Evaluation of a survey of the diplomates of the American College of Laboratory Animal Medicine on use of analgesic agents in animals used in biomedical research

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Objective—To determine the analgesic agents administered to animals frequently used in biomedical research.

Design—Telephone survey.

Sample Population—Diplomates of the American College of Laboratory Animal Medicine.

Procedure—200 of 429 active diplomates listed in the 1993 directory of the American College of Laboratory Animal Medicine were selected at random for telephone interviews. Diplomates were asked to identify the species that they cared for and the dosages, dosing intervals, and routes of administration for analgesic agents.

Results—90 of 200 (45%) diplomates completed the survey. Twenty-two analgesic agents were identified for use in 472 applications in 16 species. Opioid analgesics were the most frequently selected agents, with buprenorphine hydrochloride and butorphanol being most frequently used. Intramuscular and subcutaneous routes of administration were used most frequently.

Clinical Implications—Among diplomates of the American College of Laboratory Animal Medicine, opioids are the most frequently selected agents used to induce analgesia in animals used in biomedical research. Dosages and dosing intervals used vary widely among animals of various species as well as for animals in each species. (*J Am Vet Med Assoc* 1996;209: 918–921)

The use of analgesic agents in animals has received considerable attention.[1,2] The focus on providing adequate analgesia in animals used in biomedical research is particularly pertinent, because administration of postoperative analgesic agents essentially has been mandated by the US government.[3] The need to provide analgesia is complicated by a paucity of well-controlled studies on the safety and efficacy of analgesic agents administered to animals used in biomedical research.[4,5] The lack of information detailing dose-response characteristics and dosing intervals for analgesic agents used in most laboratory animal species has forced veterinarians and allied animal health professionals to extrapolate information obtained from studies performed in dogs, cats, and human beings.[6] These extrapolations are used for developing initial dosages and dosing intervals that subsequently are modified on the basis of subjective assessment of an animal's response.[6] Regimens and dosing protocols that apparently can be used successfully are communicated to other interested caretakers, usually on an informal basis via seminars at national and international meetings. This method of determination of efficacy and information dissemination is likely to continue, primarily because of a lack of funding for controlled studies in target species and the subsequent lack of controlled studies that would allow researchers to investigate applied aspects of an agent's analgesic effects.

The purpose of the survey reported here was to determine the analgesic agents that were being administered to animals used in biomedical research. The results would provide information about species, analgesic agents, dosages, dosing intervals, and routes of administration used to provide pain relief in animals used in biomedical research and would serve as a compilation of the collective thoughts of a population of veterinarians actively involved in the care of laboratory animals.

Materials and Methods

A survey was designed to determine the analgesic agents that were administered to animals used in biomedical research. Two hundred diplomates of the American College of Laboratory Animal Medicine were selected at random from the 429 active diplomates listed in the 1993 directory. Selected diplomates initially were mailed a letter that indicated the purpose of the survey and the proposed method of data collection. A sample of the data collection sheet was included to aid respondents in preparing for the telephone survey. Diplomates were contacted by telephone to establish a time at which the survey could be completed. The survey was completed via telephone by a registered animal health technician who had advanced training and experience in anesthesia. Diplomates were asked to identify the animal species that they were responsible for and dealt with on a regular basis (> 1 contact/mo). For each of the species indicated, diplomates were asked about the analgesic agents and techniques that were used. Species, agents, dosages, dosing intervals, and routes of administration were recorded.

Information was tabulated and analyzed. The number of respondents who used analgesics in a given species was determined, and the percentage of those respondents who used a particular drug was calculated. In addition, mean, median, and mode dosages were determined for each agent in each species.

Results

The survey was conducted between January and June 1994. Of the 200 diplomates randomly selected,

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Funded in part by a grant from Mallinckrodt Veterinary Inc, Mundelein, Ill.

The authors thank Dr. Gay Miller and Ms. Linda Bednarski for assistance with the survey.

