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Pentoxifylline in management of chronic kidney disease in dogs

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Abstract
CKD in dogs is common as they get older. There are numerous potential underlying etiological causes for canine CKD. The underlying cause of the majority of the conditions is not obvious and may no longer be present at the time of presentation or clinical diagnosis. A comprehensive medical history from the pet owner, as well as a physical examination, renal function tests, urinalysis, and renal imaging studies, are required to diagnose CKD. Pentoxifylline is a methyl xanthine medication that inhibits the synthesis of inflammatory cytokines that are required for the progression of CKD. In comparison to the supportive therapy group, there was a substantial rise in albumin, calcium, total protein, haemoglobin, hematocrit, TEC and a significant decrease in blood urea nitrogen, creatinine, CysC, phosphorous, urine protein, and UP/C Ratio in the Pentoxifylline treated group. These changes indicate a delayed or halted course of CKD.

Keywords: CKD, Pentoxifylline, blood urea nitrogen, creatinine, cystatin C

1. Introduction
As dogs became domesticated, humans began to recognise a variety of signs, symptoms, and other medical conditions that frequently afflicted them. Finding out that a beloved pet has a fatal disease such as Diabetes, Cancer, Kidney disease, Rabies, Canine Distemper, or Parvo viral gastroenteritis can be terrifying. Some diseases, such as Parvovirus infection, Rabies, and Distemper, are preventable through an effective vaccination programme, whereas others, such as chronic kidney disease (CKD), cannot be reversed or cured. Treatment and management aimed at reducing the contributing factors can slow the progression of the disease and have an impact on the dog's well-being. The present work was undertaken study the effect of pentoxifylline. Pentoxifylline is a methylxanthine drug that inhibits the synthesis of inflammatory cytokines that are required for the progression of CKD.

2. Headings and Footnotes
2.1 Materials and Methods
The therapeutic trials were conducted on dogs over the age of six, which had a history, clinical signs, laboratory findings, and renal sonography changes suggestive of chronic kidney disease. The dogs with chronic kidney disease were classified as Stage I, Stage II, Stage III, and Stage IV according to IRIS Board guidelines. Dogs in Stage II and Stage III were considered for therapeutic trials, and these dogs were divided in to two groups *viz* Group I and Group II.
Group I included ten dogs suffering from CKD stage II and ten dogs suffering from CKD stage III. The dogs in Group I was kept on supportive therapy with a regular diet that the animals were used to taking on a daily basis. Group II included 11 dogs suffering with CKD stage II and 10 dogs suffering with CKD stage III. The dogs in Group II received both supportive and specific therapy with Pentoxifylline @10mg/kg body weight BID, administered orally. The study used Pentoxifylline Sustained Release tablets, Tab Trenetal 400 mg or Tab Kinetal 400 mg from Sanofi Aventis or Cipla (Protec). During the treatment period, the dogs were fed a regular diet/homemade food. The dogs in the therapeutic trials were monitored for 45 days, and the treatment regimens were evaluated based on clinical signs, haematology, serum biochemical profile, and urinalysis improvement.

2.2 Results and Discussion
Table 1 shows the Mean SE of hematobiochemical changes in CKD stage II and stage III for both therapeutic groups. From the first to the 45th day of the therapeutic trial, there was a significant increase in creatinine, BUN, CysC, phosphorous, urine protein concentration, and

UP/C Ratio in Group I animals of both CKD stage II and III. Albumin, TPP, calcium, sodium, haemoglobin, hematocrit, TEC, and platelet levels, on the other hand, decreased significantly from day 0 to day 45. All of these changes are clearly indicative of CKD progression. Intravenous fluids, antiemetic, and antacids are effective in controlling uremic crisis for a shorter period of time, but they do not reverse, halt, or eliminate renal damage, which is the cause of CKD progression. Specific therapy, in addition to conservative treatment, is critical for better CKD therapeutic management (Brown, 1998: Roudebush *et al*. 2010) [2, 7]. From day 0 to day 45, there was a significant increase in albumin, calcium, total protein, haemoglobin, hematocrit, TEC and a significant decrease in blood urea nitrogen, creatinine, CysC, phosphorous, urine protein, and UP/C Ratio in Group II animals of both CKD stage II and III.

