Effect of acetaminophen on hepatic enzymes and renal analytes of ovary-hysterectomized dogs

Efecto del acetaminofen sobre las enzimas hepáticas y analitos renales de perras ovario-histerectomizadas

Efeito do paracetamol sobre enzimas hepáticas e analitos renais de cadelas ovário-histerectomizadas

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Abstract

Background: Pain treatment in companion animals is of great importance nowadays. Alternative pain therapies should be studied in small species to improve life quality and well-being of patients. For years, acetaminophen has been misused in dogs and cats, producing toxic effects after administration at high doses. **Objective:** To evaluate the effects of pre- and post-surgical administration of acetaminophen (also called paracetamol) on renal and hepatic enzymes in dogs undergoing ovarian hysterectomy surgery, and its effect as a trans- and post-surgical analgesic therapy. **Methods:** An acetaminophen dose was administered 30 minutes before surgery and 48 hours after the procedure. Pain was assessed with the Glasgow Pain Scale during surgery and at 2, 6, 12 and 24 hours after the surgical procedure. Blood studies were performed seven days before surgery and five days after to evaluate the effect of acetaminophen on liver enzymes and renal analytes. **Results:** No significant changes in renal analytes and liver enzymes were observed after drug application every 6 and 8 hours for 48 hours. Furthermore, anesthesia and analgesia remained stable during the surgical procedure and a low score on pain scale was observed, indicating absence of postoperative pain despite the total time of surgery was longer than usual. **Conclusion:** Acetaminophen is an excellent analgesic for prolonged surgery and also for postoperative pain. Furthermore, it does not produce hepatic or renal alterations at the tested doses.

Keywords: *acetaminophen; analgesia; canines; dog; hepatic enzymes; hysterectomy; paracetamol; postoperative pain; renal function; surgery; toxicity.*

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Resumen

Introducción: El tratamiento del dolor en animales de compañía tiene gran importancia en la actualidad. Deben estudiarse terapias alternativas para el dolor con el fin de mejorar la calidad de vida y bienestar de los pacientes en la clínica de pequeñas especies. El paracetamol (también llamado acetaminofén) se ha utilizado indebidamente -en dosis elevadas- en perros y gatos, produciendo efectos tóxicos. **Objetivo:** Evaluar el efecto de la administración pre y posquirúrgica de acetaminofén sobre las enzimas renales y hepáticas en perras sometidas a cirugía de ovariohisterectomía, y sobre la terapia analgésica posquirúrgica. **Metodología:** Treinta minutos antes del procedimiento y 48 horas después de la cirugía se administró una dosis de paracetamol a cada perra. El dolor se evaluó con la Escala de Dolor de Glasgow durante la cirugía y a las 2, 6, 12 y 24 horas después del procedimiento quirúrgico. Se realizaron estudios de sangre siete días antes de la cirugía y cinco días después para evaluar su efecto sobre enzimas hepáticas y analitos renales. **Resultados:** Después de aplicar el fármaco cada ocho horas durante 48 horas no se observaron cambios significativos en analitos renales y enzimas hepáticas. Además, la anestesia y analgesia se mantuvieron estables durante el procedimiento quirúrgico y se obtuvo una puntuación baja en la escala de dolor, indicando ausencia de dolor postoperatorio a pesar de que el tiempo total de la cirugía fue mayor de lo habitual. **Conclusión:** El acetaminofén en las dosis utilizadas no produce alteraciones hepáticas ni renales, además de ser un excelente analgésico en cirugías prolongadas y dolor postoperatorio.

