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Paracetamol: A Focus on Dogs

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Abstract: Paracetamol (APAP) is an aniline analgesic, antipyretic and non-narcotic. It is an essential drug, widely used in human medicine. In veterinary medicine it has an extra label use in many countries. It is used exclusively in some animals, including dogs. It has a mechanism of action similar to that of NSAIDs, as well as other unique characteristics. A variety of studies on APAP in dogs have been published since its introduction into several clinical practices, covering pharmacokinetics, pharmacodynamics, effectiveness and toxicity when inadvertent or accidental overdosing occurs. When taken at therapeutic doses, APAP has been proven to be a powerful and effective analgesic and antipyretic in dogs, as well as having some anti-inflammatory effects. On the other hand, it should be used with caution. This study is a documentation of the therapeutic, toxic and lethal doses of APAP in dogs, as well as the therapeutic effects, clinical application, mostly for the control of post-operative pain and its toxic effects.

Keywords: Dogs, Paracetamol, Pharmacokinetics, Pharmacodynamics, Toxicity

Introduction

Paracetamol (acetaminophen or APAP) is one of the most commonly used non-prescription drugs in the world, in human medicine. It is easily accessible and reasonably priced. While APAP is less effective as an anti-inflammatory than Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), it acts better as an analgesic (Belay *et al*., 1999). It also became the primary analgesic and antipyretic drug during the 1980's after the incident of association of aspirin to Reye's syndrome. It was also safer for children and people with ulcers (Belay *et al*., 1999).

APAP's essential pharmacological effects are only just recently becoming evident and it is now known to be an inhibitor of Prostaglandin (PG) synthesis in cellular systems under certain conditions. But what about its usage in veterinary medicine?

APAP is not licensed for veterinary usage in United States of America, but is certainly used off label. It is licensed in Europe for oral route in dogs (combined with codeine phosphate) and in pigs (Anonymous, 1999). It is used off-label when administered intravenously and as a single therapeutic agent in non-food producing animals (Serrano-Rodríguez *et al*., 2019). Large interspecies differences in the metabolic fate of APAP have been observed, making it unsuitable for usage in all animals with a limited usage in veterinary medicine because it is contraindicated in cats, ferrets, hedgehogs, sugar gliders and snakes (Johnston et al., 2002). APAP has a very small therapeutic window in cats and toxicity in these species occurs for doses close to the therapeutic range (10-40 mg/kg). In contrast, toxicity of APAP occurs at higher dosage (>200 mg/kg) in dogs (Savides *et al*., 1984). It is also generally used in the injectable form in small and large ruminants (Anonymous, 2013).

This review is a snapshot of the current knowledge concerning APAP pharmacology in dogs, focusing on its pharmacokinetics, pharmacodynamics and safety profile.

Nomenclature

The IUPAC name is N-(4-hydroxyphenyl) acetamide. In the United States, Japan, Canada, Venezuela, Colombia and Iran, acetaminophen is the name commonly used, differently the name paracetamol is commonly used in international venues, according to WHO chronicles. It is abbreviated as APAP, for acetyl-para-aminophenol, in some places, such as on prescription bottles of painkillers that contain this drug.

Physicochemical Properties

The compound APAP has a low molecular weight (151.16 g/moL). It is an odorless white crystalline solid with a bitter taste (Lewis, 2007). Since it is such a mild acid (pKa 9.0-9.5), it is effectively unionized at physiological pH levels (Craig, 1990). Its octanol-to-water partition coefficient is 6.2, which is in the range where

passive diffusion across cell membranes is possible. Melting point is around 170 °C. It has been found to be very slightly soluble in cold water, but has greater solubility in hot water (14,000 mg/L at 25°C, Yalkowsky *et al*., 2016). It is freely soluble in alcohol, methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate, slightly soluble in ether and practically insoluble in petroleum ether, pentane and benzene (O'Neil, 2013).

Chemically, APAP is a phenol and is easily oxidized. APAP synthesis involves three steps starting from phenol. First, phenol is converted to nitro phenol via electrophilic aromatic substitution. Then, the nitro group of the para-substituted nitrophenol is reduced to an amine either by sodium-borohydride ($NaBH_4$) reduction or direct hydrogenation. Finally, the para-aminophenol is converted to APAP via a reaction with acetic anhydride (Ashutosh, 2004). The chemical characteristics of APAP are summarized in Table 1.

Classification and Differentiation from NSAIDs

APAP, is an "aniline analgesic" and it is the only drug of this family still used nowadays. It is the active metabolite of phenacetin, which has fallen out of favor due to its carcinogenic potential in therapeutic doses in humans (IARC, 1987).

Despite their comparable pharmacological function, APAP is not included in the NSAIDs class due to the weak anti-inflammatory activity. When applied in recommended doses, it does not induce, unlike NSAIDs, gastrointestinal side effects. Thus, APAP has not been classified as an NSAID in pharmacological textbooks, despite the fact that it has always been discussed alongside these medications, because of their common functions, mentioned in the Table 2.

Pharmacokinetics

A number of Pharmacokinetic (PK) studies on APAP have been established in dogs. In order to determine the PK profiles, the main analytical technique for APAP concentration detection was the usage of the High Performance Liquid Chromatography (HPLC), coupled to various detectors such as Ultra Violet (UV), Diode Array Detector (DAD) and Mass Spectrometry (MS). The PK were assessed for oral, suppository and intravenous routes of administrations, at different doses. A summary on the analytical methods is described in the Table 3.

