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Jack Kottwitz adds:

Note that, unless specifically referenced the drug doses provided are anecdotal (ie most of the elephant and all of the rhino).

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RESULTS OF THE MEGAVERTEBRATE ANALGESIA SURVEY: ELEPHANTS AND RHINO

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Abstract: An online survey utilizing Survey Monkey linked through the American Association of Zoo Veterinarians listserve examined current practices in megavertebrate analgesia. Data collected included drugs administered, dosing regimens, ease of administration, efficacy, and adverse events. Fifty-nine facilities (38 housing elephants, 33 housing rhinoceroses) responded. All facilities administered nonsteroidal anti-inflammatory drugs (NSAIDs), with phenylbutazone (0.25–10 mg/kg) and flunixin meglumine (0.2–4 mg/kg) being most common. Efficacy was reported as "good" to "excellent" for these medications. Opioids were administered to elephants (11 of 38) and rhinoceroses (7 of 33), with tramadol (0.5–3.0 mg/kg) and butorphanol (0.05–1.0 mg/kg) being most common. Tramadol efficacy scores were highly variable in both elephants and rhinoceroses. While drug choices were similar among institutions, substantial variability in dosing regimens and reported efficacy between and within facilities indicates the need for pharmacokinetic studies and standardized methods of analyzing response to treatment to establish dosing regimens and clinical trials to establish efficacy and safety.

Key words: Analgesic, elephant, NSAID, opioid, pain management, rhinoceros.

BRIEF COMMUNICATION

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" by the International Association for the Study of Pain.[6] The inability of a human or an animal to communicate verbally with a caregiver does not negate the possibility that that individual is experiencing pain or is in need of appropriate pain-relieving medications.[6] It is well recognized that painful stimuli and chronic pain can have a direct impact on behavior, attitude, and responsiveness to otherwise normal stimuli, in addition to affecting normal physiologic functions such as sleep, appetite, and digestion.[6,11]

One of the first steps for effectively managing discomfort with medications in any patient is administration of drugs at species-appropriate doses and dosing intervals to control both pain and inflammation. While online and published formularies exist, there is an extremely limited number of scientific studies performed on the pharmacokinetics of analgesics in elephants.[1,2,5,9,10,15,16] To date, there are no specific pharmacokinetic studies available in any species of rhinoceros to support dosing regimens for drugs used for pain management. Published studies[8,9,12,13] of opioids administered to rhinoceros having focused on administration for sedation and general anesthesia, not analgesia. In addition, many published doses in both formularies and case reports for these species are not based on actual pharmacokinetic studies but instead are extrapolated from doses administered in domestic horses.[4,5,9,10,12–15]

To better characterize medications, usage patterns, and methods of providing analgesia to megavertebrates, a link to an online survey (using www.surveymonkey.com) was posted on the American Association of Zoo Veterinarians listserve from March 2012 through September 2013. Response to this survey was worldwide, with 59 zoological institutions from North America, Europe, Africa, and Australia participating. Of the 59 responding institutions, 35 institutions housed elephants and 33 housed at least one species of rhinoceros. Species housed by reporting institutions included Asian elephants (*Elaphas maximus*), African elephants (*Loxodanta* spp.), southern white rhinoceros (*Ceratotherium simum simum*), Indian or greater one-horned rhinoceros (*Rhinoceros unicornis*), and Sumatran rhinoceros (*Dicerorhinus sumatrensis*). For the purposes of this survey, African elephant species, including both

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Table 1. Summary of nonsteroidal anti-inflammatory drug (NSAID), opioid, and other methods of analgesia provided to captive elephants. Caution should be taken with higher dosing levels with the data in this chart. Of these analgesics, only phenylbutazone (3 mg/kg per 48 hr for Asian; 2 mg/kg per 24 hr for African), ibuprofen (6 mg/kg per 12 hr for Asian; 7 mg/kg per 12 hr for African), ketoprofen (1 mg/kg every 48 hr to 2 mg/kg every 24 hr, p.o. or i.v. for Asian), and butorphanol (single dose 0.015 mg/kg i.m. or i.v.) have drug doses and dosing schedules supported by pharmacokinetic evaluation of these drugs in elephants.[1,2,5,15] Pharmacodynamic studies are not available. Many of the drug doses listed are derived from domestic equine doses.

