg, 11–20 kg, 20–30 kg, >30 kg, respectively)

Meperidine: (2–10 mg/kg), IM or SQ every 2–3 h

## ***Alpha-Agonists***

Most are very effective analgesics but the sedative effects are so strong such that they are usually not very useful for this purpose.

## **Preanesthesia and Anesthesia in Cats**

Many of the same agents used for anesthesia in dogs are used in cats. Cats do, however, pose certain handling problems since they tend to react in a negative way to physical restraint. There are, therefore, great advantages to using preanesthetic regimens that can be administered SQ or IM, and obtaining a level of sedation that makes the placement of an intravenous catheter easier. With the IV catheter in place, it is easy to induce anesthesia, intubate the trachea, and maintain anesthesia using an inhalant anesthetic agent.

\*Acepromazine (10 µg/kg) + Buprenorphine (10 µg/kg), IM + induction with Etomidate (1–2 mg/kg), IV

Desflurane induction with facemask, endotracheal intubation, and maintenance with Desflurane. Mean alveolar concentrations over 5 h of anesthesia were  $10.27\% \pm 1.06\%$ . Rapid induction and recovery were observed.<sup>82</sup>

Ketamine: (10 mg/kg), IM, used at times but not recommended for surgical anesthesia when given alone.

Medetomidine (0.02 mg/kg), IV + Propofol (8–10 mg/kg), IV + Sevoflurane<sup>83</sup>

\*Medetomidine (1.5 mg/M<sup>2</sup> body surface area), IM + Propofol (1–2 mg/kg) for induction

\*Midazolam (1.0 mg/kg) + Ketamine (10.0 mg/kg), IM for induction

Midazolam (0.3–1.0 mg/kg) + Ketamine (2–3 mg/kg) + Butorphanol (0.4 mg/kg), IV, tracheal intubation and anesthesia with Isoflurane to effect<sup>84, 85</sup>

Midazolam (1.0 mg/kg) + Ketamine (2.0 mg/kg) + Butorphanol (0.4 mg/kg), IV + induction with Propofol (8–10 mg/kg), IV and anesthesia maintained with a continuous rate of infusion (CRI) of Fentanyl (0.02 mg/kg/h) or Fentanyl (0.02 mg/kg/h) + Sevoflurane to effect, or CRI of Propofol (12 mg/kg/h). All regimens are used to effect to maintain the desired plane of surgical anesthesia and the gas anesthetic or propofol is adjusted to maintain the predetermined level.<sup>85</sup>

Pentobarbital sodium: (20–30 mg/kg), IV, half the calculated dose rapidly and the remainder given to effect.

Propofol (5.7–12.9 mg/kg), IV + endotracheal intubation and maintenance with desflurane, sevoflurane, isoflurane or halothane<sup>86, 87</sup>

Sevoflurane or Isoflurane induction with facemask followed by endotracheal intubation and maintenance. Sevoflurane provided more rapid induction.<sup>16, 88</sup>

Sevoflurane + N<sub>2</sub>O for induction and maintenance, induction and recovery were both smooth and rapid.<sup>89</sup>

Telazol (combination of tiletamine a dissociative anesthetic agent and zolazepam an alpha-agonist) (10 mg/kg), IV + inhalation anesthesia

Xylazine (0.02 mg/kg), IV + Propofol (8–10 mg/kg), IV + Sevoflurane<sup>83</sup>

The three regimens marked with an asterisk (\*) were compared for use in cats diagnosed with cardiomyopathy. The combination of acepromazine-buprenorphine was determined to be preferred because heart rate, blood pressure, and respiratory effects were minimal.<sup>90</sup>

## Chemical Restraint (Sedation) in Cats

Acepromazine: (0.03–2.2 mg/kg), SQ, IM, or IV<sup>43, 91</sup>

Diazepam: (1.0 mg/kg), IM or IV

Hydromorphone (0.1 mg/kg) + Glycopyrrolate (0.01 mg/kg), SQ, glycopyrrolate is an anticholinergic agent, parasympatholytic.<sup>92</sup>