Table 1—Results of a survey on the use of analgesic agents administered to dogs used in biomedical research

Agent	No. of users/No. of respondents	Dosage			Dosing interval (h)	Route
		Range (mg/kg)	Mean (mg/kg)	Median (mg/kg)		
Buprenorphine	25/39	0.005–0.050	0.015	0.015	6, 8, 12	IM, SC
Butorphanol	21/39	0.025–2.000	0.390	0.200	3, 4, 6, 8, 12, as needed	IM, SC
Aspirin	8/39	8.0–40.0	13.2	10.0	8, 12, 24	PO
Morphine	5/39	0.1–5.0	1.8	1.0	4, 12	IM, SC
Pentazocine	4/39	0.25–3.30	1.55	1.60	4, 8, 12	IM, SC

Table 2—Results of a survey on the use of analgesic agents administered to mice used in biomedical research

Agent	No. of users/No. of respondents	Dosage			Dosing interval (h)	Route
		Range (mg/kg)	Mean (mg/kg)	Median (mg/kg)		
Buprenorphine	22/31	0.03–2.50	0.99	0.30	6, 8, 12, 24	IM, SC, IP
Acetaminophen	6/31	325 mg/300 ml of H_2O	NA	NA	as needed	PO
Butorphanol	5/31	0.0013–5.4000	2.92	3.00	2, 8	IM, SC

NA = not applicable.

Table 3—Results of a survey on the use of analgesic agents administered to primates used in biomedical research

Agent	No. of users/No. of respondents	Dosage			Dosing interval (h)	Route
		Range (mg/kg)	Mean (mg/kg)	Median (mg/kg)		
Buprenorphine	36/53	0.005–0.650	0.017	0.010	8, 12, as needed	IM, SC, IV
Butorphanol	21/53	0.01–0.50	0.11	0.05	4, 6, 8, 12, as needed	IM, SC
Acetaminophen	6/53	10–100	39	15	6, 8, 12, as needed	PO
Morphine	4/53	0.75–1.50	1.06	1.25	4, 8, 12	IM, SC
Meperidine	4/53	3.0–10.0	5.0	3.5	8, 12	IM
Flunixin meglumine	4/53	1.00–3.00	1.56	1.10	8, 12, 24	IM
Oxymorphone	3/53	0.01–0.15	0.10	NA	6, 12	IM
Aspirin	3/53	12.5–15.0	14.0	NA	12, as needed	PO

NA = not applicable.

Table 4—Results of a survey on the use of analgesic agents administered to rabbits used in biomedical research

Agent	No. of users/No. of respondents	Dosage			Dosing interval (h)	Route
		Range (mg/kg)	Mean (mg/kg)	Median (mg/kg)		
Buprenorphine	33/46	0.005–0.750	0.050	0.030	8, 12, single dose, as needed	IM, SC, IV
Butorphanol	13/46	0.011–4.250	0.600	0.300	4, 6, 8, 12, single dose, as needed	IM, SC, IV, per rectum
Acetaminophen	5/46	1.0–3.0 mg/ml of H_2O	1.8 mg/ml of H_2O	1.5 mg/ml of H_2O	as needed	PO
Nalbuphine	3/46	1.0–1.5	1.2	NA	8, 12	IM, SC
Meperidine	3/46	6.00–7.50, 0.200 mg/ml of H_2O	6.75	NA	as needed	IV, PO
Xylazine	3/46	1.5–10.0	6.3	7.5	12	IM

NA = not applicable.

Table 5—Results of a survey on the use of analgesic agents administered to sheep and goats used in biomedical research

Agent	No. of users/No. of respondents	Dosage			Dosing interval (h)	Route
		Range (mg/kg)	Mean (mg/kg)	Median (mg/kg)		
Buprenorphine	15/17	0.0050–0.1050	0.0240	0.0075	1, 8, 12	IM, SC
Flunixin meglumine	8/17	0.50–1.10	0.94	1.00	8, 24	IM, SC, IV
Butorphanol	4/17	0.025–0.400	0.160	0.100	8, 12	IM, SC, IV

Table 6—Results of a survey on the use of analgesic agents administered to cats, guinea pigs, ferrets, and hamsters used in biomedical research

Agent	No. of users/No. of respondents	Dosage			Dosing interval (h)	Route
		Range (mg/kg)	Mean (mg/kg)	Median (mg/kg)		
Cats						
Buprenorphine	12/17	0.005–0.100	0.016	0.0075	6, 12, as needed	IM, SC
Butorphanol	4/17	0.30–0.40	0.40	0.40	8, 12	IM, SC
Guinea pigs						
Buprenorphine	12/14	0.025–0.300	0.060	0.050	8, 12	IM, SC
Butorphanol	5/14	0.025–0.40	0.110	0.040	4, 6, 8, 12	IM, SC
Ferrets						
Buprenorphine	4/7	0.005–0.100	0.030	0.0125	12	IM, SC
Butorphanol	4/7	0.025–0.500	0.260	0.250	8, 12	IM, SC
Hamsters						
Buprenorphine	6/6	0.005–0.300	0.120	0.047	8, 12	IM, SC
Butorphanol	3/6	0.125–2.000	0.840	0.400	4, 12	IM, SC

90 (45%) completed the survey. A minimum of 3 attempts to contact diplomates during a 3-week period was made. We were unable to contact 19 diplomates, 21 diplomates referred us to co-workers who had already completed the survey, 40 diplomates were not actively involved in anesthesia of laboratory animals at the time of the survey, and 30 diplomates declined to participate for various reasons.

