

Effects of pentoxifylline in experimental acute renal failure

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Effects of pentoxifylline in experimental acute renal failure. The beneficial effects of post-insult administration of pentoxifylline, a novel hemorheologic agent experimentally studied in various ischemic diseases, were evaluated in two models of acute renal failure (ARF): direct nephrotoxicity (mercuric chloride 4 mg/kg via femoral vein) and hemoglobinuria (glycerol 10 ml/kg i.m.). Glomerular filtration rate (GFR) was estimated at baseline and following drug administration by creatinine clearances; tubular function was assessed by renal fractional and absolute electrolyte excretions. The incidence of mortality was decreased with a single dose of pentoxifylline 45 mg/kg (21.4%) compared to control rats (71.4%) 48 hours following induction of ARF with mercuric chloride. Although GFR and renal electrolyte excretion were significantly greater in rats given pentoxifylline compared to saline, the magnitude of difference was minimal. A return to baseline GFR was observed in the glycerol group administered a single i.p. dose of pentoxifylline 45 mg/kg ($100.8 \pm 54.8\%$) compared to saline controls ($45.6 \pm 22.7\%$; $P < 0.05$). No differences in renal electrolyte excretion or mortality were observed in this model. Taken together, these data suggest that pentoxifylline, administered shortly after the initiation of ARF, exerts an ameliorative effect on the course and mortality of experimental ARF. The mechanism of amelioration most likely involves the stimulation of renal vasodilator prostaglandins as well as prevention of vascular congestion.

Experimental acute renal failure (ARF) can be induced using a wide variety of methods including bilateral renal artery and ureteral occlusion, as well as the introduction of toxic agents such as mercuric chloride and glycerol [1-5]. These models have been employed in the study of the prevention and treatment of the syndrome in the clinical arena. However, their pathological and clinical significance remains controversial [6]. Nonetheless, certain theories have been postulated to explain the hemodynamic changes including thromboxane A_2 synthesis and inhibition of prostacyclin, disturbances in intracellular calcium transport, and increased amounts of extracellular adenosine generated from cellular depletion of adenosine triphosphate (ATP). Studies using prostaglandin stimulants and inhibitors, calcium channel antagonists and adenosine receptor antagonists have consistently demonstrated the involvement of one or more of these pathways in the pathogenesis of ARF [7-12].

To date, drug regimens have been aimed at pre-treatment of the kidney prior to the insult. However, it is rare, clinically, that the nephrologist can predict the onset of ARF, particularly in

the critically-ill patient population. Often, the diagnosis of ARF is made only after the renal damage has occurred. Due to the high morbidity and mortality of the syndrome [13], studies should be targeted towards post-insult treatment and amelioration.

Pentoxifylline, a non-specific hemorheologic agent for the treatment and prevention of intermittent claudication [14-16], has been extensively studied in the prevention of ischemic diseases, in particular, ischemic cerebral edema, nonhemorrhagic stroke and, recently, experimental ischemic ARF [17-20]. Also, the co-administration of pentoxifylline has significantly reduced cyclosporine-associated nephrotoxicity in the murine model [21]. Although its mechanism of action is not well understood, pentoxifylline decreases blood viscosity by altering erythrocyte deformability [22], reducing platelet aggregability and fibrinogen levels [23], and increasing neutrophil mobility [24]. Also, pentoxifylline is a potent stimulator of prostacyclin in vascular beds [23, 25] and, like other xanthines such as theophylline, is an adenosine receptor antagonist (unpublished observations).

Since the pathogenesis of ARF may involve vascular congestion [26] and/or the arachidonic acid pathway [7-9], the present study investigated the potential benefits of pentoxifylline administration. Two murine models of ARF, glycerol-induced hemoglobinuria and direct nephrotoxicity with mercuric chloride, were administered a single dose of pentoxifylline following the insult. Renal function was serially measured and compared to baseline as well as saline controls. Significant improvement in morbidity and mortality suggests the potential benefit of pentoxifylline in clinical ARF.

Methods

Animals

Adult male Sprague-Dawley albino rats (220 to 325 g, Charles River Breeders, Wilmington, Massachusetts, USA) were maintained on standard rat chow (Ralston Purina Co, St. Louis, Missouri) and tap water *ad libitum*. The rats were housed in a timed 12-hour light/dark cycle animal facility with controlled humidity and temperature. Each animal was allowed to acclimate to the metabolism cage for at least two days prior to renal function assessment [27]. To avoid chronobiologic variation in serum creatinine production and clearance, timed collections were performed for 24 hours starting at the same time each morning [28]. The experimental protocol used in this study was in accordance with the Animal Care Committee of the University of Houston. Rats in the study were maintained in accordance with the guidelines established by the Committee on the

