UNIVERSITI PUTRA MALAYSIA

EVALUATION OF ANTINOCICEPTIVE AND ANALGESIC PROPERTIES OF TRAMADOL IN CATS

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Veterinary Science

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This thesis is dedicated to:

All cats who have once suffered from pain and my beloved ones: Prince, Bala, Tom, Velvet, Copper and Snow-White.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia, in fulfillment of the requirement for the degree of Master of Veterinary Science

EVALUATION OF ANTINOCICEPTIVE AND ANALGESIC PROPERTIES OF TRAMADOL IN CATS

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February 2013

Chairperson: Chen Hui Cheng, DVSc

Faculty: Veterinary Medicine

The need for safe and cost effective analgesic in cats prompted investigation into the potential use of tramadol for acute pain. The hypothesis was that tramadol at a higher dose can provide a more significant analgesic effect in the post-operation period. In the first part, we assessed the thermal and mechanical thresholds following a high (4 mg/kg) and a low (2 mg/kg) dose of tramadol in comparison to acepromazine at 0.1 mg/kg, administered subcutaneously (SC) in cats without undergoing surgery. Three female and 3 male cats were utilized in a randomized cross-over manner. Thermal and mechanical thresholds were determined using two custom-made analgesiometric devices. Both thermal and mechanical thresholds were significantly higher than baseline at 3, 4, 5 and 6 hours after 4 mg/kg tramadol. Following 2 mg/kg tramadol, both thermal and mechanical thresholds were higher than baseline at 4 and 5 hours only. There were no significant changes in both thermal and mechanical thresholds at any time point after administration of 0.1

mg/kg acepromazine. The above results demonstrated that the methods of threshold measurements used in this study can differentiate if a treatment had analgesic effect. Furthermore, they showed dose-dependent response to tramadol. In the second part, we investigated the analgesic effects of 4 and 2 mg/kg of tramadol, SC, in addition to 0.1 mg/kg acepromazine as pre-medication in cats undergoing ovariohysterectomy (OHE). Following surgery, pain scores did not increase significantly from baselines in cats that received 4 mg/kg (AT4 group: 6 cats) and in 2 mg/kg (AT2 group: 6 cats) tramadol at pre-medication. Composite pain scores were lower in AT4 compared to AT2 at 4.5 and 6.5 hours after pre-medication. Pain scores increased significantly at 2.5 and 3.5 hours post-treatment in the 3 cats that received only acepromazine without tramadol (Ace group). All cats in Ace required rescue analgesia. Metatarsal pad mechanical thresholds showed a significant increase from baseline at 3.5, 4.5 and 6.5 hours post-treatment in AT4, and at 4.5 hours in AT2. Thresholds in AT4 were higher than AT2 at 4.5 and 6.5 hours. No significant change was observed in Ace. Mechanical thresholds at surgical site decreased from baselines following surgery and persisted throughout the 36 hours observation in all groups. The decrement tended to be less in AT4 compared to AT2. These results showed the requirement of an analgesic in addition to acepromazine in the pre-medication for cats undergoing OHE. In the third part, we studied the effect of tramadol at 4 mg/kg, SC, on secondary hyperalgesia. Metatarsal pad mechanical thresholds after tramadol but without undergoing surgery were compared to thresholds following tramadol and gonadectomy in six cats. There was no difference in the increment of thresholds following tramadol, with or without gonadectomy. Thresholds increased significantly from baseline between 3 to 6 hours post-

tramadol, with or without gonadectomy. The results of these studies supported the use of tramadol for acute pain management in cats. Tramadol at 4 mg/kg provided more profound and longer analgesic effect than 2 mg/kg. If used at 4 mg/kg, tramadol may prevent secondary hyperalgesia for up to 6 hours after medication.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains Veterinar

PENILAIAN CIRI ANTINOSISEPTIF DAN ANALGESIK TRAMADOL PADA KUCING

Oleh

BITA BASIRI

Februari 2013

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Perlunya ada analgesik yang selamat dan berkesan kos untuk kucing telah mendorong penyelidikan terhadap penggunaan tramadol untuk melegakan kesakitan akut. Hipotesis untuk kajian ini ialah tramadol pada dos tinggi boleh memberi kesan analgesik tererti pada tempoh pasca-pembedahan.Dalam bahagian pertama, kami menilai ambang terma dan mekanikal berikutan pemberian subkutis (SC) dos tinggi (4 mg/kg) dan rendah (2 mg/kg) tramadol berbanding 0.1 mg/kg asepromazin, diberi kepada kucing yang tidak dibedah.Tiga ekor kucing betina dan 3 jantan telah diguna mengikut reka bentuk pindah silang rawak. Ambang terma dan mekanikal telah ditentukan dengan mengguna dua alat analgesiometri buatan tersuai. Kedua-dua ambang terma dan mekanikal didapati lebih tinggi tererti daripada nilai asas pada jam 3, 4, 5 dan 6 selepas disuntik dengan 4 mg/kg tramadol. Berikutan suntikan 2 mg/kg tramadol, kedua-dua ambang terma dan mekanikal didapati lebih tinggi daripada nilai