Respondents reported the use of 22 analgesic agents in 472 applications in 16 species (amphibians, bovids, canids, caprids, equids, felids, gerbils, guinea pigs, hamsters, mice, mustelids, ovids, primates, rabbits, rats, and swine). Responses were reported for those species that were identified by 6 or more respondents (Tables 1–6). Within a species, agents that were identified by 3 or more respondents for use in that species were reported.

The most commonly used agents were buprenorphine hydrochloride (223 responses, 14 species), butorphanol (100 responses, 13 species), acetaminophen (26 responses, 8 species), flunixin meglumine (23 responses, 9 species), aspirin (17 responses, 5 species), oxymorphone hydrochloride (15 responses, 9 species), meperidine hydrochloride (15 responses, 9 species), nalbuphine hydrochloride (12 responses, 6 species), xylazine hydrochloride (10 responses, 7 species), morphine (9 responses, 2 species), pentazocine (7 responses, 3 species), phenylbutazone (2 responses, 2 species), bupivacaine hydrochloride (2 responses, 2

species), diazepam (2 responses, 2 species), fentanyl citrate-droperidol (2 responses, 1 species), and fentanyl, promazine hydrochloride, chlorpromazine, dexamethasone, lidocaine, mepivacaine hydrochloride, and proparacaine hydrochloride, each with 1 response in 1 species.

Of 472 applications of analgesic agents, 384 (81%) involved use of opioids (buprenorphine, butorphanol, meperidine, oxymorphone, nalbuphine, pentazocine, morphine, fentanyl, and fentanyl citrate-droperidol). Sixty-eight (14%) applications of analgesic agents involved use of nonsteroidal anti-inflammatory agents (acetaminophen, flunixin meglumine, aspirin, and phenylbutazone), 10 (2%) involved use of alpha-2 adrenoceptor agonists (xylazine), and 5 (1%) involved use of local anesthetics (bupivacaine, mepivacaine, lidocaine, and proparacaine). The reported use of phenothiazine tranquilizers (chlorpromazine and promazine), benzodiazepine tranquilizers (diazepam), and corticosteroids (dexamethasone) comprised 5 of 472 (1%) responses.

The most commonly used routes of administration reported were intramuscular (286 applications), subcutaneous (145), oral (43), intravenous (32), intraperitoneal (3), rectal (1), and topical (1). Some respondents indicated multiple routes of administration for a particular agent in a specific species.

Discussion

Most of the responses in the survey reported here reflected the parenteral route for use of analgesic agents known to produce their effects at the level of the brain and spinal cord. A wide range of dosages and dosing intervals were used. Most reported applications were of opioid drugs, predominately the long-acting opioid partial agonist buprenorphine.

Several factors influence analgesic agent selection. Painful stimuli vary in intensity. In human beings, mild-to-moderate pain sensations may be eliminated by administration of nonsteroidal anti-inflammatory drugs.[7] More severe pain sensations, such as those associated with orthopedic surgery, may require administration of more potent compounds, such as opioids.[7] We did not ask questions regarding the type of painful stimuli that were being treated and, thus, were not able to establish those agents that were most effective across the spectrum of potential painful intensities. We would expect that the responses we received represented treatment of signs of pain produced by a variety of stimuli and represented the respondents' collective general impressions. The wide range of dosages and dosing intervals within animals of the same species and among animals of several species were additional indicators of the varying intensity of painful stimuli being treated. The need for initial administration of analgesic agents or the need for readministration of analgesic agents often is predicated on the use of predetermined protocols, knowledge of the procedure performed, and the ability to recognize physical manifestations of pain in a given species.[8] Specific adverse effects of particular agents also influence selection. Historically, opioids have been used with some reluctance, because they produce respiratory depression, gastrointestinal ileus, and cardiovascular depression.[9] Analysis of the results of the survey reported here indicated that this reluctance has changed. Newer opioids such as buprenorphine and butorphanol have fewer adverse effects than most other opioids, perhaps accounting for their frequent use. The challenge when selecting an appropriate analgesic agent is to choose the agent that provides sufficient analgesia while minimally depressing homeostasis, within the context of the needs of an animal.