Palabras clave: *acetaminofén; analgesia; caninos; cirugía; dolor posoperatorio; enzimas hepáticas; histerectomía; función renal; paracetamol; perro; toxicidad.*

Resumo

Antecedentes: O tratamento da dor em animais de companhia tem uma grande importância na atualidade. A presença de vários medicamentos como terapias alternativas para a dor deve ser estudada para melhorar a qualidade de vida e o bem-estar dos pacientes na clínica de espécies pequenas. Desde anos atrás, o paracetamol ou também chamado acetaminofeno tem sido usado indevidamente em cães e gatos, produzindo efeitos tóxicos após sua administração em doses elevadas. **Objetivo:** O presente estudo tem como objetivo avaliar os efeitos de paracetamol sobre as enzimas renais e hepáticas após a administração pré e posquirúrgica em cães durante cirurgias de ovário-histerectomia, realizadas pelos estudantes dos últimos semestres na universidade, e avaliar seu efeito como trans-e terapia analgésica posquirúrgica. **Métodos:** Para isso, administre uma dose de acetaminophen (paracetamol) 30 minutos antes do procedimento e 48 horas após a cirurgia. A dor foi avaliada pela Balança da Dor de Glasgow durante a cirurgia e nas 2, 6, 12 e 24 horas após o procedimento cirúrgico. Para avaliar o efeito sobre as enzimas hepáticas e os analitos renais, foram efeituadas análises ao sangue 7 dias antes da cirurgia e 5 dias depois. **Resultados:** Não foram observadas alterações significativas nas análises renais e nas enzimas hepáticas após a aplicação do medicamento a cada 8 horas durante 48 horas. Além disso, durante o procedimento cirúrgico, uma anestesia e uma analgesia para os mantidos estáveis, assim como uma pontuação baixa na escala da dor, o que indica ausência da dor pós-operatória, apesar de que o tempo total da cirurgia ter sido mais longa do que o habitual. **Conclusões:** O uso de paracetamol em dose adequada não produz alterações hepáticas e renais, além de ser um excelente analgésico em cirurgias longas e doloridas pós-operatórias.

Palavras-chave: *acetaminofeno; analgesia; cães; canines; cirurgia, cão, enzimas hepáticas, histerectomia; dor pós-operatória; função renal; paracetamol; toxicidade.*

Introduction

Pain is one of the most informative phenomena for dog and cat veterinarians. Several pharmacological therapies are available for the treatment of acute and chronic pain (Gruen *et al.*, 2022). Opioid administration to canines is a frequent treatment, decreasing mortality and morbidity during perioperative surgery (Donati *et al.*, 2021). Currently, several alternatives are being sought. These include the use of CBD, which has beneficial effects for the treatment of epilepsy, anxiety, inflammation, pain, nervous system and gastrointestinal disorders, and even for managing cancer pain (Yu *et al.*, 2021). Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of postoperative pain due to their analgesic, anti-inflammatory, and fever-reducing effects. They inhibit COX1, COX2, and COX3 cyclooxygenases in the cerebral cortex and the periphery. Acetaminophen (paracetamol) is said to have an inhibitory effect on COX3 (Hernández-Ávalos *et al.*, 2020). Although the exact mechanism of action is unknown, it is believed that the analgesic effect of acetaminophen occurs by inhibition of prostaglandin synthesis in the central nervous system and blockade of peripheral pain receptors. Inhibition of brain cyclooxygenase is responsible for the antipyretic effect of acetaminophen, generating the concept of a central mechanism of action (Simmons, 2004). In addition, cardioprotective and antiarrhythmic effects have been described in dogs (Serrano *et al.*, 2019). Therefore, the aim of this study was to evaluate the analgesic efficacy and hepatic and renal effects of acetaminophen administered as a pre-, trans- and post-surgical treatment in dogs undergoing sterilization surgery.

Materials and Methods

This study was approved by the Bioethics and Animal Welfare Committee of the Faculty of Veterinary Medicine and Animal Husbandry of Universidad Veracruzana (Mexico) and accepted under number 007/23 in compliance with provisions in NOM-ZOO-062-1999. The dog owners signed a consent letter for anesthesia and surgery prior to the procedure and treatment.