Hydromorphone: (0.1 mg/kg), SQ<sup>92</sup>

Ketamine: (3.0–30.0 mg/kg), IM<sup>91, 93</sup>

Medetomidine: (20 µg/kg), IM, determined to be safe in cats with left ventricular hypertrophy<sup>94</sup>

Morphine: (0.1 mg/kg), IM<sup>91</sup>

Telazol (combination of tiletamine and zolazepam): (6–20 mg/kg), IM or IP

Telazol (10 mg/kg) + Etomidate (0.3 mg/kg), IM or IP

Thiopental sodium: (10–20 mg/kg), IV<sup>91</sup>

Xylazine: (2.2 mg/kg), IM<sup>91</sup>

Niedfeldt and Robertson<sup>95</sup> report a correlation between postanesthesia hyperthermia and hydromorphone in cats, while acepromazine, acepromazine + buprenorphine, and acepromazine + buprenorphine + ketoprofen did not show these effects. Ketamine has been associated with nonreversible cerebellar damage in Persian-cross cats.<sup>96</sup> The combination of midazolam + oxymorphone for preanesthesia sedation, thiopental or etomidate for induction and isoflurane for anesthesia was found to be the most commonly used regimen for anesthesia in cats with congenital or acquired heart disease.<sup>73</sup> Thiopental sodium, ketamine, acetylpromazine, xylazine, and morphine chemical restraint were evaluated, and all of these agents interfered with glucose tolerance testing in cats.<sup>91</sup>

## **Pain Recognition in Cats**

Cats are, by nature, much more stoic than dogs and other species. A cat experiencing pain is generally quiet. Some individuals may have an apprehensive facial expression, including the appearance of a creased forehead. Pain in the head or ears can cause the animal to tilt the head toward the affected side. Generalized pain in the thorax and/or abdomen can cause the animal to crouch or hunch its back. If the pain is only thoracic, the head, neck, and body can be extended. Cats with abdominal or back pain sometimes stand with the back arched and walk with a stiff or stilted gait. General postural changes can include a hunched back with lowered head, guarding or protecting the painful area, sitting or laying in abnormal positions for that individual. Movement changes can include stiffness, limping, or reluctance to bear weight on a limb including resting with the affected limb raised, restlessness and thrashing, trembling or shaking, reluctance to move when awake, and/or a slowness to rise when stimulated to do so. Vocalization changes include screaming, yowling, hissing, or crying, especially when a painful area is palpated. An individual that is normally vocal, purring, etc. may not vocalize. Behavioral changes include hyperventilation, an agitated state, lack of grooming, loss of appetite and weight loss, dull attitude, excessive sleeping, noticeably less activity, inappropriate urination or defecation and not moving away from soiled areas, excessive licking of an area, hiding and vigorous attempts to escape when handled.

## **Treatment of Pain in Cats**

### ***Local Anesthetics***

Same as for other animals, i.e. local infusion at incision sites before closing.

### ***NSAIDs***

Carprofen: (4 mg/kg, initial dose followed by 1.4 mg/kg, tid)<sup>97</sup>

Flunixin meglumine: (1 mg/kg), IV or IM qid, do not treat for more than 5 days<sup>43</sup>

Ketoprofen: (1.0 mg/kg), IM, bid<sup>43</sup>

### ***Narcotics***

Buprenorphine: (0.004–0.01 mg/kg), SQ every 8–12 h<sup>43</sup>

Butorphanol: (0.1–0.4 mg/kg), SQ, every 6 h<sup>43</sup>

Levomethadone: (0.3 mg/kg), SQ every 8 h<sup>97</sup>

Morphine: (0.1 mg/kg), SQ every 4–6 h<sup>43</sup>

## ***Alpha-Agonists***

Same as for dogs, good analgesia but too much sedation for most applications. Midazolam (0.652 mg/kg) prevented conscious perception of a stimulus to the ulnar nerve in 95% of cats tested. Nine of 12 cats exhibited an abnormal arousal state with four being restless and five being sedated. Seven of the 12 cats exhibited abnormal behaviors when approached and 8 of the 12 abnormal behaviors when restrained. Five of the 12 cats vocalized more during recovery.<sup>93</sup>

## **Preanesthesia and Anesthesia in Guinea Pigs**

Anesthetizing guinea pigs is reported to be difficult and induction times, depth of anesthesia, and recovery times can vary.