Opioid agents have a long and extensive history of use in human beings and other animals as analgesics; thus, it is not surprising that they are the dominant class of agents used to obtund pain in laboratory animals. Opioid administration is generally considered to be the most practical and effective method of producing analgesia. Selection of specific analgesic agents usually is determined by a caretaker's knowledge of pharmacologic effects of an agent, analgesic potency of that agent, potential adverse effects, and expected duration of action.

Buprenorphine accounted for 223 of 384 (58%) opioid applications reported in the survey. Buprenorphine is a partial agonist at opioid receptors, with most of its activity attributed to stimulation of mu receptors.[10] In human beings, buprenorphine is approximately 30 times more potent than morphine and is supplied as a clear solution (0.3 mg of buprenorphine/ml) intended for intravenous or intramuscular injection.[10] Analgesic activity peaks in 1 hour and lasts for 6 hours or longer.[10] Factors accounting for the frequent use of buprenorphine in laboratory animals may include that it has few adverse effects and has a prolonged duration of action in laboratory animals, determined on the basis of subjective assessments and studies in human beings.[9]

Butorphanol, an opioid agonist-antagonist, produces its primary agonist activity at the kappa receptor, and it has mixed activity at the mu receptor.[11] In human beings, butorphanol is approximately 5 times more potent than morphine; however, its duration of action is shorter than buprenorphine, and it can cause mood alterations when given in higher dosages to dogs.[11] Unlike other opioids, butorphanol does not require special licensure.

Analysis of the results of the survey reported here indicated that alpha-2 adrenoceptor agonists and local anesthetics were used infrequently for pain relief. Use of drugs that have little or no analgesic activity was reported, but was rare (5/472 applications, 1%). Chlorpromazine, promazine, and diazepam are tranquilizers that do not have demonstrable analgesic activity, whereas dexamethasone is a corticosteroid. Chlorpromazine, promazine, and diazepam may resolve some signs of pain through their ability to alter behavior and suppress CNS sympathetic tone. Dexamethasone, although not an analgesic drug per se, may act to reduce inflammation and, thus, provide relief.

Subcutaneous and intramuscular routes for administration of analgesic drugs were the most frequently reported. Reasons for the selection of these routes may include ease of administration, increased duration of action as a result of slowed drug absorption, fewer adverse effects, and lack of vascular access,

particularly in smaller animals. Oral administration of agents was limited to nonsteroidal anti-inflammatory drugs. Intravenous administration was reported in rabbits and larger animals. Intraperitoneal, rectal, and topical routes of administration were infrequently used.

The ideal analgesic agent or administration technique does not exist. The ideal analgesic drug would provide continuous relief from pain, but would not have adverse effects. The ideal analgesic agent would be administered by a route other than injection, and the dose could be titrated to provide the minimum amount needed to eliminate signs of pain. Various analgesic agents and alternative methods of delivery currently are being investigated for use in human beings and other animals.[12] Results of those investigations should produce information useful for future application to animals that are used in biomedical research.

References

1. Kitchell RL, Erickson HH. *Animal pain perception and alleviation*. Bethesda, Md: American Physiological Society, 1983.
2. Short CE, Van Poznak A. *Animal pain*. New York: Churchill Livingstone Inc, 1992.
3. USDA. *Animal welfare act*. 9 CFR ¶231 (1992).
4. Flecknell PA. *Laboratory animal anesthesia*. London: Academic Press Inc, 1987;80–88.
5. Morton DB. Epilogue: summarization of colloquium highlights from an international perspective. *J Am Vet Med Assoc* 1987; 191:1292–1296.
6. Benson GJ, Thurmon JC. Species difference as a consideration in alleviation of animal pain and distress. *J Am Vet Med Assoc* 1987;191:1227–1230.
7. Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsteroidal anti-inflammatory drugs. *Anesth Analg* 1994;79:1178–1190.
8. Flecknell PA. Recognition and alleviation of pain in animals. In: Fox MW, Mickley L, eds. *Advances in animal welfare science*. The Hague, Netherlands: Martinus Nijhoff Publishing, 1986;61–77.
9. Flecknell PA. Post-operative analgesia in rabbits and rodents. *Lab Anim* 1991;20:34–37.
10. Heel RC, Brogden RN, Speight TM, et al. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1979;17:81–110.
11. Hosgood G. Pharmacologic features of butorphanol in dogs and cats. *J Am Vet Med Assoc* 1990;196:135–136.
12. Glass PSA. Principles of analgesia delivery systems. In: Short CE, Van Poznak A, eds. *Animal pain*. New York: Churchill Livingstone Inc, 1992;133–141.