PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS OF TAPENTADOL IN YELLOW-BELLIED SLIDER TURTLES (*TRACHEMYS SCRIPTA SCRIPTA*) AFTER A SINGLE INTRAMUSCULAR INJECTION☆

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Abstract

In reptiles, administration of opioid drugs has yielded unexpected results with respect to analgesia. Tapentadol (TAP) is a novel atypical opioid drug labelled for human use. The objective of this study was to evaluate the pharmacokinetics and the pharmacodynamics of this drug in yellow-bellied sliders, after a single intramuscular (IM) injection of 5 mg/kg of TAP. Turtles ($n = 9$) were randomly assigned to 2 treatment groups, according to a single-dose, single-treatment, unpaired, 2-period crossover design. Group A ($n = 5$) received a single IM (proximal front limb) dose of TAP (5 mg/mL) at 5 mg/kg. Group B ($n = 4$) received a single IM injection of saline (equivalent volume to opioid volumes) of TAP at the same site. After a 1-month washout period, groups were rotated and the experiment repeated. TAP plasma concentrations were determined by a validated high-performance liquid chromatography-fluorescence method, and an infrared thermal stimuli was applied to the plantar surface of the turtles' hind limbs to evaluate the thermal withdrawal latency (TWL). TAP plasma concentrations were detectable between 1 and 24 hour(s) (1619 and 37 ng/mL, respectively). The TAP-treated group showed an increase in TWL 1 hour after drug administration (13.32 ± 6.40 seconds). Subsequently, TWL decreased with time and significant differences between treatment and control groups were apparent up to 10 hours following treatment. A linear relationship ($r^2 = 0.99$) between TAP plasma concentration and effect was found. Given these findings, TAP appears to be an attractive option for antinociception in turtles, owing to its rapid onset and acceptable duration of effect. Copyright 2015 Elsevier Inc. All rights reserved.

Key words: Opioids; pharmacokinetics; tapentadol; thermal withdrawal latency; turtles

Veterinary medicine faces the unique challenge of having to treat many animal species, including mammals, birds, reptiles and fish. The main challenge for veterinarians is not just to select a drug but to determine, for the selected agent, a rational dosing regimen. Determining a rational dosing regimen is a long and complicated endeavour because of differences in the expression of enzymes, receptors and signal transduction molecules between species.[1] Both inter- and intraspecies differences in drug response can be accounted for as either being due to variations in drug pharmacokinetics (PKs) or drug pharmacodynamics (PDs), the magnitude of which varies from drug to drug.[2] Hence, PK/PD studies are critical when a drug is applied to a new animal species.

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Mercifully, at this time, we are far more cognisant of pain in animals. Animal species that years ago were considered wild animals are now pets and owners expect an adequate level of health care. This change in attitude has resulted in an impetus for the development of more effective and innovative veterinary therapies.[3-5] With the increasing popularity of herpetoculture, there is more information on associated diseases and treatment options are being investigated, starting with the classes of drugs that have proven efficacy in other species. This research has emphasised the inaccuracies that result when the effects and consequences of drugs for the species of interest are predicted based on extrapolation from other species, which have marked physiologic differences.[6]

Opioids are considered to be the most effective drugs for controlling pain in mammals.[7] Veterinary clinicians have a number of options in the opioid class of drugs: the classical μ-opioid receptor (MOR) agonists (e.g., morphine); the partial MOR agonists (e.g., buprenorphine); the mixed opioid κ-receptor agonists and MOR antagonists (e.g., butorphanol); and the atypical opioids (e.g., tramadol).

In reptiles, opioid drug administration has yielded poor to inconsistent results with respect to analgesia. Butorphanol does not change thermal withdrawal latencies (TWLs) in red-eared sliders (*Trachemys scripta elegans*)[8] and bearded dragons (*Pogona vitticeps*)[9] or thermal thresholds in green iguanas (*Iguana iguana*).[10] Buprenorphine did not alter responses to a noxious electrical stimulus administered to green iguanas,[11] nor did it provide an analgesic effect in red-eared sliders exposed to a noxious thermal stimulus.[12] Morphine increased TWL in red-eared sliders[8] and bearded dragons[9] at doses ranging between 1.5 and 20 mg/kg, but was ineffective at doses up to 40 mg/kg in corn snakes.[9] Conversely, the atypical opioid tramadol, when used in mammals, has been widely questioned,[13-15] but it has provided antinociception (10 mg/kg subcutaneous [SC]) for at least 48 hours following administration in red-eared sliders.[16] Tramadol produces MOR activation (6000 times less than that of morphine) as well as inhibition of serotonin (5HT) and norepinephrine (NE) reuptake in mammals. It has been reported that the analgesic efficacy of tramadol is mediated by the M1 metabolite (200 to 300 times more potent on MOR activation than the parental compound).[17]

Tapentadol (TAP) is a novel atypical opioid drug labelled for human use. Based on its unique mechanism of action, it has been proposed as the first representative of a new pharmacological class of centrally acting analgesics: the MOR agonist, NE reuptake inhibitors (MORNRI).[18] Interestingly, although its MOR affinity is 50-fold lower than that of morphine, it has shown an equivalent analgesic activity. Additionally, after systemic administration in humans, TAP is associated with a 2- to 3-fold reduction in the rate of adverse effects reported with oxycodone.[19] This finding, consistent across different pain relief evaluation models, may be due to the increased blood brain barrier penetration of TAP, but also suggests that the NE reuptake-inhibitory property contributes to a more potent analgesia than would be expected solely from its MOR agonism.[20] If the reduction in adverse effects observed in humans holds true in reptiles, TAP could be an attractive analgesic option. The objective of this study was to perform initial investigations on this promising molecule by assessing the PK/PD in yellow-bellied sliders (*Trachemys scripta scripta*), after a single intramuscular (IM) injection of TAP.

MATERIALS AND METHODS

Animals and Experimental Design

In all, 9 yellow-bellied sliders of both genders (7 females and 2 males), with body weights ranging from 0.5 to 1.3 kg (mean = 0.78 kg), were used for the study. The turtles were supplied by a local park. Turtles were acclimated for a 2-week period before the commencement of the study. Turtles were judged to be in good health based on physical examination at the time of acquisition and at the start of the study, and through daily observation of behaviour and appetite. These observations were made by specialized veterinary personnel (S.R.). Turtles were divided according to the inclusion group (A or B) into 2 different 300-L plastic pools, with a water depth of 20 cm and water temperature of 27°C, which contained custom-built mechanical and biological filtration. A dry basking area was heated to 30°C using an infrared lamp. Ambient temperature in the room varied from 25°C to 26°C (electronic temperature sensors assured the constant temperature in both the water and basking area). Turtles were fed with a floating pelleted diet (a mix of fish and soy bean flour supplemented with vitamins and calcium chloride) 3 times per week. Animal care and handling was performed according to the provision of the European Commission council Directive 86/609 EEC and also according to Institutional Animal Care and Use directives issued by the Animal Welfare Committee of the