Ketamine (35 mg/kg), IP + Xylazine (5 mg/kg), IP<sup>43</sup>

Pentobarbital sodium (35–45 mg/kg), IP<sup>43</sup>

Telazol (10 mg/kg) + Medetomidine (20 µg/kg), IM<sup>98, 99</sup>

Telazol (10 mg/kg) + Xylazine (5 mg/kg), IM<sup>98</sup>

Telazol (100 mg/kg) + Xylazine (10 mg/kg), IP<sup>100</sup>

Telazol (60 mg/kg), IP + Xylazine (5 mg/kg), IP + Butorphanol (0.1 mg/kg), IM, provided smooth induction and recovery with deep surgical anesthesia of long duration<sup>101</sup>

Radde et al.<sup>102</sup> compared telazol at two different dosages, pentobarbital, methoxyflurane, and three different doses of ketamine/xylazine and ketamine/xylazine + methoxyflurane. They found that telazol induced a short period of chemical restraint but lacked analgesic effects at the doses used. Pentobarbital induced prolonged chemical restraint but the analgesic effects were brief. Methoxyflurane induced transient anesthesia and analgesia but is no longer on the market. The ketamine/xylazine combinations all produced good analgesia and chemical restraint but at low doses were suitable only for mildly painful procedures.

## **Chemical Restraint (Sedation) in Guinea Pigs**

The same agents used for anesthesia are used for chemical restraint in this species.

## **Pain Recognition in Guinea Pigs**

Normal guinea pigs will stampede and squeal when frightened or when attempts are made by strangers to handle them. Some animals may run to hide, squealing when strangers enter the room. Sick guinea pigs or guinea pigs in pain will usually



hide and be quiet. Other signs of pain in guinea pigs are similar to those observed in rats and mice.

## **Treatment of Pain in Guinea Pigs**

### ***Local Anesthetic Agents***

The same as for other species, infusion of incision sites before closure.

### ***NSAIDs***

Flunixin: (2.5–5.0 mg/kg), SQ, every 12–24 h, maximum of 5 days of treatment. Other NSAIDs can be used at the same dosages cited for rats and mice.

### ***Narcotics***

Buprenorphine: (0.1–0.5 mg/kg), SQ every 8–12 h  
Meperidine: (10–20 mg/kg), SQ or IM, every 2–3 h  
Morphine: (2–5 mg/kg), SQ or IM, every 4 h

### ***Alpha-Agonists***

Products and doses the same as for rats and mice.

## **Preanesthesia and Anesthesia in Pigs**

Malignant hyperthermia is a genetic disorder of skeletal muscle and is seen in susceptible pigs exposed to inhalation anesthetics, particularly halothane, and some depolarizing muscle relaxants.<sup>103</sup> Malignant hyperthermia susceptible and malignant hyperthermia nonsensitive pigs are being bred and used for a variety of studies aimed at understanding and diagnosing this condition.<sup>103–105</sup>

Our experience is that positive end-expiratory pressure (PEEP) needs to be employed (3–7 cm H<sub>2</sub>O) to maintain adequate pulmonary function and normal acid-base balance during general anesthesia, particularly when associated with open thorax

procedures in pigs, sheeps, and goats.<sup>106-108</sup> The following anesthetic regimens are used in swine:

- Acepromazine (2 mg/kg) + Ketamine (10 mg/kg) + atropine (0.05 mg/kg), IM + isoflurane by mask, tracheal intubation and maintenance with Isoflurane to effect<sup>109</sup>
- Acepromazine (4 mg/kg), IM + Metomidate (10 mg/kg), IP + Etomidate (0.3 mg/kg), IV + Fentanyl (10 µg/kg), IV + continuous infusion of Etomidate (2.5 mg/kg/h) and Fentanyl (50 µg/kg/h) + N<sub>2</sub>O (66%) in oxygen<sup>104</sup>
- Diazepam (0.25 mg/kg) + atropine (0.005 mg/kg), IM + sodium Thiopental (30 mg/kg), IV + additional doses of thiopental as needed<sup>110</sup>
- Isoflurane (2 vol%) by face mask for induction) + tracheal intubation and Isoflurane (0.5 vol%) for maintenance<sup>111</sup>
- Ketamine (22 mg/kg) + Acepromazine (1.1 mg/kg), IM + Pentobarbital sodium (20 mg/kg), IV the latter given to effect
- Ketamine (10 mg/kg) + Diazepam (0.5 mg/kg), IM + Thiopental (5 mg/kg), IV to effect + tracheal intubation and Isoflurane (0.8–1.5 vol%) + Fentanyl (5 µg/kg/h)<sup>112</sup>
- Ketamine (15 mg/kg) + halothane (1.0 vol%), oxygen (59 vol%) and N<sub>2</sub>O (40 vol%)<sup>113</sup>
- Ketamine (20 mg/kg) + Midazolam (0.1 mg/kg), Atropine (0.25 mg/kg), IM + induction with Midazolam (0.1 mg/kg) + Sufentanil (0.5 mg/kg), IV + maintenance with continuous infusion of Midazolam (0.15 mg/kg/h) + Sufentanil (0.5 µg/kg/h), IV<sup>114</sup>
- Ketamine (8–10 mg/kg), IM + Propofol (0.2–0.4 mg/kg/min), IV<sup>103</sup>
- Ketamine (10 mg/kg) + Xylazine (4 mg/kg), IM + alpha-chloralose (50 mg/kg), rapid IV infusion + alpha-chloralose (40 mg/kg/h) continuous IV infusion<sup>115</sup>
- Ketamine (20 mg/kg) + Xylazine (0.05 mg/kg), IM + induction with Isoflurane (5 vol%) by face mask and maintenance with isoflurane (1.5–2.5 vol%) to effect<sup>116</sup>
- Medetomidine (80 µg/kg) + Ketamine (10 mg/kg) + Butorhanol (200 µg/kg), IM + tracheal intubation and isoflurane to effect<sup>117</sup>
- Midazolam (1.5 mg/kg) + Ketamine (20 mg/kg), IM + Atropine (0.05 mg/kg), IV + tracheal intubation and ventilation with oxygen (30 vol%), N<sub>2</sub>O (67 vol%), and Isoflurane (3 vol%)<sup>118</sup>
- Propofol (2.5–15 mg/kg), IV<sup>119</sup>
- Telazol (4.4 mg/kg) + Ketamine (2.2 mg/kg) + Xylazine (2.2 mg/kg), IM + tracheal intubation and inhalation anesthetic<sup>120, 121</sup>
- Telazol (4.4 mg/kg) + Xylazine (2.2 mg/kg), IM + tracheal intubation and inhalation anesthetic<sup>120, 121</sup>
- Telazol (4.4 mg/kg) + Xylazine (2.2 mg/kg) + atropine (0.04 mg/kg), IV + tracheal intubation and Isoflurane (1–3 vol%) to effect<sup>122</sup>
- Thiamyl sodium (30 mg/kg), IV + tracheal intubation and halothane anesthesia (0.5–1.5 vol%, to effect)<sup>123</sup>

A novel new inhaler system used to administer isoflurane to piglets for minor surgical procedures such as castration was recently described. The system consists of a mask, a center body with a valve that can be opened or closed, a vaporization

chamber with a wick system and an injection port, and a rebreathing bag. Isoflurane is delivered via the injection port and the rebreathing bag is filled with oxygen. The mask is fitted over the piglet's nose, the valve is opened and the respiration of the pig moves gases in and out of the inhaler and rebreathing bag. The system provides economical, safe and rapid induction and a safe, smooth recovery in piglets.<sup>124</sup>

## **Chemical Restraint (Sedation) in Pigs**

Many of the same protocols described previously for preanesthesia in pigs can and are used for sedation. Other agents for sedation in pigs have also been approved by animal care and use committees and published. These include:

Acepromazine: (0.04–0.06 mg/kg), SQ, IM or IV, bid

Diazepam: (0.5–8.5 mg/kg), IV, bid<sup>43, 123</sup>

Medetomidine (80 µg/kg) + Ketamine (10 mg/kg), IM<sup>125</sup>

Medetomidine (80 µg/kg) + Midazolam (0.1 mg/kg), IM<sup>126</sup>

Telazol: (4.0–5.0 mg/kg), IM<sup>120, 121, 127</sup>

Telazol (4.4 mg/kg) + Ketamine (2.2 mg/kg), IM<sup>120, 121</sup>

Telazol (3.3 mg/kg) + Xylazine (1.3 mg/kg), IM using blow darts on wild pigs. It was found that some of the wild pigs were only partially immobilized at this dose so the authors recommended 4.0 mg/kg Telazol + 2.0 mg/kg Xylazine<sup>128</sup>

Xylazine (5 mg/kg) + Ketamine (10 mg/kg), IM<sup>125</sup>

## **Pain Recognition in Pigs**

Pigs in pain usually demonstrate changes in their social behavior, (i.e., interactions with other pigs), gait, and posture. They will frequently not indulge in bed making behavior. They normally squeal and attempt to escape when handled and pain will usually accentuate those behaviors. They will usually squeal or grunt loudly when a painful area is palpated and may exhibit loud and persistent vocalization. Adult animals may become aggressive, hide, or be reluctant to move about. They will act dull and depressed with the head held low. They may exhibit rapid shallow respirations, excessive grunting, and/or grinding of the teeth.<sup>5</sup>

## **Treatment of Pain in Pigs**

### ***Local Anesthetic Agents***

The same as for other species, the use of local anesthetics by infusion along incision sites before surgical closure has proven to be very effective.

## ***NSAIDs***

Flunixin-meglumine: (0.5–1.5 mg/kg), SQ or IV, every 12–24 h, five day maximum

Flunixin-meglumine (1.1 mg/kg) + Ceftiofur (Naxcel) (2.2 mg/kg), IV<sup>117</sup>

Ketoprofen: (1.0 mg/kg), IM, bid

Phenylbutazone: (1.0–4.0 mg/kg), IV or PO, every 12 h

## ***Narcotics***

Buprenorphine: (0.005–0.01 mg/kg), SQ or IM every 6–12 h

Butorphanol (0.1–0.3 mg/kg), IM or IV every 8–12 h

Fentanyl patch (25, 50, 75, or 100 µg/h patches) depending upon the size of the animal

Meperidine (2.0–10.0 mg/kg), IM or SQ, every 2–4 h

## ***Alpha-Agonists***

Acepromazine: (0.1–1.1 mg/kg), IM

Midazolam: (0.1–0.5 mg/kg), IM or IV

Xylazine: (0.2–2.0 mg/kg), IM

## **Preanesthesia and Anesthesia in Calves, Sheep, and Goats**

Small ruminants are usually docile enough to make induction of anesthesia with Isoflurane or Desflurane very easy using a facemask (3–5 vol%) followed by tracheal intubation and maintenance with low levels (0.5–2.0 vol%) of the same agent. The advantage of the technique is smooth induction and very fast recovery from anesthesia. Many animal care and use committees consider these to be the agents of choice for general anesthesia in calves, sheep, and goats.<sup>43, 129, 130</sup> Other anesthetic regimens include the prior use of sedatives as preanesthetic agents and combinations of agents for either preanesthesia, including enough sedation to make tracheal intubation possible, or anesthesia with additional doses of one or more agents. These protocols include:

Diazepam (0.25 mg/kg) + Ketamine (4 mg/kg), IV, tracheal intubation + Halothane (2 vol%) for maintenance<sup>131</sup>

Halothane (4 vol%) + N<sub>2</sub>O (50 vol%) for induction + maintenance with Halothane (1.0–2.0 vol%) to effect<sup>132</sup>

Ketamine (15 mg/kg) + Acepromazine (0.5 mg/kg) + atropine (2 mg/kg), tracheal intubation + maintenance of anesthesia in a surgical plane with Halothane to effect<sup>133</sup>

Ketamine (5–15 mg/kg) + Xylazine (0.1–0.2 mg/kg), IM<sup>134</sup>

Ketamine (20 mg/kg) + Xylazine (0.5 mg/kg), IM + Isoflurane to effect<sup>106</sup>

Propofol (2.5–15 mg/kg), IV induction and continuous infusion<sup>119</sup>

Telazol (13.2 mg/kg) + Xylazine (0.11 mg/kg), IV produced good muscle relaxation and a usefully long duration of anesthesia but a high incidence of apnea lasting as long as 2 min in sheep<sup>135</sup>

