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SHORT CONTRIBUTION

Multimodal analgesia in a Southern White Rhinoceros (*Ceratotherium simum*) with pentosan polysulfate, gabapentin, amantadine and phenylbutazone to manage chronic pain

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A 38-year-old white rhinoceros bull (*Ceratotherium simum*) was treated with phenylbutazone over a period of four years for chronic osteoarthritic and neuropathic pain of the thoracic limbs. Initially the lameness was sporadic and responded well to phenylbutazone (4 mg/kg PO SID). The lameness increased in severity during the winter months. Four years after treatment was initiated, there was an increase in the severity and incidence of the lameness. Analgesia was augmented by the addition of non-conventional analgesic drugs. Pentosan polysulfate was administered IM at 3 mg/kg once a week for two treatments and thereafter monthly when possible. Gabapentin was used at 8 mg/kg but produced ataxia and anorexia. The dose was reduced to 4-5 mg/kg PO SID. Amantadine (3 mg/kg PO BID) was added to the multimodal analgesia and produced a significant improvement in the clinical lameness. Chronic inflammation was monitored using both automated and manual fibrinogen methods. Eventually the rhinoceros was euthanized on humane grounds when treatment was unable to produce suitable clinical relief.

Keywords amantadine; analgesia; *Ceratotherium simum*; gabapentin; Southern White Rhino; pentosan polysulfate
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There are large numbers of rhinoceros in captivity around the world (1033 animals held by ZIMS® registered facilities worldwide) and due to their longevity, these animals often require treatment for chronic painful conditions. Despite their large numbers in captivity there is minimal scientific literature available on the use of analgesics in any of the five rhinoceros species.[1] To date, there is only a single pharmacokinetic study published on the use of analgesics in rhinoceros.[2] Despite the recent publication of a zoo and wild mammal formulary with an entire chapter dedicated to rhinoceros, there remains a significant lack of published data on the use of analgesics in rhinoceros. Few drug classes are described clinically save for the routine use of non-steroidal anti-inflammatories non-steroidal anti-inflammatory drug (NSAID) or opiates.[3] Most of the data available on the use of analgesics in rhinoceros is based on extrapolations from equine or other large domestic animal doses; and the effects of treatment remain subjective to efficacy, as perceived by the attending clinician or animal husbandry staff.[1] An international survey of routine treatments of captive rhinoceros, with 33 responding facilities, documented a heavy reliance on NSAID for rhinoceros analgesia with few other drug classes reported as being used.[1]

A 38-year-old Southern White Rhinoceros (*Ceratotherium simum*) bull was treated for suspected chronic osteoarthritic and neuropathic pain of the thoracic limbs. The bull first presented with a sporadic thoracic limb lameness five years ago and was treated with phenylbutazone (1 g/sachet phenylbutazone, Apex Laboratories, NSW, Aust) at 4 mg/kg single in day (SID) per os (PO) for periods lasting from a few days to multiple consecutive months. Distal limb radiographs of the carpus and structures distally obtained under anaesthesia were unremarkable. The lameness was scored a numerical value on a 5-point scale, with 5 being the most severe. The lameness was also subjectively described and a combination of the two was used to allocate a subjective lameness score. This lameness waxed and waned and manifested as a shifting thoracic limb lameness with increasing bouts of clinical lameness reported in colder months. The lameness was characterized between grade 1 and 4, with a rolling action of his thoracic limb and accompanying head bob and was exacerbated on turning. Uneven nail wear was observed. Four years after the lameness was first reported, there was increased frequency, duration and degree of lameness reported despite symptomatic treatment with phenylbutazone and the long-term administration of two nutraceuticals – Equine joint guard powder (Chondroitin sulfate, glucosamine hydrochloride and MSM, Ceva, NSW, Aust) and 4Cyte horse granules (Epiitalis, Interpath, VIC, Aust). No adverse or positive effects were observed with the use of nutraceuticals. Fibrinogen levels showed a significant and continuous increase over this time period and were assumed to be associated with ongoing chronic inflammation associated with degenerative osteoarthritis. Fibrinogen is considered one of the most accurate clinicopathological measurements of inflammation in the white rhinoceros.[4] It was therefore decided to utilize the fibrinogen measurement to tract inflammation over time. Originally fibrinogen was determined through the manual heat precipitation method. This is a crude method for extrapolation of fibrinogen levels. Later fibrinogen levels were determined comparatively using both the manual and the automated Clauss method, producing a more reliable determination of fibrinogen. Manual values appeared to be 30%–50% higher than those reported for the automated method. Despite this difference, values at the start of initial clinical signs were on the high end of reported values in the ZIMS system (8.4 g/L). Results obtained in the latter month of treatment were 11.7 g/L with the manual method and 4.5 g/L with the automated method. These results supported a

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Table 1. Mode of action for multimodal pharmacological analgesia