This prospective randomized experimental trial was carried out in the teaching operating rooms of Facultad de Medicina Veterinaria y Zootecnia of Universidad Veracruzana, located in Veracruz, Mexico. A total of 12 clinically healthy mixed-breed females between 1 and 5 years of age, with no alterations in biometry and blood chemistry ((creatinine, urea, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase)) were selected. Samples were taken seven days before ovarian hysterectomy surgery. Analytes were analyzed again five days after surgery. Surgeries were performed by students of the class on surgical techniques of the same faculty. The bitches that did not comply with the age or alterations in the tests were excluded.

Anesthetic plan

For anesthetic management, tiletamine – zolacepam (Zoletil®100, Virbac, France) at 5 mg/kg IV and xylazine (PROCIN, Pisa, Italy) at 1.1 mg/kg IV were used, with trans-surgical fluid therapy of 5 mL/kg/h with 0.9% sodium chloride solution and Hartmann (HT, Pisa, Mexico). A dose of 15 mg/kg IV acetaminophen (Salpifar, Pisa, Mexico) was administered 30 minutes before surgery. The animals were then divided into two groups of six dogs indistinctly: the first group (G1) every 6 hours, while the second group (G2) every 8 hours for 48 hours postoperatively, with acetaminophen administered orally at 10 mg/kg.

Pain measurement and rescue therapy

Heart rate, respiratory rate, CO_2, SPO_2, pulse, blood pressure, temperature, and ocular reflex were monitored every 5 minutes during surgery using a multiparameter monitor (UMEC12, Mindray Bio-medical Electronics Co., Germany). Pain was measured according to Glasgow (Murrell *et al.*, 2008) during 2, 6, 12, and 24 hours after surgery. If the patient showed more than six points, buprenorphine (Bosprina, Pisa,

Mexico) 20 µg/kg was applied subcutaneously. If gastrointestinal signs were present, 1.1 mg/kg IV single application of omeprazole (Pentren, Pisa, Mexico), and subcutaneous 1 mg/kg antiemetic maropitant (Cerenia, Zoetis, Mexico) were administered.

Statistical analysis

Descriptive statistics and analysis of variance was performed with the analysis of representative data before and after acetaminophen treatment.

Results

The bitches did not present serum alterations of hepatic enzymes and renal analytes, as shown in Tables 1 and 2. The statistical analysis showed relevance ($p<0.05$) in urea and BUN analytes (Table 3). Regarding the Glasgow pain scale, G1 group maintained an average of 4 points and G2 remained at 5 points, demonstrating analgesia of the drug after surgery. Although the surgeries had an average duration of 4 hours –being performed by students, the bitches maintained their physiological constants stable during anesthetic monitoring, with no apparent signs of pain.

Two of the 12 dogs in the experiment occasionally presented with vomiting as a side effect of paracetamol at 8 and 12 hours, respectively; both were dogs in G1 and underwent gastrointestinal rescue and analgesic therapy. Their acetaminophen treatment was suspended, but there were no significant alterations in biometry or blood chemistry post-treatment.

Discussion

Dogs and most animal species absorb acetaminophen primarily through the small intestine (Gramatté, 1994); its small size and binding state facilitate diffusion through biological membranes and lead to passive absorption (Rodríguez-Fernández *et al.*, 2023). Absorption of easily soluble drugs is not affected by gastric and intestinal emptying time (Kelly *et al.*, 2003). Its antipyretic and analgesic effectiveness has already been reported, related to indirect activity on endocannabinoid CB1 receptors and descending inhibition of serotonin (Hernández-Ávalos *et al.*, 2020).

Table 1. Serum urea, blood urea nitrogen (BUN) and creatinine values seven days before and five days after the surgical procedure, and reference values in dogs.