Bioavailability

Dogs and most animal species absorb APAP primarily through the small intestine (Gramatté and Richter, 1994; Yamada *et al*., 1993; Reppas *et al*., 1998). Its small size, favorable log P and unionized state facilitate diffusion through biological membranes and lead to passive absorption (Swaan *et al*., 1994). Assuming that the absorption is complete in most species, the first-pass metabolism accounts for the incomplete bioavailability (Rawlins *et al*., 1977; Perucca and Richens, 1979; Clements *et al*., 1984). As a result, variations in bioavailability of APAP are most likely due to differences in the degree of first-pass hepatic extraction between organisms and not by absorption. Absorption of readily-soluble drugs is unaffected by gastric and intestinal emptying time (Kelly *et al*., 2003; Sabnis, 1999). Consequently, the oral bioavailability differences reported in dogs (Neirinckx *et al*., 2010 44%; Koyanagi *et al*., 2014 100%) might be assumed to be due to diverse metabolisms in canine breeds (1st pass and glucuronidation) (Bock *et al*., 2002). A recent study (Sartini *et al*., 2021), in line with the human findings, affirmed that no statistically significant differences were found between fasted and fed dogs regarding bioavailability, C_{max} and T_{max}, thus feeding did not significantly affect the APAP absorption process neither its PK.

A study in which APAP was administered rectally showed that it had a much lower bioavailability than orally administered APAP (Sikina *et al*., 2018). Although it was rapidly absorbed and eliminated, at a dose of 9.5-14 mg/kg, it was unlikely to achieve therapeutic concentrations. Further investigations are recommended, such as improving the formulation, increasing the dose (especially that APAP's toxic dose [200 mg/kg] is far away from the suppository dose given) and adding some absorption enhancers (poloxamer 188 and menthol).

In line with these findings, former studies reported a low rectal bioavailability of human suppository formulations, like tramadol, when administered to dogs (Giorgi *et al*., 2009).

Plasma Protein Binding and Volume of Distribution

Plasma protein binding of APAP is very low in dogs (Koyanagi *et al*., 2014). The average protein binding of APAP was between 27% in young dogs and 23% in aged dogs. It was also estimated to be 13% by Duggin and Mudge (1975). As a consequence to this low plasma protein binding, an extensive systemic distribution takes place in dogs, confirmed by the volume of distribution values that ranged from 0.87 to 1.32 L/kg. The large systemic distribution is also a consequence of the small molecular weight of APAP (Martinez, 1998), combined with its unionized state at all physiological pH values. Unlike most conventional NSAIDs, APAP's phenolic structure is more lipophilic than the carboxylic acid structure of NSAIDs (Ali *et al*., 1996). Very low degree of binding to plasma and serum proteins was also confirmed in humans and pigs (Gazzard *et al*., 1973; Milligan *et al*., 1994).

Clearance

Differences in the pharmacokinetic parameters of APAP in different dogs' breeds were found. These differences were assumed to be due to clearance inversely

related to body weight (Neirinckx *et al*., 2010). This is not surprising, given the comparatively larger liver and kidney size, the higher relative amount of hepatic enzymes and number of nephrons in proportion to the weight of kidney tissue in smaller animals, as well as the higher cardiac output and the faster blood flow (Lin, 1995; Toutain and Bousquet-Melou, 2004).

The clearance of APAP in dogs ranged from 0.42 L/h/kg (Sartini *et al*., 2021) to 1.74 L/h/kg (Neirinckx *et al*., 2010). The clearance was slower in Labrador retriever dogs compared to that found in Beagles, Greyhounds and Galgo Español dogs (Kukanich, 2010; Neirinckx *et al*., 2010; Koyanagi *et al*., 2014; Serrano-Rodríguez *et al*., 2019). This range may appear wide but pharmacokinetic breed-specific differences are well known in canine species (Fleischer *et al*., 2008; Martinez *et al*., 2009; Middleton *et al*., 2017). These variations must be linked to differences in physical features, body weight and animal size, amount of fat reserves, as well as differences in phase I and II enzyme isoforms involved in drug metabolism (MacNaughton, 2003).

It was anticipated that APAP's clearance in dogs is not influenced by changes in urinary pH within the achievable physiological range since APAP is a weak acid with a pKa of 9.5 (Duggin and Mudge, 1975). The clearance of APAP depends on urine flow rate but not pH, which was similar to results in humans (Prescott, 1980).

Metabolism, Metabolites and Excretion

APAP is mainly metabolized in the liver by phase I and II enzymes. After 24 h, most of the drug is recoverable in the urine as conjugates (Savides *et al*., 1984). Oxidation, reduction and hydrolysis are all possible phase I reactions for APAP in dogs, however, a small proportion only compared to phase II. For the phase II enzymes, in canine species, as in humans, glucuronidation accounts for the majority of the metabolism of APAP (76%), with a lesser contribution of sulfation and some other pathways (Patel *et al*., 1992; Prescott, 1983; Savides *et al*., 1984). Glucuronidation and sulfation yield final products are inactive, nontoxic, hydrophilic and are excreted by the kidneys. However, the small percentage of APAP that is oxidized by Cytochrome P450 (CYP) enzyme transforms to a reactive toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) (Davis *et al*., 1976). At therapeutic doses of APAP, NAPQI binds to Glutathione (GSH) which is a potent tripeptide antioxidant present in all tissues and is then excreted in the urine with the other metabolites, as cysteine and mercapturic acid. The metabolism of APAP in the liver is shown in Fig. 1.

Savides *et al*. (1984) assessed the presence of the metabolites in dogs' urine, at 100 mg/kg APAP administration: APAP-glucuronide (75%), APAP-sulfate (17%), APAP-cysteine (5%) and unchanged APAP (2%). APAP-mercapturic acid accounted for 1%, only after giving a dose of 500 mg/kg. The production of cysteine and mercapturic acid conjugates of APAP is of major toxicological significance (Mitchell *et al*., 1973; 1974; 1977).