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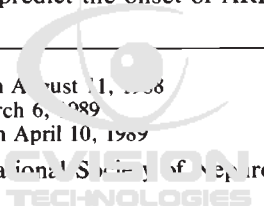


Table 1. Effect of a single 45 mg/kg i.p. dose of pentoxifylline compared to saline in mercuric chloride-induced ARF

	Saline			Pentoxifylline		
	Baseline	24	48	Baseline	24	48
Weight (g)	309 (21)	294 (20)	280 (18)	296 (61)	271 (58)	259 (60)
Q _u (μl/min/100 g)	2.87 (1.29)	3.19 (2.43)	0.43 ^a (1.02)	3.68 (0.97)	4.90 ^a (2.88)	2.10 ^b (1.28)
S _{Cr} (mg/dl)	0.60 (0.31)	4.66 ^a (0.96)	9.04 ^a (1.55)	0.55 (0.07)	4.23 ^a (1.36)	7.43 ^a (2.67)
Cl _{Cr} (μl/min/100 g)	333.6 (168.7)	5.5 ^a (3.6)	0.4 ^a (0.7)	386.6 (186.8)	27.2 ^{a,b} (36.5)	26.2 ^a (76.5)
FR _{Na} (%)	99.1 (0.6)	72.6 ^a (20.0)	61.4 ^a (21.8)	99.4 (0.4)	84.4 (16.2)	85.3 ^{a,b} (11.1)
U _{Na} V (μM/min/100 g)	0.412 (0.223)	0.312 (0.306)	0.038 ^a (0.058)	0.303 (0.255)	0.340 (0.302)	0.078 ^a (0.015)
U _K V (μM/min/100 g)	0.306 (0.081)	0.369 (0.249)	0.025 ^a (0.030)	0.374 (0.141)	0.535 (0.342)	0.068 ^a (0.053)

Data are means ± SD.

^a *P* < 0.05 from baseline

^b *P* < 0.05 from saline

Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

Experimental protocol

Baseline renal function was estimated from two consecutive, 24-hour urine collections (Nalge metabolic cage) with pre- and post-collection blood samples (0.5 ml) obtained via tail bleed under light ether anesthesia. For replacement of blood volume loss, an equivalent volume of physiologic saline was administered intraperitoneally following each blood sample. Complete bladder void was prompted with an ether nose cone. Powdered food and water was unrestricted throughout the study except where specified. The experimental protocol was initiated 24 hours following the final blood sample.

Each rat was randomized (stratified on baseline creatinine clearance) to receive a single dose of mercuric chloride 4 mg/kg (4 mg/ml dissolved in saline via femoral vein; Sigma Chemical), glycerol 10 ml/kg (50% vol/vol in sterile saline i.m. after 16 hour water deprivation; Sigma Chemical) or saline on day 1 following baseline assessment. Within one hour following the toxic injection (or control), each rat was administered a single intraperitoneal injection of pentoxifylline 45 mg/kg (pentoxifylline 45 mg/ml in physiologic saline) or saline. The dose was chosen arbitrarily to exceed the normal therapeutic concentration [29] and yet be less than the maximal allowable amount prior to CNS toxicities in the murine model [30]. The rat returned to the metabolism cage for two further, 24-hour urine collections with pre- and post-collection blood samples. No further injections of either saline or pentoxifylline were administered. Water and food were maintained *ad libitum*.

Sample analysis

All blood samples were collected via tail bleed into drug-free polypropylene microcentrifuge tubes on ice, centrifuged for five minutes (3000 × g), and the serum harvested and stored at -20°C until analyzed (within one month). Urine and serum samples were assayed for sodium and potassium concentrations by ion-selective electrodes (NOVA Analyzer 11+11). Creati-

nine was measured in urine and serum utilizing the modified Jaffe method (Beckman Creatinine Analyzer II).

Data analysis

Creatinine clearance (Cl_{Cr}) was calculated by the equation:

$$Cl_{Cr} = (U_{Cr}/S_{Cr}) \times Q_u$$

where U_{Cr} and S_{Cr} were concentrations of creatinine in the urine and serum, respectively. Urinary flow rate (Q_u) was corrected to total body weight. Fractional reabsorption of sodium (FR_{Na}) and renal sodium and potassium excretions (U_{Na}V and U_KV, respectively) were estimated by standard methods.

Statistical analysis

Mean data of each model were compared with and without pentoxifylline at each time point and versus the mean baseline function by between-within/split-plot analysis (PCANOVA), with post-hoc Newman Keuls test to assess critical differences. A difference was considered significant when the probability of chance was reduced to less than 5% (*P* < 0.05). All data are presented as mean ± standard deviation ($\bar{X} \pm SD$).

Results

No differences in baseline Cl_{Cr}, Q_u, S_{Cr}, or electrolyte handling were observed in control rats (*N* = 6) 48 hours after a single dose of pentoxifylline. Furthermore, no mortality and weight loss were found in the control rats.