Patient	Pre-surgery			Post-surgery			Reference values		
	Urea	BUN	Creatinine	Urea	BUN	Creatinine	Urea (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)
1	27.5	12.85	1.04	64.7	30.23	1.5	20 - 50	7 - 27	0.5 - 1.8
2	38.76	18.11	1.09	37.81	17.07	1.25	20 - 50	7 - 27	0.5 - 1.8
3	38.2	17.85	1.23	48.24	22.54	1.27	20 - 50	7 - 27	0.5 - 1.8
4	39.6	18.5	1.08	36.02	16.83	0.92	20 - 50	7 - 27	0.5 - 1.8
5	22.8	10.65	0.9	46.7	21.83	1.22	20 - 50	7 - 27	0.5 - 1.8
6	36	16.82	0.74	37.75	17.64	0.9	20 - 50	7 - 27	0.5 - 1.8
7*	27	12.61	0.78	33.83	14.23	0.92	20 - 50	7 - 27	0.5 - 1.8
8*	39.6	16.07	0.91	39.6	18.5	1.02	20 - 50	7 - 27	0.5 - 1.8
9*	43.77	20.45	1.23	40.31	18.83	1.18	20 - 50	7 - 27	0.5 - 1.8
10*	33.83	15.8	1.05	39.07	18.25	1.14	20 - 50	7 - 27	0.5 - 1.8
11*	30.5	14.0	1.0	35.1	15.5	1.10	20 - 50	7 - 27	0.5 - 1.8
12*	28.6	12.2	1.5	33.3	16.5	1.15	20 - 50	7 - 27	0.5 - 1.8

*G2=second group.

Table 2. Serum values of liver enzymes (AST: Aspartate aminotransferase; ALT: Alanine aminotransferase) seven days before and five days after the surgical procedure, and reference values in dogs.

Patient	Pre-surgery		Post-surgery		Reference values	
	ALT	AST	ALT	AST (U/L)	ALT (U/L)	AST (U/L)
1	40.16	54.6	31.43	50.63	16 - 49	15 - 36
2	36.67	45.87	55.87	45.4	16 - 49	15 - 36
3	34.92	49.08	47.14	68.09	16 - 49	15 - 36
4	68.09	90.79	24.44	48.89	16 - 49	15 - 36
5	33.17	62.86	69.84	57.62	16 - 49	15 - 36
6	50.63	68.09	43.65	34.92	16 - 49	15 - 36
7*	43.65	78.57	22.21	40.16	16 - 49	15 - 36
8*	73.33	87.9	68.09	90.79	16 - 49	15 - 36
9*	92.54	39.2	29.68	43.65	16 - 49	15 - 36
10*	27.94	29.68	34.92	29.68	16 - 49	15 - 36
11*	26.5	25.6	33.2	27.6	16 - 49	15 - 36
12*	34.0	55.2	36.5	44.8	16 - 49	15 - 36

*G2=second group.

Table 3. Analysis of variance (p-value).

	ALT	AST	UREA	BUN	Creatinine
p- value	0.48	0.19	0.03	0.02	0.29

Recently, studies have been published on blood evaluation after acetaminophen application in dogs. Hernández-Ávalos *et al.* (2020) did not observe significant findings in liver enzymes, kidney enzymes, and blood count with pre-surgical application of acetaminophen at 15 mg/kg intravenously and post-surgery every 8 hours for 48 hours.