Drug	Institutions reporting use of drug in elephants ($n = 38$)	Species treated	Dose administered (mg/kg)	Route	Dosing frequency[a]	No. of institutions reporting perceived efficacy					Adverse effects noted
						Excellent	Good	Fair	Poor	No response	
NSAIDs											
Phenylbutazone	27	Asian elephant, African elephant	0.25–6	p.o.	s.i.d. to b.i.d.	6	18	1	0	2	1 institution reported oral ulceration
Flunixin meglumine	25	Asian elephant, African elephant	0.28–1.1	p.o.	s.i.d. to b.i.d.	6	15	1	1	3	2 institutions reported loss of appetite, gastrointestinal upset, gas distension, mild colic
	2	African elephant	0.4–1.0	i.v.	s.i.d. to b.i.d.						1 institution reported sloughing of ear post i.v. injection
	4	Asian elephant, African elephant	0.28–1.1	i.m.	s.i.d. to b.i.d.						—
Ibuprofen	20	Asian elephant, African elephant	1–6 mg/kg for Asian 1–7 mg/kg for African	p.o.	s.i.d. to b.i.d.	6	16	1	2	2	Questionable efficacy for more severe pain management
	2	Asian elephant	1–7	Rectally	s.i.d. to b.i.d.						—

Table 1. Continued.

Drug	Institutions reporting use of drug in elephants ($n = 38$)	Species treated	Dose administered (mg/kg)	Route	Dosing frequency[a]	No. of institutions reporting perceived efficacy					Adverse effects noted
						Excellent	Good	Fair	Poor	No response	
Ketoprofen	8	Asian elephant, African elephant	1 mg/kg every 48 hr to 2 mg/kg every 24 hr	p.o.	s.i.d. to b.i.d.	3	4	0	0	0	—
	1	Asian elephant	1.0–2.0	i.v.	s.i.d. to b.i.d.						1 institution reported sloughing of ear post i.v. injection
	1	African elephant	0.963	i.m.	s.i.d.						—
Firocoxib	4	African elephant	0.1	p.o.	—	2	2	0	0	0	—
Carprofen	3	African elephant, Asian elephant	0.2–0.3	p.o.	s.i.d.	0	1	1	1	0	2 institutions reported gastrointestinal upset, moderate colic postadministration
Meloxicam	3	African elephant	0.2	p.o.	s.i.d.	1	1	1	0	0	—
Acetaminophen	3	African elephant	0.5–1.5	p.o.	s.i.d. to b.i.d.	0	0	1	2	0	—
Vedaprofen	2	Asian elephant, African elephant	0.45–0.7	p.o.	s.i.d. to b.i.d.	0	0	1	0	1	—
	1	Asian elephant	0.5–1	Rectally	b.i.d.						—
Etodolac	1	Asian elephant	2–2.7	p.o.	s.i.d.	0	1	0	0	0	—
Aspirin	1	Asian elephant	62.5 mg total (weight not given)	p.o.	b.i.d.	0	0	0	1	0	Questionable efficacy, no analgesic effect observed

Table 1. Continued.

Drug	Institutions reporting use of drug in elephants ($n = 38$)	Species treated	Dose administered (mg/kg)	Route	Dosing frequency[a]	No. of institutions reporting perceived efficacy					Adverse effects noted
						Excellent	Good	Fair	Poor	No response	
Opioids											
Tramadol	4	Asian elephant, African elephant	0.5–3	p.o.	b.i.d.	1	1	1	2	0	Questionable efficacy with doses of 1.0 mg/kg or less; decreased responsiveness and depression noted at higher doses
	1	Asian elephant	1	Rectally	Not reported						—
Butorphanol	4	Asian elephant	0.01–0.08	i.m.	s.i.d.	0	3	1	0	0	Mild sedation with higher doses
Fentanyl	2	Asian elephant, African elephant	0.078 mcg/kg	Transdermal patch	Not reported	0	2	0	0	0	Mild sedation with higher doses
Other modes of analgesia											
Glucosamine and chondroitin sulfate	14	Asian elephant, African elephant	Extrapolated from horse dose or 1.1 to 1.5	p.o.	s.i.d. or b.i.d.	0	5	4	3	2	Multiple compounded products have been utilized
Gabapentin	6	Asian elephant, African elephant	0.4–6	p.o.	s.i.d. or b.i.d.	1	2	2	0	1	1 institution reported difficulty administering due to taste aversion
	1	Asian elephant	1	Rectally	s.i.d.	0	1	0	0	0	None noted

Table 1. Continued.