Concerning the excretion, only a very small amount of APAP is bound to plasma proteins and therefore the major part undergoes glomerular filtration. It is reabsorbed in the renal tubules by simple diffusion. The excretory mechanisms for the conjugates are different from those of the parent APAP compound and the excretory pattern of sulphate and glucuronide conjugates are somewhat different from each other (Duggin and Mudge, 1975). For both, clearance is not affected by urine pH or the rate of urine flow, but is strongly influenced by the concentration of the conjugate in the plasma. Clearance, corrected for plasma binding, shows net tubular secretion at low plasma levels and net reabsorption at high levels. Thus, each conjugate undergoes bidirectional tubular transport.

The sulfate and the glucuronide, both undergo glomerular filtration, being weakly protein bound. At low concentrations in plasma, both compounds are secreted by an active transport process. At higher concentrations, both compounds are reabsorbed. For the reabsorption, APAP itself undergoes reabsorption throughout the nephron while the conjugates are transported in the proximal tubule. The mechanism is explained in details in Duggin and Mudge (1975).

A summary on the studies description, main pharmacokinetic parameters of APAP and safety profiles found in the various literature on dogs, is shown in Table 4 and 5.

Table 1: Chemical characteristics of APAP

Alternate names	Paracetamol, acetaminophen, p-hydroxyacetanilide, p-acetyl aminophenol, abensanil.
Chemical formula	$C_8H_9NO_2$
Appearance	White odorless crystalline powder; large monoclinic prisms from water
Molecular weight	151.16 g/mol
Melting point	169-170.5°C
pH	5.3 to 6.5 at 25°C.
Density	1.293 g/cc
Solubility	Soluble in water (1:70, 1:20 at 100°C), ethanol (1:7), acetone (1:13), chloroform (1:50), glycerol (1:40), methanol (1:10), propylene glycol (1:9) and solutions of alkali hydroxides; insoluble in diethylether. Slightly soluble in ether. It is insoluble in petroleum ethers, pentone and benzene.
Stability	Dry, pure APAP is stable to 45°C
Dissociation constant	pKa = 9.0-9.5
Partition coefficient	Pc = 6.237 (octanol: pH 7.2 buffer)

Table 2: Pharmacological activities of APAP, selective COX-2 inhibitors and non-selective NSAIDs

Pharmacological activity	APAP	Selective COX-2 inhibitor	Non-selective NSAID
Analgesia	Active	Active	Active
Antipyresis	Active	Active	Active
Anti-inflammatory	Active in mild inflammation	Active	Active
Anti-platelet	Low activity	Inactive	Active
Damage to stomach and small intestine	Low activity	Low activity	Active
Blood pressure	Variable data	Increase	Increase
Renal	Lesser effects than both NSAIDs classes	Impaired function in stressed kidneys	Impaired function in stressed kidneys
Increased risk of thrombosis	Inactive	Active	Active

Table 3: Summary of the analytical methods used in the various literature

Reference	Clean-up	LOD μg/mL	LOQ μg/mL	Analytical method/PK model	Validated following FDA/EMA guideline
Sikina *et al*. (2018)	Liquid-liquid extraction	NA	NA	UPLC-MS Non-compartmental	Yes
Sartini *et al*. (2021)	Liquid-liquid extraction	0.01	0.05	HPLC-Diode Non-compartmental	Yes
Serrano-Rodríguez *et al*. (2019)	Solid phase extraction	0.01	0.05	HPLC-UV Bi-compartmental	Yes
Neirinckx *et al*. (2010)	Liquid-liquid extraction	NA	0.05	HPLC-UV Non-compartmental	Yes
Koyanagi *et al*. (2014)	Liquid-liquid extraction	NA	NA	LC-MS/MS Non-compartmental	NA
Kukanich (2016)	Solid phase extraction	NA	NA	HPLC-UV Non-compartmental	Yes
St. Omer and Mohamed (1984)	NA	NA	NA	Colorimetric method -Spectrophotometer	NA
Granados *et al*. (2021)	Solid phase extraction	0.01	0.05	HPLC-Diode Bi-compartmental	NA

NA: Not Available, LOD: Limit Of Detection, LOQ: Limit Of Quantification, FDA: Food and Drug Administration, EMA: European Medicines Agency

Table 4: Summary of the pharmacokinetic and safety studies published in the literatures

Reference	*n*	Species	Health status	Feed status	ROA and formulation	Dosage schedule	Dose mg/kg	Safety data
Sikina *et al*., 2018	26	Random dogs	6 Healthy and 20 Ill	Random	Oral tablet (APAP Plus pharma) Suppository rectally (G&W laboratories)	Single dose	9.3-13 10	No visible side effects
Sartini *et al*., 2021	6	Labrador retrievers	Healthy	Fasted Fed	PO fasted capsule (Paracetamolodoc) PO fed capsule IV (Perfalgan)	Single dose	20 PO 10 IV	No visible side effects
Serrano-Rodríguez *et al*., 2019	20	10 Beagles and 10 Galgo Espanol	Healthy	NA	IV	Two single doses	10 20	No visible side effects
Neirinckx *et al*., 2010	6	Beagles	Healthy	Fasted	IV (Bristol-Myers Squibb) PO (Ph. Eur. grade)	Single dose	10 10	No visible side effects
Koyanagi *et al*., 2014	6	Beagles	Healthy	Fasted	IV PO	Single dose	0.2 1	No visible side effects
Kukanich, 2016	6	Greyhounds	Healthy	Fasted	PO(Tablets of 300 mg APAP and 60 mg codeine)	Single dose	10.46	No visible side effects
St. Omer and Mohamed, 1984	8	Beagles	Healthy	NA	IV(4 dogs with oral N-acetylcystein and 4 dogs only with oral saline solution)	Single dose (toxic, not lethal)	150	After 2-3 hours, animals were weak, depressed, some recumbent and some had methemoglobinemia
Granados *et al*., 2021	9	Beagles	Healthy	Fasted (12 h earlier)	IV	Single dose	20	No visible side effects