Analgesic drug	Mode of action	Dosage mg/kg	Dosing interval	Comments
Phenylbutazone	Non-steroidal anti-inflammatory	4	SID PO 5 days to 120 days	Potentially might contribute to inappetence due to gastric mucosa side-effects. May have contributed to kidney disease.
Pentosan polysulfate	Mimics proteoglycans and glycosaminoglycans activity	3	IM once weekly 30 days, thereafter once a month	Produces injection site reaction. Could consider intravenous administration. Extend dosing interval to once a month after initial weekly treatments for 30 days.
Gabapentin	Gamma-aminobutyeric acid agonist, presynaptic pain modulation	4–8	SID PO >95 days	Associated with ataxia and anorexia at 8 mg/kg. No obvious side-effects at 4-5 mg/kg.
Amantadine	NMDA (N-methyl-D-aspartate) antagonist, postsynaptic pain modulation	3	BID PO >75 days	Dramatic improvement within 4 days of first dose.

progressive hyperfibrinogenaemia with values in excess of twice the upper reference interval reported for white rhinoceros.[4] Daily ranitidine (220 mg/mL ranitidine, Ulcerguard, Ranvet, NSW, Aust) was added to the clinical regimen at 6–7 mg/kg BID PO to alleviate possible gastric pathology associated with long-term NSAID delivery. A decision was made to provide additional therapies to achieve multimodal analgesia in efforts to improve the bull's quality of life to more effectively address his chronic pain. Initially, pentosan polysulfate (Cartrophen Forte, 250 mg/mL pentosan polysulfate, Biopharm, NSW, Aust) was used once weekly for two treatments at 3 mg/kg IM based on the authors previous experience in pachyderms and published equine dosages, 4 years after the initial lameness was first observed.[5] The bull showed a dramatic improvement in his gait and appetite subsequent to the initial treatments. A local injection site reaction was noted that persisted for up to four days. No abscessation was noted. The treatment was then repeated four months later when the lameness deteriorated again. The treatment was again repeated three months later, and a decision was made to move the bull to an enclosure that facilitated safe handling to inject the drug once a week for three weeks and then continuously at an interval of once a month. This adjunct therapy provided apparent analgesia for seven months before it was determined that suitable analgesia could not be provided by phenylbutazone and pentosan polysulfate alone. Gabapentin (Neurontin, 800 mg gabapentin, Pfizer, NSW, Aust) was added to the analgesic protocol at 8 mg/kg SID. Due to the development of low-grade ataxia and anorexia the dosage was scaled back to 4-5 mg/kg SID based on oral pharmacokinetics studies of gabapentin in horses.[6] Despite minor improvements in the lameness over a period of weeks there was consensus among veterinarians and zookeepers that his pain remained inadequately managed. Amantadine (Symmetrel, 100 mg amantadine hydrochloride, Novartis Pharmaceuticals, NSW, Aust) was added to the analgesic protocol at 3 mg/kg BID PO, based on the authors experience in equids. Amantadine has been used safely in horses at 10 mg/kg without any side-effects as a treatment adjunct in equine influenza.[7] Within four days of BID amantadine, significant positive changes in play behaviour, willingness to participate in training and improved appetite were observed. The bull was perceived as being more active and utilizing much larger areas of the exhibit. Multimodal analgesia was continued using all four drugs for an additional two and a half months. The bull developed a profound lameness and reluctance to ambulate and partial anorexia for four days. Additionally, clinical pathology results were suggestive of chronic renal failure. At this point humane euthanasia was indicated and carried out. Bilateral severe erosive lesions with eburnation of the subchondral bone of the humeral head were detected on necropsy. Moderate renal pathology associated with long-term NSAID use was recorded. The addition of other analgesic modalities might allow for the reduction in the dose and frequency relied upon to produce analgesia with NSAID. This may decrease the likelihood of developing kidney disease and other NSAID-associated side-effects such as inappetence (Table 1).

There are no published reports of the use of amantadine in any rhinoceros species that the authors are aware of and therefore conclude this may be the first reported use of this alternative analgesic in a rhinoceros.

In dogs with chronic osteoarthritis that is refractory to treatment with NSAID, it has been shown that the addition of amantadine to the treatment regimen increased the degree of comfort and physical activity of these animals.[8] Considering the difficulties in quantifying pain in zoo veterinary patients, it would seem pertinent to treat perceived chronic pain more aggressively than a pure reliance on NSAID. In horses with neuropathic pain it has been suggested that the addition of gabapentin may substantially improve the perception of pain in these patients.[9] Of the three additional non-NSAID drugs used, the most significant clinical improvement was observed with the addition of pentosan polysulfate and amantadine. Considering the occasional injection site reactions to intramuscular pentosan polysulfate, potentially future treatments can be administered intravenously through a large easily accessible blood vessel such as the radial vein. This route of pentosan administration has shown very good results in the treatment of equine osteoarthritis.[5] There

appeared to be excellent synergism in the combination of these three drugs as an adjunct to NSAID in this white rhino.

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