The study by Serrano *et al.* (2019) demonstrated that several laboratory parameters, such as red blood cell counts, hematocrit, hemoglobin, white blood cell count, and ALT differed between both groups because of breed (Spanish Greyhound and Beagle). However, no significant differences in clinical or laboratory variables were detected in any breed after 72 hours of IV administration of 10 to 20 mg/kg acetaminophen. They demonstrated that doses even higher than those reported for clinical use and their frequency over time (up to every 8 hours) were safe in terms of clinical laboratory evaluations. Salem *et al.* (2010) used high doses of acetaminophen (up to 200 mg/kg) observing adverse clinical signs at 72 hours such as gastrointestinal problems, methemoglobin and hematuria. In the present study, doses of 15 mg/kg were evaluated at different time intervals (every 6 (G1) and 8 (G2) hours) with only 2 cases of vomiting in G1, but without changes in blood analytes, although acetaminophen was administered intravenously and orally for 48 hours and evaluated up to 96 hours. This is associated with the low dose administered; up to 100 mg/kg lower than what is allowed (Satirapoj *et al.*, 2007), and not supramaximal doses used by other researchers (Salem *et al.*, 2010) obtained the benefits of this drug. Hepatoxicity and possible renal damage of NSAIDs has been demonstrated (Ghanem *et al.*, 2016; Hernández-Avalos *et al.*, 2020). Acetaminophen is considered an atypical NSAID because it acts on COX-3, and not on COX-1 or COX-2, which have direct activity on renal function (Mondragón-Huerta *et al.*, 2022). Although urea and BUN were within range in post-treatment blood chemistry, they presented significant difference with these two analytes.

This could be associated with renal hypoperfusion caused by hemodynamic changes occurring during surgery (Zhang *et al.*, 2022). It should be noticed that the procedures were performed by veterinary students, so duration of the surgeries was longer.

Regarding pain, the scores were low (less than 6) during the evaluation period, so it was not necessary to apply rescue analgesia to any group of dogs; additionally, no dogs presented gastrointestinal conditions.

Non-steroidal anti-inflammatory drugs are commonly used for postoperative analgesia in dogs. It has been reported that acetaminophen analgesia is not inferior compared to meloxicam or codeine, and its application every 8 hours is ideal (Pacheco *et al.*, 2020). In the present study, adequate analgesia was verified during surgery and after its application despite not simultaneous use of other opioid-opiate analgesics –unlike what was done in other studies where the analgesic effects of acetaminophen were evaluated in combination with other drugs (Hernández-Ávalos *et al.*, 2020).

All surgical procedures were performed by students of veterinary medicine in the last semester of the program, leading to longer surgical times than usual. According to Freeman *et al.* (2017) the average duration of surgery during learning ranges between 45 and 55 minutes. In the present study, it took the students up to 4 hours in said procedure. Furthermore, inexperienced surgeons cause more trauma to tissues than experienced surgeons (Annandale *et al.*, 2020). Therefore, the benefits of acetaminophen are confirmed, being a pharmacological alternative for this common emergency in daily clinic and veterinary teaching.

Although measuring intraoperative pain was carried out through a multiparametric monitor and during the subsequent 48 hours with follow-up as indicated by the Glasgow Scale, it is known that this is not sufficient; other monitoring techniques, such as measurement of parasympathetic pain activity, should be conducted for proper evaluation; however, our institution does not have the required equipment, so we did not do it.

In conclusion, paracetamol does not generate changes in liver enzymes, renal analytes or hemogram in the short term; all patients in both groups tested in the normal range. Finaly, paracetamol does fulfill the analgesic function for the management of pre-surgical and post-surgical pain in ovarian hysterectomy performed by students –where surgery can take up to four hours, keeping the dogs in stable physiological conditions; thus, in adequate doses, paracetamol is a valid analgesic alternative in veterinary medicine.

Declarations

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Conflict of interest

The authors declare they have no conflicts of interest regarding the work presented in this report.

Author contributions

Olivares-Muñoz A, Martínez-Hernández I, Martínez-Hernández K and Salgado-Romero M designed the experiment. Medina-Magariño E, Canales-Rubio M and Espín-Iturbe T worked on the methodology. Gamboa-Prieto J, Bravo-Ramos JL and Olivares-Muñoz A wrote the manuscript. All authors provided critical feedback of the writing and editing.

Use of artificial intelligence (AI)

The authors used "Linguee" during the preparation of this paper to assist in the translation into Portuguese. After using this translation tool, the authors reviewed and edited the content as necessary and take full responsibility for the content of the publication.

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