Drug	Institutions reporting use of drug in elephants ($n = 38$)	Species treated	Dose administered (mg/kg)	Route	Dosing frequency[a]	No. of institutions reporting perceived efficacy					Adverse effects noted
						Excellent	Good	Fair	Poor	No response	
Corticosteroids	5	African elephant	Prednisolone: up to 1	p.o.	s.i.d.	1	3	0	1	0	—
	1	African elephant	Dexamethasone: 0.05	p.o.	s.i.d.						—
	1	African elephant	0.05	i.v.	Single dose						—
Local anesthesia infusion	3	Asian elephant, African elephant	To effect (10–30 ml 1% Lidocaine)	s.q.	s.i.d.	0	2	1	0	0	Limited time of effect reported by all institutions
Acupuncture	2	Asian elephant	N.A.	—	1 to 2 times per week	0	0	2	0	0	—
Polysulfated glycosamino glycans	2	African elephant	Dose extrapolated from horse dose	i.m.	Every 3 days for 5 doses	Appeared to have mild positive effect					—
Cold laser therapy	2	Asian elephant	80 joules across 4–8 points	—	Reducing frequency: 3 times per week for 3 wk, then once a week, then every other week	0	0	2	0	0	—
Pentosan polysuflate	1	Asian elephant	3	i.m.	Every 7 days	No effect noted posttherapy					Administered to treat long-standing gait abnormality, with no change in gait noted
Omega fatty acids	1	African elephant	No dose reported	p.o.	s.i.d.	No efficacy reported					—
Amantadine	1	—	No dose reported	p.o.	—	No efficacy reported					—
α-2 agonists	1	Asian elephant	No dose reported	i.m.	s.i.d.	No efficacy reported					Administered for sedation purposes

[a] s.i.d. = once per day; b.i.d. = twice per day or every 12 hr.

African bush elephants (*Loxodonta africana*) and African forest elephants (*Loxodonta cyclotis*), were grouped together under their common genus.

Data collected about drugs utilized and modality of analgesia provided were compiled using Microsoft Access into the following categories: facility information; signalment (age, genus, and species); drug or modality, including name and specific drug formulation utilized; and dosing regimen, including route, drug vehicle, dose in "mg/kg," dosing interval, and duration. Patient information regarding pain treated was also collected. Pain duration was defined as "acute" if of less than 3 mo and as "chronic" if of more than 3 mo. Types of pain treated included somatic (activation of pain receptors in either the body surface or musculoskeletal tissues), visceral (activation of pain sensors when internal organs are damaged or injured), neuropathic (pain caused by injury or malfunction to the spinal cord and peripheral nerves), or mixed (pain involving two or more of the first three categories). Perceived efficacy of analgesia provided, defined as the perception by associated humans of resolution of the painful condition warranting administration of an analgesic drug or other form of pain relief, was ranked subjectively on a scale of 1 (poor) to 4 (excellent). Ease of use and complications associated with using each method of analgesia were described as comments from the respondent. Adverse events were characterized as reported by responding institutions. Mild adverse events described included mild colic and loss of appetite, while severe adverse events described included complete loss of appetite, severe colic, or evidence of physiologic changes, such as elevated renal values. All institutions reported administration of oral medications in both elephants and rhino using a variety of food items, including fruit, such as cored apples or watermelon, bread products, or peanut butter. All modalities utilized, number of institutions utilizing each, dosing-treatment schedules, perceived efficacies, and reported side effects are outlined in Table 1 for elephants and in Table 2 for rhino.

Analgesics were divided into three drug categories: nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and other non-NSAID–non-opioid drugs. Nonpharmacologic analgesic interventions also were recorded. NSAIDs administered to both elephants and rhinoceroses included phenylbutazone, flunixin meglumine, ibuprofen, ketoprofen, firocoxib, carprofen, and meloxicam. NSAIDs that were administered to elephants, but not to rhinoceroses, included acetaminophen, vedaprofen, etodolac, and aspirin. Opioid drug administration was much less commonly reported than was NSAID use for both elephants and rhinoceroses. Opioids administered included tramadol, butorphanol, and fentanyl. Other products administered to both elephants and rhinoceroses with the intent of controlling pain included gabapentin, corticosteroids, α-2 agonists, local anesthesia infusion, pentosan polysulfate, glucosamine and chondroitin sulfate, and omega 3/6 fatty acids. Amantadine was administered to elephants only. Other nonpharmaceutical methods of analgesia reported in elephants exclusively included acupuncture and cold laser therapy.

NSAIDs were administered for all four types of pain to both elephants and rhinoceros, with somatic pain being the most common indication, and neuropathic pain the least. As with NSAIDs, opioid drugs were administered most commonly for somatic pain followed by visceral, mixed, and, lastly, neuropathic pain. Interestingly, combinations of analgesics were used more commonly for neuropathic pain than for visceral or mixed pain, presumably in an attempt to deliver multimodal analgesia in the face of an insufficient response to previous therapy. The perceived efficacy of NSAIDs was variable, with acetaminophen, carprofen, and aspirin all reported as the least effective for analgesia in elephants (Table 1). Carprofen also had a low reported perceived efficacy score in rhinos. NSAIDs generally demonstrated higher perceived efficacy scores in all rhinoceros species compared to elephants (Table 2).