PO: Orally, IV: Intravenously, NA: Not Assessed, ROA: Route of Administration, N: Number of individuals

Table 5: Main pharmacokinetic parameters of APAP found in the literature in dogs

	C_{max} or C_0 µg/mL	T_{max} h	$t_{1/2\ kel}$ h	Cl L/h/kg	AUC Last µg*h/mL	V_{ss} h*µg/mL	F %
Sikina *et al*. (2018)	PO: 2.69	1.04	1.81	-	7.04	-	-
	Suppository: 0.52	0.67	3.21	-	1.05	-	-
Sartini *et al*. (2021)	IV: -	-	1.35	0.42	48.01	0.87	-
	$PO_{fasted:}$ 11.11	3	1.25	-	34.61	-	72.09
	$PO_{fed:}$ 9.27	2	1.77	-	40.30	-	84.05
Serrano-Rodríguez *et al*. (2019)	At 20 mg/kg:						
	$IV_{Galgo:}$ -	-	4.87	1.08	18.48	1.24	-
	$IV_{Beagle:}$ -	-	2.86	1.62	12.36	1.32	-
Neirinckx *et al*. (2010)	IV: -	-	0.37	1.74	6.10	0.92	-
	PO: 3.08	0.25	0.38	-	6.28	-	44
Koyanagi *et al*. (2014)	IV: -	-	0.94	0.79	0.26	0.90	-
	PO: 0.429	0.50	2.30	-	1.50	-	108
Kukanich (2016)	PO: 6.74	0.85	0.96	-	13.78	-	-
St. Omer Mohamed (1984)	$IV_{with\ NAC}$ -	-	1.06	6.52	0.39	0.59	-
	$IV_{without\ NAC}$ -	-	1.78	4.04	0.65	0.60	-
Granados *et al*. (2021)	IV concious -	-	2.45	1.52	13.17	1.41	-
	IV anesthetized -	-	3.57	1.60	12.51	1.72	-

C_{max}, peak plasma concentration; T_{max}, time of peak concentration; $t_{1/2kel}$, terminal half-life; Cl, plasma clearance; V_{ss}, volume of distribution at the steady state; F, oral bioavailability. -, not determinable; NAC: N-acetylcystein

Table 6: The variable therapeutic effects of APAP in dogs

Cases	Results	Notes	References
Swelling after orthopedic surgery in dogs	Swelling reduced to very similar extent by APAP (33%) compared to aspirin (24%) and significantly less pain (55%) vs placebo	APAP 0.5 g was given three times daily after surgery. No complications in wound healing occurred	Mburu *et al*. (1988)
Effects on lameness after experimentally induced synovitis in dogs	Reduced lameness and pain, but not as effective as Carprofen	The formulation consisted of APAP (15.5 to 18.5 mg/kg) and codeine (1.6 to 2 mg/kg)	Budsberg *et al*. (2020)
Postoperative pain control in dogs following tibial plateau leveling osteotomy	Hydrocodone-APAP provided better postoperative analgesia (as determined by pain score analysis and frequency of rescue analgesic treatment) compared	Each drug PO every 8 h. Hydrocodone 0.6 mg/kg and APAP 6 mg/kg. Tramadol 7 mg/kg. The percentage of dogs to administered tramadol (minor difference) with treatment failure in both groups was considered unacceptable	Benitez *et al*. (2014)
Postoperative pain control in dogs undergoing ovariohysterectomy	APAP provided equivalent analgesic effects to those achieved with meloxicam and carprofen in bitches 48 hours post-ovariohysterectomy (gradual reduction in pain for all groups)	15 mg/kg APAP IV group 1, Carprofen 4 mg/kg IV group 2, Meloxicam 0.2 mg/kg IV	Hernández-Avalos *et al*. (2020)
Peri- and postoperative pain control in dogs undergoing soft tissues and orthopedic surgeries including: Achilles tendon repair, elbow dysplasia, hindlimb soft tissue sarcoma removal, maxillectomy, ear canal ablation, laryngeal tieback, dermoid sinus exploration, hip replacement...	Significantly reduced pain and inflammation. APAP/codeine combined drug shown to be very effective post-operatively and showed non-inferiority (same efficacy) to the NSAID Meloxicam	APAP+codeine (Pardale-V) once every 8 h orally, starting 2 h before the anesthesia. Meloxicam 0.2 mg/kg loading dose 2 h before anesthesia and then 0.1 mg/kg every 24 h	Pacheco *et al*. (2020)
Surgically induced myocardial infarction in dogs + exogenously administered hydrogen peroxide	After APAP administration: reduced infarctus size, decreased myocardial tissue necrosis and ischemia and enhanced reperfusion, less damage to myofibrils compared to control groups. Evidence of anti-arrhythmic effects and heart stabilization too	750 mg APAP IV bolus, divided in 2 doses. This Mechanism is mediated by catalase/ superoxide dismutase. APAP was discovered to be among the most efficacious cardioprotective agents. It is a potent anti-oxidant, also reduces the activity of myeloperoxidase (Brennan *et al*., 2002), which in turn significantly reduces the oxidation of low-density lipoproteins (LDLs) in macrophages (Podrez *et al*., 2000; Golfetti *et al*., 2003).	Merrill *et al*. (2004. To also check Merrill *et al*., 2001, Merrill 2004; Nakamoto *et al*., 1997)