These observations are in accordance with Nenad *et al.*, (2009) [5] and Belde *et al.*, (2013) [1] where the authors observed the renoprotective effect of Pentoxifylline in laboratory animal models. Regardless of the etiology, chronic kidney disease is characterized by renal fibrosis. The initial damage leads to inflammatory response with the generation and local release of soluble mediators, an increase in local vascular permeability, activation of endothelial cells, diapedesis of leukocytes along the endothelium, subsequent secretion of various mediators by infiltrating leukocytes and tubulointerstitial cells, and activation of profibrotic cells. As a consequence, a vicious cycle of cell stress is initiated generating profibrotic and pro-inflammatory mediators, leukocyte infiltration and fibrosis (Matovinovic, 2009) [4].

Pentoxifylline suppresses synthesis of inflammatory cytokines, such as Interleukin-1 (IL-1 beta), IL-2, IL-6, and TNF α and also inhibits lymphocyte activation as indicated by Wenisch *et al*. (1998) [8], Espinoza *et al*. (2012) [3] and Papich (2016) [6]. These factors may have contributed to the observation of improvements in parameters indicating the prevention of further renal damage when pentoxifylline was administered to CKD dogs in Group II.

Table 1: Mean±SE of Hematobiochemical changes observed in CKD stage II and CKD Stage III therapeutic groups

Parameters	Group	CKD II		CKD III	
		Day 0	Day 45	Day 0	Day 45
Hemoglobin (g %)	Group I	10.03±0.14	9.04±0.14	9.88±0.18	8.94±0.06
	Group II	10.1±0.08	10.87±0.11	9.84±0.14	10.5±0.07
Hematocrit (%)	Group I	30.57±0.36	30.74±0.44	29.02±0.59	24.58±0.65
	Group II	25.67±0.28	32.86±0.49	27.58±0.24	29.99±0.44
TEC ($x10^6$/µl)	Group I	4.58±0.12	4.62±0.1	4.16±0.02	3.71±0.07
	Group II	3.89±0.1	4.93±0.08	4.17±0.04	4.43±0.09
WBC ($x10^3$/µl)	Group I	17.27±0.62	11.61±0.09	17.5±0.56	11.88±0.07
	Group II	18.04±0.84	10.59±0.18	18.09±0.36	11.33±0.12
Platelets (lakhs/µl)	Group I	3.1±0.18	2.76±0.24	2.82±0.08	2.48±0.09
	Group II	3.08±0.11	3.05±0.11	2.86±0.08	2.84±0.06
Blood urea nitrogen (mg/dL)	Group I	58.29±2.1	89.14±1.82	82.67±1.69	112.33±2.79
	Group II	60.29±2.29	14.14±0.46	86.57±1.86	14.57±0.65
Creatinine (mg/dL)	Group I	1.8±0.06	2.14±0.04	3.75±0.31	4.65±0.22
	Group II	1.73±0.05	0.76±0.04	3.79±0.27	1.67±0.09
Phosphorous (mg/dL)	Group I	5.27±0.5	6.67±0	6.37±0.53	7.43±0.4
	Group II	5.29±0.67	4.7±0.51	6.24±0.53	5.59±0.47
UP/C Ratio	Group I	2.04±0.1	2.7±0.07	2.6±0.13	3.53±0.1
	Group II	1.97±0.07	1.32±0.06	2.78±0.13	1.87±0.06
Cystatin C (mg/dL)	Group I	0.7±0.02	0.76±0.02	1.73±0.03	1.79±0.02
	Group II	0.69±0.02	0.57±0.02	1.74±0.03	1.59±0.01

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