Mercuric chloride model

Since rats were randomized stratified on baseline renal function, there were no differences in any measured renal functional parameters at baseline between groups administered pentoxifylline or saline (*N* = 14 each). The administration of pentoxifylline following mercuric chloride induction of ARF significantly reduced mortality compared to saline controls (21.4 vs. 71.4%, *P* < 0.05). Three rats treated with pentoxifylline died at

Table 2. Effect of a single 45 mg/kg i.p. dose of pentoxifylline compared to saline in glycerol-induced ARF

	Saline			Pentoxifylline		
	Baseline	24	48	Baseline	24	48
Weight (g)	198 (59)	169 (40)	166 (40)	198 (48)	179 (33)	180 (36)
Q_u ($\mu\text{l}/\text{min}/100\text{ g}$)	6.78 (3.90)	9.88 (4.46)	8.97 (5.57)	4.24 (1.72)	9.12 ^a (3.14)	8.59 ^a (2.50)
S_{Cr} (mg/dl)	0.42 (0.05)	0.84 ^a (0.34)	0.84 ^a (0.29)	0.48 (0.12)	0.89 ^a (0.72)	0.63 (0.22)
Cl_{Cr} ($\mu\text{l}/\text{min}/100\text{ g}$)	600.9 (183.7)	320.6 ^a (171.3)	282.3 ^a (105.8)	573.6 (211.9)	329.3 ^a (120.7)	517.5 ^b (145.0)
FR_{Na} (%)	96.4 (0.7)	98.0 (1.9)	98.8 (1.0)	98.5 (2.4)	98.9 (0.6)	99.3 (0.5)
U_{NaV} ($\mu\text{M}/\text{min}/100\text{ g}$)	0.640 (0.205)	0.694 (0.456)	0.453 (0.322)	0.647 (0.186)	0.499 (0.200)	0.520 (0.289)
U_{KV} ($\mu\text{M}/\text{min}/100\text{ g}$)	0.777 (0.255)	1.040 (0.555)	0.789 (0.365)	0.737 (0.272)	0.801 (0.273)	0.935 (0.426)

Data are means \pm SD.

^a $P < 0.05$ from baseline

^b $P < 0.05$ from saline

48 hours, whereas four and six rats given saline died at 24 and 48 hours, respectively, following mercuric chloride administration. Significant renal dysfunction, measured by increases in S_{Cr} with corresponding decreases in Cl_{Cr} , were observed in all rats independent of post-induction treatment (Table 1). Although Cl_{Cr} was significantly greater 24 hours post-induction with pentoxifylline compared to saline, the magnitude of difference was minimal. Final Cl_{Cr} returned to $10 \pm 23\%$ of baseline Cl_{Cr} with pentoxifylline versus anuria in the saline group. Q_u was similarly increased with pentoxifylline after 48 hours (48 ± 67 vs. $9 \pm 19\%$ of baseline, pentoxifylline vs. saline, $P = 0.08$). Renal sodium and potassium excretions were significantly reduced in groups administered saline; a significant decrease in baseline U_{KV} , but not U_{NaV} , was found in pentoxifylline-treated rats. Moreover, the FR_{Na} of the pentoxifylline group was significantly greater at 48 hours compared to controls ($P < 0.05$).

Glycerol model

All rats survived 48 hours following induction with glycerol; there were no differences in weight loss between the two groups. Although significant reductions in Cl_{Cr} were observed in both pentoxifylline ($N = 12$) and saline ($N = 6$) rats in the first 24 hours, the magnitude of difference between the two groups was not significant (Table 2). Rats given pentoxifylline returned to $100.8 \pm 54.8\%$ of baseline Cl_{Cr} within 48 hours compared to $45.6 \pm 22.7\%$ of baseline in the control group ($P = 0.048$). A similar trend in Q_u was observed. Renal electrolyte handling was unchanged throughout the study period independent of treatment protocol.

Discussion

The present study examined the effects of post-induction administration of pentoxifylline in two experimental murine models of ARF, hemoglobinuria and direct nephrotoxicity. In each model, the introduction of pentoxifylline afforded significantly improved renal function compared to control rats. Although Cl_{Cr} returned to 10% of the baseline value in the pentoxifylline-mercuric chloride rats compared to anuria in the

controls, the magnitude of benefit was minimal. In the glycerol model, pentoxifylline administration was associated with significantly improved GFR and preservation of renal electrolyte handling.