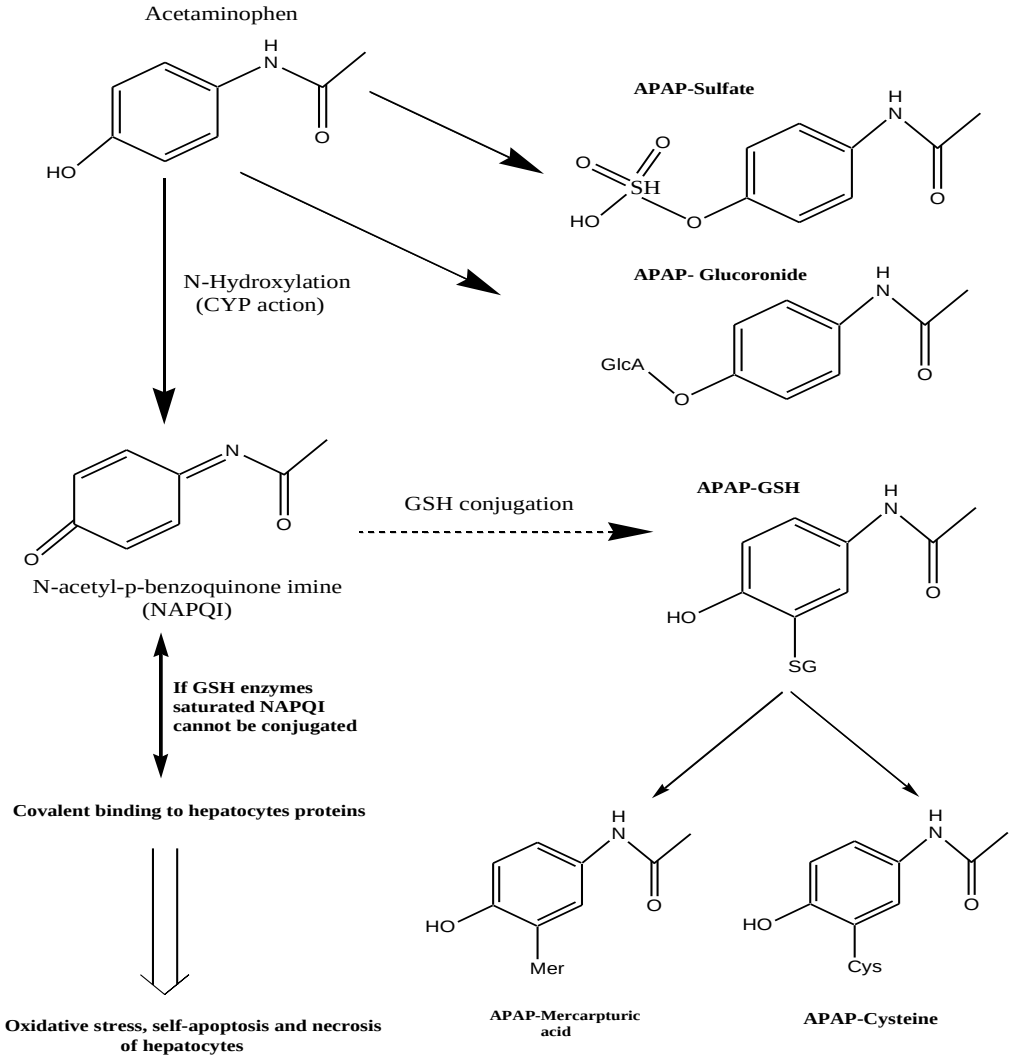

Fig. 1: Metabolic pathways of APAP in mammals

Pharmacodynamics

The mechanism of action of APAP, which is established mainly in mice, rats and humans, is not fully understood in dogs yet. Thus this review will briefly discuss the findings on APAP's Pharmacodynamics (PD), followed by evidence on the therapeutic effects found in dogs.

APAP is not directly a PGs synthesis inhibitor. APAP inhibits PG activity by acting as a substrate of the peroxidase cycles of COX-1 and COX-2 but, the main impact is frequently on COX-2 (Boutaud *et al*., 2002; Graham and Scott, 2005; Aronoff *et al*., 2006; Graham *et al*., 2013). When concentrations of arachidonic acid are low, the COX-2 pathway is activated in preference to the COX-1 pathway (Graham and Scott, 2005). APAP can inhibit COX, both centrally and peripherally, when ambient concentrations of peroxides are low. However, under pro-inflammatory conditions, when peroxide concentrations are high, APAP is ineffective peripherally and is only active in the brain, where baseline peroxide concentrations are very low. The inhibition of cerebral COX is responsible for the antipyretic effects of APAP (Ouellet and Percival, 2001).

In dogs, a described third isoform, COX-3, has been identified in the cerebral cortex, with minimal amounts found peripherally. This new enzyme was discovered to be inhibited by APAP (Jóźwiak-Bebenista and Nowak, 2014; Chandrasekharan *et al*., 2002). However, its activity and physiological effects in dogs, rats and humans have been the source of some debate and speculation (Kis *et al*., 2005; Lucas *et al*., 2005).