Thiopental: (25 mg/kg), IV, half dose rapidly and then to effect, for induction of anesthesia, since intravenous injections are done very easily in small ruminants this technique can be very useful

Xylazine (0.2 mg/kg), IM + a mixture of Xylazine (0.1 mg/mL) + Guaiphenesin (50 mg/mL) + Ketamine (1 mg/mL) was continuously infused at 1.1 mL/kg/h<sup>136</sup>

Xylazine (0.1 mg/kg), IM + Ketamine (5–20 mg/kg), IV until a surgical plane of anesthesia is achieved<sup>137</sup>

## Chemical Restraint (Sedation) in Small Ruminants

Acepromazine: (0.05–0.2 mg/kg), IM or SQ

Diazepam: (0.5–1.5 mg/kg), IM or IV

Midazolam: (0.4–1.3 mg/kg), IV

Telazol: (5–13.2 mg/kg), high doses frequently result in apnea<sup>135</sup>

Xylazine: (0.05–0.3 mg/kg), IM or SQ

## Recognition of Pain in Small Ruminants

When experiencing pain, small ruminants will often appear dull and depressed with changes in posture and movement. Knowledgeable caretakers often report changes in facial expression by these species when in pain. Heads may be held low and the animals may demonstrate a lack of interest shown in their surroundings or when approached. There is almost always a loss of appetite and weight loss. Severe pain may be manifest in rapid, shallow breathing. When handled calves, sheep, and goats might react violently or adopt a very rigid posture designed to immobilize the region of pain. Grunting and teeth grinding may accompany pain. These species will demonstrate restlessness by repeatedly lying down then getting up indicating an inability to become comfortable. Localized pain can be associated with persistent

licking, nuzzling, or kicking at the injured area. This is especially common with joint pain in goats. If pain is severe it can be expressed by excessive vocalization, bellowing in calves, bleating in sheep and goats.

A study by Kock et al.<sup>138</sup> compared physiological parameters including; pulse rates, rectal temperatures and respiratory rates and selected biochemical measurements including; cortisol, CPK, AP, BUN and others, in free-ranging bighorn sheep captured with drop-nets, drive-nets, net-guns, and chemical immobilization with Telazol. They determined that chemical immobilization resulted in the largest changes in the various parameters measure.

## **Treatment of Pain in Small Ruminants**

### ***Local Anesthetic Agents***

Local infiltration of surgical incisions with long acting local anesthetic agents has been repeatedly shown to result in significant pain reduction.

### ***NSAIDs***

Flunixin-meglumine: (1.0–2.0 mg/kg), IV, tid

Phenylbutazone: (1.0–4.0 mg/kg), IV, tid

### ***Narcotics***

Buprenorphine: (0.005–0.015 mg/kg), SQ or IM every 4–12 h

Butorphanol: (0.2–0.5 mg/kg), SQ or IM every 4 h

Fentanyl patch: (25, 50, 75, or 100 µg/h patches depending upon body weight). Do not forget to shave the area before applying the patch.

Meperidine: (2–10 mg/kg), SQ or IM every 4 h, do not exceed 200 mg total dose

### ***Alpha-Agonists***

Acepromazine: (0.04–0.06 mg/kg), SQ, IM or IV, bid

Diazepam: (0.5–1.5 mg/kg), IV, bid

## Preanesthesia and Anesthesia in Rhesus Monkeys

Although nonhuman primates of other species are used for cardiovascular studies, their use is becoming more difficult and less common. Significant numbers of Rhesus monkeys are still being used and for this reason, and because more data are available for this species, only Rhesus will be discussed in this text. However, many of the agents described in this section can be and are used in other species of nonhuman primates and at similar doses.