Adverse effects associated with NSAIDs in elephants were largely gastrointestinal, including loss of appetite and mild to moderate colic. Difficulties in oral administration of some of the drugs were noted in multiple institutions, which was attributed to elephants avoiding the taste of compounded and commercially available oral preparations. Data were not sufficient to allow identification of any one NSAID associated with taste aversion in elephants. A single incidence of sloughing of the ear after intravenous injection in an ear vein was described for both flunixin meglumine and ketoprofen in elephants. The only adverse event associated with NSAIDs reported in rhinoceroses was taste aversion, particularly for both flunixin meglumine and phenylbutazone.

Opioid drugs, specifically tramadol, butorphanol, and fentanyl, were less commonly administered, with only 11 institutions housing elephants and seven housing rhinoceroses reporting their use. Tramadol appeared to have the lowest perceived efficacy of these three drugs, with question-

Table 2. Summary of nonsteroidal anti-inflammatory drug (NSAID), opioid, and other methods of analgesia provided to captive rhinoceroses. Caution should be taken when considering higher dosing levels with the data in this chart. To date there have been no experimental pharmacokinetic or pharmacodynamic studies performed for any of these drugs or scientific evaluations of these methods of providing analgesia in rhino. Many of the drug doses listed are derived from domestic equine doses.

Drug	Institutions reporting use of drug in rhinoceros ($n = 33$)	Species treated	Dose administered (mg/kg)	Route	Dosing frequency[a]	No. of institutions reporting perceived efficacy					Adverse effects noted
						Excellent	Good	Fair	Poor	No response	
NSAIDs											
Phenylbutazone	25	White rhino, Black rhino, Indian rhino	3–10	p.o.	s.i.d. to b.i.d.	5	16	4	0	0	Higher doses (>4 mg/kg not given more than 3 days); taste aversion noted with some animals
	1	White rhino	4	i.v.	One-time dose						—
	4	White rhino, Indian rhino	1.1	i.m.	s.i.d.						—
Flunixin meglumine	24	White rhino, Black rhino, Indian rhino, Sumatran rhino	0.20–1.6	p.o.	s.i.d. or e.o.d.	6	14	4	0	0	Taste aversion noted with some animals
	4	White rhino, Black rhino	0.5–1	i.v.	s.i.d. or b.i.d						—
	5	Black rhino, Indian rhino	0.50–1.1	i.m.	s.i.d.						—
Ibuprofen	1	White rhino	1	p.o.	s.i.d.	—	—	—	—	—	—
Ketoprofen	3	White rhino, Black rhino	0.5	p.o.	s.i.d. to b.i.d.	1	1	0	0	1	—
	1	Black rhino	0.5	i.v.	s.i.d. to b.i.d.						
Firocoxib	4	White rhino	0.088–0.1	p.o.	s.i.d.	2	2	0	0	0	No adverse events reported
Carprofen	2	Black rhino	0.78–2.0	p.o.	s.i.d.	0	0	2	0	0	—
Meloxicam	2	Indian rhino	0.2	p.o.	s.i.d.	0	0	2	0	0	—
Suxibuzone	1	White rhino	6	p.o.	b.i.d.	0	1	0	0	0	—

Table 2. Continued.

Drug	Institutions reporting use of drug in rhinoceros ($n = 33$)	Species treated	Dose administered (mg/kg)	Route	Dosing frequency[a]	No. of institutions reporting perceived efficacy					Adverse effects noted
						Excellent	Good	Fair	Poor	No response	
Opioids											
Tramadol	4	White rhino, Black rhino	0.8–3.0	p.o.	b.i.d.	1	2	0	0	1	Mild to moderate sedation noted
Butorphanol	3	White rhino, Black rhino	0.05–1.0	p.o.	b.i.d.	2	1	0	0	0	Sedation, anorexia, decreased appetite noted on 1.0 mg/kg dose
Fentanyl	1	White rhino	0.09 mcg/kg per hr	Transdermal patch	—	0	0	0	1	0	Sedation noted, but no apparent analgesia observed
Other modes of analgesia											
Glucosamine and chondroitin sulfate	7	White rhino, Indian rhino	1.1–4.0	p.o.	s.i.d. or b.i.d.	0	2	2	1	2	Questionable efficacy reported by 2 institutions
	2	White rhino	1–22.5	i.m.	Once per week to once per month						
Gabapentin[b]	4	Black rhino	2.5–5.0	p.o.	s.i.d.	0	1	1	0	3	—
	1	White rhino	1	Rectally	s.i.d.						
Corticosteroids	1	White rhino	Prednisolone: 0.2	i.m.	One-time administration	0	0	0	0	1	Site of dart injection
	1	White rhino	Dexamethasone: 10	p.o.	s.i.d.	0	0	0	0	1	became infected
Local anesthesia infusion	1	Indian rhino	Topical Lidocaine–Applied to skin	Topically	s.i.d.	0	0	0	1	0	No effect noted after 5 days of therapy

Table 2. Continued.