Concerning the central nervous system effect, many studies showed how APAP inhibits central neurotransmitters including substance P (Crawley *et al*., 2008; Choi *et al*., 2001; Björkman *et al*., 1994) and

glutamate (Choi *et al*., 2001; Raffa and Codd, 1996; Mallet *et al*., 2008) and activates opioidergic system, CB1 cannabinoid receptors, nitric oxid and the 5-HT-3 receptor antagonist (Sandrini *et al*., 2003; Roca-Vinardell *et al*., 2003; Bonnefont *et al*., 2003). Peripherally, APAP prevents the synthesis of PG by a number of peripheral nervous cells and alters the activity of acetylcholine and noradrenaline (Dani *et al*., 2007; Lee *et al*., 2007; Graham and Scott, 2005; Graham *et al*., 2013; Moore *et al*., 1992).

Regarding the therapeutic effects in dogs, APAP is safe when prescribed at a therapeutic dose and for a limited period of time (Serrano-Rodríguez *et al*., 2019). In all the studies, it has been noticed that no visible side effects are seen with APAP doses below 100 mg/kg. Many studies have been established, however, further investigations are needed. For instance, the plasma concentration of APAP that can provide analgesia in dogs is unknown. A study published in 2006 reported that a plasma concentration close to 4 μg/mL was sufficient to provide analgesia in humans (Pickering *et al*., 2006). Despite that the PK/PD relationship for most of the analgesic or an anti-inflammatory drugs obeys to some indirect effects (Sharma and Jusko, 1998), oral acetaminophen in humans suggests to have a minimal hysteresis (nearly a direct effect) (Pickering *et al*., 2006). Then, if assumed that dogs and humans have the same minimal effective concentration, plasma concentrations of APAP above 4 μg/mL might provide antinociceptive effect for a few hours (Giorgi *et al*., 2012; Giorgi *et al*., 2016).

Further evidencing its potential for post-surgical use, the administration of the recommended dose of APAP in dogs (20 mg/kg every 8 h) (Sartini *et al*., 2021) can be used instead of NSAIDs, especially if these are contraindicated (Berry, 2015). To note that recently, a recommended drug combination suggested for analgesia in dogs, is an oral opioid formulation plus APAP (Plumb, 2015; Muir, 2015). Opioids that have been combined with APAP for this purpose include codeine, oxycodone and hydrocodone (approved for usage in Europe) (Egger *et al*., 2014; Benitez *et al*., 2015; Kukanich, 2010).

APAP is also included in opioid-free anaesthesia protocols, which are often combined with other anesthetic/analgesic drugs, including medetomidine, ketamine, lidocaine, bupivacaine, carprofen and meloxicam in dogs (White *et al*., 2017).

The documented therapeutic effects of APAP in dogs are summarized in Table 6.

Toxicology and Pathology

The clinical signs of APAP toxicity are generally seen with doses above 150 mg/kg (St. Omer and Mohamed, 1984). APAP is one of the most common household medications and it is not surprising that APAP toxicity, as an unintentional or accidental overdose in dogs, is frequently reported (Caloni *et al*., 2014).

Toxic effects of APAP in canine species include hepatic damage, kidney failure, serious hematologic disorders and hemoglobin damage (Satirapoj *et al*., 2007; Pereira *et al*., 1992). Clinical signs reported in toxic doses were similar and included: Anorexia, weight loss, face swelling, weakness, depression, tachypnea, dyspnea, icterus, vomiting, hypothermia, lethargy and apathy, prolonged capillary refill time, cyanotic or pale mucous membranes and abdominal discomfort (Salem *et al*., 2010; St. Omer and Mohamed, 1984; Wongnawa *et al*., 2005; Satirapoj *et al*., 2007; Savides *et al*., 1984; Ortega *et al*., 1985; Villar and Buck, 1998).

The APAP is often poorly used in veterinary medicine because of the wrong belief that it possesses a narrow therapeutic index and several potential increases in toxicity when used in combination with other drugs or natural compounds. Concerning the drug-drug interaction and the resulting toxicity, it was affirmed that maximal enzymatic induction with ethanol in humans is not capable of increasing APAP toxicity when administered within the therapeutic range (Thummel *et al*., 2000; Rumack, 2004). Phenytoin was also thought to enhance APAP toxicity (Manyike *et al*., 2000; Brackett and Bloch, 2000). As a CYP3A4 inducer, it does not increase APAP toxicity. Indeed CYP3A4 accounts for only a small portion of APAP metabolism. CYP2E1 is the principal metabolic enzyme for APAP metabolism to NAPQI. Another wrong theory is that barbiturates (i.e., phenobarbital), acting as a pleiotropic inducer of phase I and phase II reactions, can induce all the metabolic enzymes and consequently the CYP2E1. If theoretically this hypothesis has some basis, it has been experimentally assessed that phenobarbital has no effect on any of the processes of APAP-toxic metabolites (Rumack, 2002; 2004).

General Toxicity

At toxic doses (> 150 mg/kg), sulfate and glucuronosyl transferases become saturated and NAPQI production increases. If GSH is depleted to < 20% of its usual concentration, NAPQI binds covalently to cysteine groups on hepatocellular proteins via cysteine residues, disrupting cellular integrity and yielding hepatocyte necrosis (Pumford *et al*., 1990). Most of the covalent binding occurs centrolobularly, being preferentially localized in the endoplasmic reticulum and in the enzymes of the cytoplasm. This injury likely takes place very rapidly once GSH depletion is accomplished, leading to the extraordinary levels of aminotransferases and other cellular enzymes, but also a very rapid decline upon cessation of liver injury. Likewise, a free radical formed through the Mixed Function Oxidase (MFO) system causes oxidative damage to cellular molecules (Pereira *et al*., 1992).