Glycopyrrolate (0.01 mg/kg) + Ketamine (15 mg/kg), IM + Fentanyl (3 µg/kg) + Thiopental (5 mg/kg), IV + Isoflurane + Fentanyl (3 µg/kg/h)<sup>139</sup>

Ketamine (15 mg/kg), IM<sup>140</sup>

Ketamine (15 mg/kg), IM + Glycopyrrolate (12.5 µg/kg), IV + Halothane (1–2 vol%) to effect<sup>141</sup>

Ketamine (15 mg/kg), IM + Halothane (1.5–2.5 vol%) to effect<sup>142</sup>

Ketamine (10 mg/kg) + Xylazine (0.25–2.0 mg/kg), IM

Isoflurane, Desflurane, Halothane, or Sevoflurane delivered by face mask for induction (4–5 vol%) and then maintained with lower concentrations (1.5–2.5 vol%) to effect<sup>140, 143–145</sup>

Pentobarbital sodium (25 mg/kg), IV, half of dose delivered rapidly the remainder slowly to effect, additional doses as required to maintain the desired plane of anesthesia<sup>143, 146, 147</sup>

## Chemical Restraint (Sedation) in Rhesus Monkeys

Acepromazine: (0.2 mg/kg), SQ, IM, or IV

Diazepam: (1.0 mg/kg), IM or IV

Ketamine: (5–10 mg/kg), IM

## Pain Recognition in Rhesus Monkeys

This species can demonstrate very little reaction to surgical procedures or injury, especially when they are aware of human observation. Experienced investigators feel that viewing animals from a distance or with video makes it more likely to make the necessary observations to diagnose pain. Loud and persistent vocalization is more likely to signify alarm or anger than pain in this species. In general, these animals will have a general appearance of misery and dejection when in pain. They might huddle in a crouched posture and hold their arms across their chest with the head bent forward. Some observers report a “sad” facial expression or grimacing and/or a glassy eyed appearance. The animal might moan or scream, particularly



with acute severe pain. There is a tendency to avoid companions in the cage and to stop grooming activities. When in pain they may also attract altered attention from cage mates varying from lack of normal social grooming to attacks. Acute abdominal pain can be demonstrated by facial contortions, clenching or grinding of teeth, general restlessness, and shaking, accompanied by grunts and moans. When in pain these animals will generally refuse food and water.<sup>5</sup>

There have been some interesting studies conducted regarding stress and distress in Rhesus monkeys. When Ketamine was used to restrain animals not preconditioned to handling, definitive baseline plasma glucose tolerance curves could not be established. When the same animals were conditioned and trained in restraint chairs, clear baseline control data were obtained.<sup>148</sup> Similar results were obtained for hematological, biochemical, and ECG data but a minimum of 3 months of training (conditioning) was required.<sup>149</sup> A large number of adult male Rhesus monkeys were studied for behavioral and hypothalamic-pituitary-adrenal activity as a result of seven consecutive days of physical restraint. These data showed that behavior was not necessarily an indicator of underlying physiological processes and the observed reduction in hypothalamic-pituitary-adrenal activity that was observed with repeated restraint was due to a physiological adaptation to the high cortisol concentrations and not to psychological habituation to the restraint procedures.<sup>150</sup>

## **Treatment of Pain in Rhesus Monkeys**

### ***Local Anesthetics***

As in all other species where it has been evaluated infusion of surgical incisions during closure is quite effective.

### ***NSAIDs***

Flunixin meglumine: (1.1 mg/kg), IV or IM every 24 h or (0.3–1.0 mg/kg) SQ or IV every 12–24 h, five days maximum of treatment

Tylenol Pediatric Suspension (Acetaminophen): (5–10 mg/kg), PO every 6–12 h

### ***Narcotics***

Buprenorphine: (0.01–0.04 mg/kg), SQ, every 6–12 h

Butorphanol: (0.1–0.2 mg/kg), IM, every 12–48 h

Meperidine: (2.0–4.0 mg/kg), IM, every 8–12 h

## Conclusions

It is clear from the studies reported in this chapter that many different drugs, drug combinations, and drug dosages are being used for anesthesia, chemical restraint, and analgesia in animals for a wide variety of experimental procedures. The treatment of pain in animals is becoming a subspecialty within veterinary anesthesiology. We can expect considerable new understanding and the development of new and more effective protocols as the science matures. Many analgesics are now available that have not yet been fully tested in all animal species. Investigators must and should consult with knowledgeable sources when making a choice about anesthesia, chemical restraint, or analgesia.

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