asas hanya pada jam 4 dan 5.Tiada sebarang perubahan tererti terdapat pada ambang terma atau mekanikal selepas 0.1 suntikan mg/kg asepromazin. Keputusan di atas menunjukkan bahawa kaedah penentuan ambang terma dan mekanikal yang digunakan dalam kajian ini berupaya untuk menentukan sama ada sesuatu rawatan itu dapat memberi kesan analgesik atau tidak. Juga, ambang tersebut menunjukkan berlaku gerak balas yang bersandarkan dos terhadap suntikan tramadol.Dalam bahagian kedua, kami menyelidik kesan analgesik 4 dan 2 mg/kg tramadol yang disuntik secara SC, bersama 0.1 mg/kg asepromazin sebagai prapengubatan pada kucing yang menjalani ovariohisterektomi (OHE). Selepas pembedahan, skor kesakitan tidak meningkat secara tererti daripada nilai asas pada kucing yang menerima 4 mg/kg (Kumpulan AT4) dan 2 mg/kg (Kumpulan AT2) tramadol semasa prapengubatan. Skor kesakitan komposit adalah lebih rendah dalam Kumpulan AT4 berbanding Kumpulan AT2 pada jam 4.5 dan 6.5 selepas prapengubatan. Skor kesakitan meningkat secara tererti pada jam 2.5 dan 3.5 pasca-rawatan pada kucing yang menerima asepromazin tanpa tramadol (Kumpulan Ace). Semua kucing dalam Kumpulan Ace memerlukan analgesia penyelamat. Ambang mekanikalpad metatarsus menunjukkan peningkatan tererti daripada nilai asas pada jam 3.5, 4.5 dan 6.5 prapengubatan dalam kumpulan AT4, manakala peningkatan tererti berlaku pada jam 4.5 dalam kumpulan AT2. Ambang pad metatarsus dalam Kumpulan AT4 adalah lebih tinggi daripada Kumpulan AT2 pada jam 4.5 dan 6.5. Tiada perubahan ambang yang tererti dilihat dalam Kumpulan Ace. Ambang mekanikal pada tapak pembedahan menurun daripada nilai asas berikutan pembedahan dan ini berterusan selama 36 jam tempoh pemerhatian dalam semua kumpulan. Kumpulan AT4 menunjukkan penurunan ambang yang kurang daripada Kumpulan AT2. Hasil kajian

di atas jelas menunjukkan perlunya analgesik sebagai tambahan kepada asepromazin dalam prapengubatan kucing yang menjalani OHE. Dalam bahagian ketiga kami mengkaji kesan 4 mg/kg tramadol SC terhadap hiperalgesia sekunder. Ambang mekanikal pad metatarsus selepas suntikan tramadol, tanpa pembedahan telah dibanding dengan ambang mekanikal berikutan suntikan tramadol dan gonadektomi dalam enam ekor kucing. Tiada perbezaan dilihat dalam peningkatan ambang berikutan suntikan tramadol, dengan atau tanpa gonadektomi. Ambang mekanikal meningkat secara tererti daripada nilai asas di antara jam 3 hingga 6 selepas suntikan tramadol, sama ada dengan atau tanpa gonadektomi. Hasil kajian menyokong penggunaan tramadol untuk pengurusan kesakitan akut pada kucing.Tramadol pada dos 4 mg/kg memberi kesan analgesik yang lebih mendalam dan lebih lama berbanding dos 2 mg/kg. Sekiranya tramadol diguna pada dos 4 mg/kg, ia mungkin melambatkan berlakunya hiperalgesia sekunder sehingga 6 jam selepas suntikan.

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I certify that a Thesis Examination Committee has met on 26 February 2013 to conduct the final examination of Bita Basiri on her thesis entitled "Evaluation of Antinociceptive and Analgesic Properties of Tramadol in Cats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the degree of Master of Veterinary Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Veterinary Science. The members of the Supervisory Committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

BITA BASIRI

Date: 26 February 2013

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