Nephrotoxicity

Renal damage is a secondary effect described following APAP administration (Salem *et al*., 2010). Nephrotoxicity is caused by a deacetylation of APAP in the kidney to form p-aminophenol (PAP), a minor

metabolite, however a potent nephrotoxin (Carpenter and Mudge, 1981; Crowe *et al*., 1979). This compound may be oxidized to p-benzoquinoneimine, which is very unstable and has a cytotoxicity comparable to NAPQI. Although produced by different metabolic routes, PAP and NAPQI can be produced in the kidney (Bessems and Vermeulen, 2001). These two compounds produced severe congestion of the cortex and medulla, proteinaceous tubular casts and nephrosis after 500 mg/kg APAP administration (Savides *et al*., 1984).

A 200 mg/kg dose produced an increased echodensity in kidney parenchyma that matched with renal damage in dogs. In Salem *et al*. (2010), renal smears upon cytology showed moderate to severe degree of vacuolation and degeneration of cells and tubular cells degenerated into dark gray amorphous debris representing the necrotic material. This nephrotoxicity is most likely attributed to a depletion of GSH in the renal parenchyma (Loh and Ponampalam, 2006; Kurtovic and Riordan, 2003). On histology, congestion with vasculitis, thickened renal capsule (perinephritis), vacuolation of the glomerular and tubular epithelium, necrosis and perivascular fibrosis were observed. Increased concentrations of Blood Urea Nitrogen (BUN) and serum creatinine reflect this renal damage and were consistent in all reports (Savides *et al*., 1984; Salem *et al*., 2010; MacNaughton, 2003; Ortega *et al*., 1985; Savides and Oehme, 1983; Schlesinger, 1995).

Hematotoxicity

APAP hematotoxicity in dogs is mainly attributed to PAP (Mc Conkey *et al*., 2009; Allen, 2003; Taylor and Dhupa, 2003). The toxic metabolites bind to iron and cellular material, resulting in methemoglobinemia, membrane oxidative injury and Heinz bodies formation (Rianprakaisang *et al*., 2019). The deficiency of arylamine N-acetyltransferase (NAT) activity (polymorphic cytosolic conjugating enzymes) in dogs (and cats) contributes to this species-dependent methemoglobinemia (Mc Conkey *et al*., 2009).

This blood toxicity does not occur in all cases. It is claimed to be a chronic consequence after a long term administration, however, in many reports it seems to be an acute symptom, with or without hepatotoxicity (Schlesinger, 1995; MacNaughton, 2003).

In all of the references mentioned above for dogs, the hematology repercussions were similar. A mild to severe regenerative anemia, accompanied by a mild to severe stress leukogram were noted. In all reports, significant neutrophilia was consistent. In some cases, there were fragmented red blood cells, poikilocytosis, mild agglutination, spherocytes, acanthocytes, anisocytosis and polychromasia (MacNaughton, 2003; Schlesinger, 1995; Salem *et al*., 2010; Harvey *et al*., 1986).

Hepatotoxicity

The clinical severity of hepatotoxicity is proportional to the dose and ranges from mild to severe acute hepatitis. Liver lesions were similar in most studies (Ortega *et al*., 1985; Gazzard *et al*., 1975; Salem *et al*., 2010) and analogous to morphological changes described by other authors in man and in several animal species (McGregor *et al*., 2003; Sheen, 2002; Dixon *et al*., 1975; Mitchell, 1977).

At a dose of 200 mg/kg of APAP, liver cytology showed damaged hepatocytes distended by multiple lipidic vacuoles of different sizes and the nuclei pushed to the periphery. Histopathology showed a congested liver, mainly in the portal tract, with swelling, centrolobular necrosis and hyperplasia of the bile duct, in Salem *et al*. (2010). Elevated serum bilirubin concentration (especially unconjugated one), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Gamma-Glutamyltransferase (GGT) levels were increased in all the studies (MacNaughton, 2003; Ortega *et al*., 1985; Savides and Oehme, 1983; Schlesinger, 1995; Savides *et al*., 1984; Salem *et al*., 2010).

Dogs receiving 250 mg/kg showed acute hepatitis and focal necrosis in the centrilobular region with inflammatory infiltrates. Some livers, in addition, showed granulomatous aggregates in acinus and portal space consisting of epithelioid cells with peripheral lymphocyte infiltration (Ortega *et al*., 1985).

Dogs receiving 500 mg/kg (lethal dose), all died after 76 h and showed massive hepatic necrosis extended from terminal hepatic venules to portal spaces, hyperemic sinusoids and hypertrophic sinusoidal cells. Subcellular changes also took place with formation of lamellar structures on the nucleus and mitochondria (Dixon *et al*., 1975).

Similar liver lesions were also found, with congestion, extensive necrosis, fatty vacuoles at an APAP dose of 3000 mg/kg (Gazzard *et al*., 1975). All dogs died in approximately 8 h. Raised levels of arterial ammonia, reduced arterial partial pressure of oxygen, methemoglobinemia and markedly increased Aspartate Aminotransferase (AST) levels occurred for those who survived more than 24 h.

The ingested dose or, more precisely, plasma concentrations of APAP, can predict the incidence and severity of hepatotoxicity. Only when the time of acute ingestion of APAP is known, the Rumack-Matthew nomogram is used to estimate the probability of hepatotoxicity. Plasma concentrations higher than 150 μg/mL suggest possible hepatotoxicity in humans (Rumack and Matthew, 1975). Figure 2 represents the nomogram consisting of a semi-logarithmic curve of plasma APAP levels versus time.