Drug	Institutions reporting use of drug in rhinoceros ($n = 33$)	Species treated	Dose administered (mg/kg)	Route	Dosing frequency[a]	No. of institutions reporting perceived efficacy				Adverse effects noted
						Excellent	Good	Fair	Poor	No response	
Pentosan polysulfate	1	Black rhino	3	i.m.	Every 7 days	No effect noted post therapy					—
Omega fatty acids	1	Black rhino	No dose reported	p.o.	s.i.d.	0	1	0	0	0	—

[a] s.i.d. = once per day; b.i.d. = twice per day or every 12 hr.

[b] Note: Gabapentin often administered in conjunction with NSAID or opioid drugs, including phenylbutazone and tramadol.

able perceived efficacy, if any, reported at lower doses. Fentanyl was administered to elephants at two institutions in the form of a transdermal patch, with good perceived efficacy reported by both institutions. This is in contrast to one institution utilizing a transdermal fentanyl patch for rhinoceros analgesia, which reported poor perceived efficacy. Adverse events reported for opioid drugs in elephants were limited to tramadol, which included sedation, depression, and decreased responsiveness after tramadol administration. Questionable perceived efficacy, if any effect for tramadol at low doses, was also reported by three institutions. Anorexia and decreased appetite were noted at doses greater than 0.7 mg/kg of butorphanol administered orally to rhinoceroses. There were reports of mild to moderate to severe sedation and decreased responsiveness in rhinoceroses with all opioid drugs.

Non-NSAID–nonopioid methods of analgesia had variable perceived efficacy, with perceived efficacy ranging from no effect noted for glucosamine and chondroitin sulfate, pentosan polysulfate, and amantadine to fair for low-level laser therapy (Tables 1, 2). The most significant adverse events reported with nonpharmaceutical methods of analgesia, such as low-level laser therapy or acupuncture, were lack of cooperation from the patient being treated or no noted effect from treatment.

An important limitation to this study is that survey results reflected institutional rather than individual animal responses. Institutions reporting also included historical information for animals that were no longer alive or no longer at that individual institution. Unfortunately, not all institutions reported the individual information as historic or current collection data, so it is not possible to accurately calculate individual population numbers for statistical analysis of perceived efficacy or incidence of side effects. Data can only be reported as institutional data. Despite the limitations of calculating exact numbers of animals as responses, the results of this survey clearly show that NSAIDs are the most common form of analgesia administered to captive elephants and rhinoceroses, with phenylbutazone and flunixin meglumine being the most common of the NSAIDs utilized. Interestingly, there were no adverse events associated with NSAID administration reported in rhinoceroses. A previous case report[14] describes bullous skin lesions in a southern white rhinoceros associated with oral administration of firocoxib. However, no lesions of this type were reported by any institution

administering firocoxib to either elephants or rhinoceroses in this survey.

Sedation associated with opioid drug administration to both elephants and rhinoceroses is an expected side effect, especially considering the known sensitivities to these drugs and their use as anesthesia drugs in these species.[7–10,12,13,15,16] Improved information from pharmacokinetic trials of these drugs will likely alleviate these negative dose-related effects.

Based upon institutional responses, nonpharmaceutical methods of analgesia were often utilized in conjunction with pharmaceutical methods or were utilized in an attempt to minimize total drug doses out of concern for variable perceived efficacy or possible negative side effects.

The variability reported in dosing regimens for NSAIDs and opioid drugs is of concern. This survey identified variability in doses that varied as much as 20-fold between institutions or within individual institutions. The commonly accepted narrow safety margin of many NSAIDs is of concern in megavertebrates, in part because of the lack of scientific drug trials upon which dosing regimens are based.[3,4] While the information presented here may be utilized as general guidelines, it is not to be used as a specific reference for drug doses or method of analgesia. Further studies in the specific pharmacokinetics of the more commonly utilized methods of analgesia, including NSAID and opioid drugs, are needed to fully analyze the safety and efficacy of these medications in megavertebrates.

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