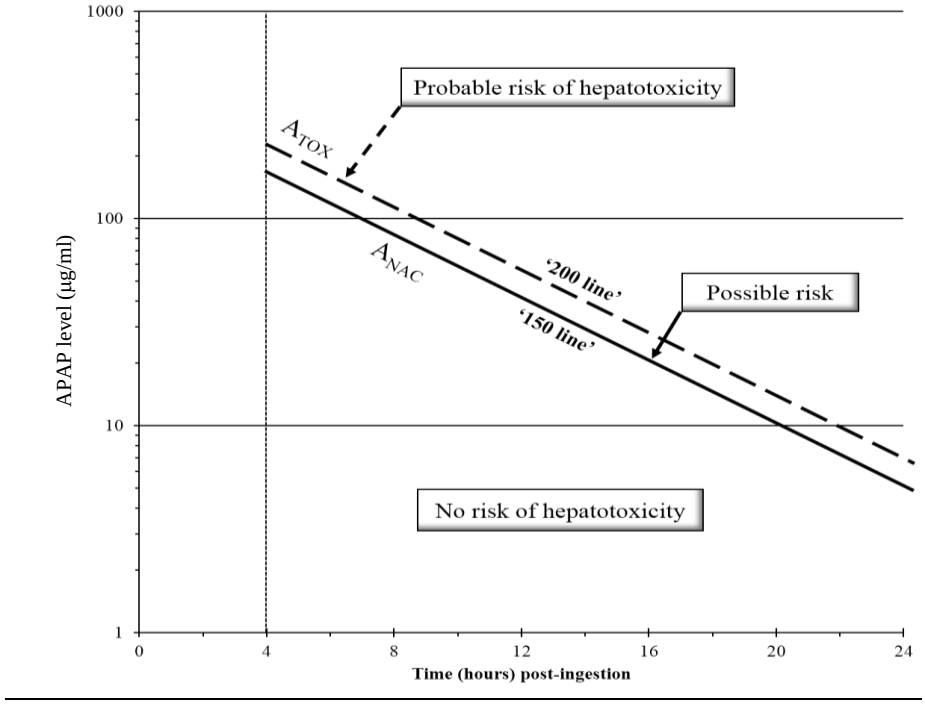

Fig. 2: The Rumack-Matthew Nomogram for APAP poisoning and treatment. After a single acute overdose, the patient's plasma APAP concentration is plotted on the graph using the time from overdose to blood draw. If above the risk line, 150 µg/mL, hepatotoxicity is possible and the patient receives acetylcysteine treatment at a dose of 300 mg/kg body weight. Toxicity is very probable above 200 µg/mL. If the plasma concentration is below 150 µg/mL, hepatotoxicity is unlikely and no need for treatment

This approach is established in human medicine but with some adjustments it might also fit in canines. Additional tests are recommended if poisoning is confirmed or highly suspected, or if the time of consumption is uncertain. If severe intoxication is suspected, liver enzymes tests and prothrombin time should be conducted. The AST and ALT levels appear to be proportionally related to the stage of poisoning. Bilirubin also increases if the intoxication is severe (O'Malley and O'Malley, 2020).

Antidotes against APAP Toxicity

N-acetylcysteine (NAC), the precursor of GSH, is a specific antidote against APAP toxicosis in dogs and cats (St. Omer and McKnight, 1980; St. Omer and Mohammad, 1984) and liver necrosis in man (Prescott and Wright, 1973). It is currently the only FDA approved antidote for APAP overdose in humans (Khayyat *et al*., 2016). NAC restores GSH levels which acts directly on NAPQI to form an acetyl-cysteine conjugate which is excreted in bile. Additionally, NAC supplies mitochondrial energy substrates in the Krebs cycle and restores hepatic ATP levels by providing excess amino-acid and uses it as energy substrates (Saito *et al*., 2010; Lauterburg *et al*., 1983).

The minimum recommended clinical dosing schedule of NAC for the treatment of APAP toxicosis in dogs is 140 mg/kg orally, repeated every 4 hours for three treatments (St. Omer and McKnight, 1980). It has been reported that NAC alters the pharmacokinetics of APAP (St. Omer and Mohammad, 1984). It decreased the elimination terminal half-life of APAP by 40% and increased its clearance by 60%. Similar results were obtained in rats (Galinsky and Levy, 1979).

Moreover, it has been demonstrated that cimetidine, an inhibitor of some cytochrome oxidase enzymes, decreases the production of NAPQI by blocking CYP 450 (Ruepp *et al*., 2002). This would be of benefit to species that develop centrolobular necrosis due to NAPQI, like dogs (Sajedianfard *et al*., 2009; Rudd *et al*., 1981; Mitchell *et al*., 1984).

Conclusion

APAP, when used in the therapeutic levels, has shown to be a potent and effective analgesic and antipyretic in dogs, with some anti-inflammatory activity. When used in doses below 100 mg/kg, no side effects occur and at recommended therapeutic levels, generally between 10 and 20 mg/kg, is effective for postoperative pain control. It can also be used instead of NSAIDs when these are contraindicated, in combination with opiods and in opioid-free anesthesia surgery protocols. APAP also showed cardioprotective and anti-arrhythmic effects in dogs, nevertheless more details are needed.

APAP, however, must be used with caution. Doses above 150 mg/kg are toxic and the repercussions are severe, with hepatotoxicity, hematotoxicity and nephrotoxicity. Doses above 250 mg/kg can be lethal. Antidotes of APAP such as NAC and cimetidine are shown to effectively reverse, partially, the toxicity.

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Author's Contributions

Charbel Fadel: Developed the literature search and wrote the draft version of the review. Reviewed and approved the final version of the paper.

Irene Sartini: Contributed in the literature search, planned tables and plots. Verified the consiastency of the information. Reviewed and approved the final version of the paper.

Mario Giorgi: Conceived of the presented idea and supervised the project. Provided critical feedback and helped shape manuscript Reviewed and approved the final version of the paper.

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