ARF continues to be a significant therapeutic dilemma to the clinician resulting in greater than 60% mortality [13]. Its treatment has been hampered, in part, by a relative lack of understanding into the pathogenesis of ARF, as well as the heterogeneity of the syndrome. Indeed, the patient may present with clinical ARF secondary to various endogenous and exogenous factors including septic shock, muscle breakdown, urinary tract obstructions, and a number of nephrotoxins such as drugs and dyes. Many animal models of ARF have developed, attempting to correlate experimental findings with clinical observations. Ideally, an experimental model should possess the same precipitating factors that ultimately lead to acute tubular necrosis in humans. To date, five murine models of ARF have been studied extensively which closely resemble many of the characteristics of ARF observed clinically: glycerol, mercuric chloride, uranyl nitrate, intrarenal norepinephrine, and renal artery occlusion [1–5]. The pathophysiologic differences, as well as merits of each model, have been summarized elsewhere [1, 2, 6].

Independent of the model used, efforts to reduce the extent of experimental kidney damage have been targeted at prevention rather than treatment. As discussed earlier, clinical ARF is often diagnosed in the presence of established renal damage; hence, protective modalities may offer insight into the pathogenesis of the syndrome but would rarely be of benefit in the clinical arena. Recently, studies have directed experimental drug regimens at the reversal or, at least, attenuation of the course of ARF. Clonidine [31] and prostaglandin E_1 [8] are two examples of drug therapies that have been administered during or shortly after the insult to minimize renal damage; hence, the renin-angiotensin system, endothelin, and cyclooxygenase pathways play a role in the pathogenesis of experimental ARF. Recent evidence has also suggested that vascular decongestion may prevent the reflow phenomenon following ischemia [26].

The potential benefits of the use of pentoxifylline, a novel

hemorheologic agent, in the amelioration of ARF are appealing for a number of pharmacologic properties: antagonism of adenosine receptor activity, reduction in platelet and neutrophil aggregation, increased erythrocyte deformability, and stimulation of prostacyclin production. Theophylline, a competitive, adenosine receptor antagonist [32] structurally related to pentoxifylline, has demonstrated beneficial effects in post-ischemic ARF in the murine model [11, 12]. By blocking the receptors for the increased extracellular adenosine produced during the ischemia of ARF, the hemodynamic changes associated with the initiation phase were prevented. It is tempting to speculate that the benefits of pentoxifylline in the glycerol model were related to actions on adenosine receptors (unpublished observations). However, this remains to be proven.

Hypoxia is known to reduce erythrocyte deformability in several animal species [26, 33–35], most likely due to intracellular ATP deficiency and inactivity of the Na/K pump. The subsequent cell swelling and plasma water depletion result in erythrocyte and platelet aggregation and blood stasis. A vicious circle is initiated with a greater degree of vascular congestion causing increased hypoxia and ischemia, which in turn results in persistent cell swelling. Reduction in erythrocyte mass or prevention of cellular aggregation has demonstrated benefit in arresting the ischemia/congestion cycle [24, 35]. Pentoxifylline exerts predominantly hemorheologic effects, reducing erythrocyte, neutrophil and platelet aggregation [22–24], increasing erythrocyte deformability [36], and reducing circulating fibrinogen levels [37]; hence, the net effect is reduced blood viscosity.

It is unclear why benefit was derived with the co-administration of clonidine [31] and not pentoxifylline in the mercuric chloride-induced ARF model. Although the mechanism of protection of clonidine has not been elucidated, it may stabilize membrane function, preventing irreversible shifts in intracellular calcium. Pentoxifylline, in turn, appears to act on modulators of renal flow, such as prostacyclin and vascular decongestion. Although speculative at best, the present data demonstrates the heterogeneity of the ARF syndrome within the same experimental model. Nonetheless, the protection afforded by either treatment resulted in significant reductions in animal mortality. Eknoyan et al reported a fatality rate of 70% in controls and 11% with clonidine [31]. In the present study, there was a similar reduction in the fatality rate with 71% in controls and 21% with the co-administration of pentoxifylline.

The first model, the introduction of mercuric chloride, mimics direct nephrotoxic ARF manifested by tubular collapse and filtration failure [38]. It was not surprising, therefore, that a single dose of pentoxifylline resulted in little benefit once the rats had been poisoned with mercuric chloride. The glycerol model induces hemoglobinuria in the rat with rapid ARF which is reversible with infused saline [4]. In the present study, a single 0.5 ml dose of physiologic saline was administered to the control rats which did not result in significant improvement in renal function. Glycerol stimulates the biosynthesis of vasodilator prostaglandins, PGI₂ and PGE₂, and the vasoconstrictor thromboxane A₂ [3, 39]. Pentoxifylline stimulates the renal production of prostacyclin while inhibiting the vasoconstrictor, thromboxane A₂ [25]. The importance of vasodilating prostaglandins in limiting ischemic injury has been demonstrated previously [7–9, 40]. In the mercuric chloride model, stimulation is

thought to be the mechanism of protection from cyclosporine-associated nephrotoxicity in rats co-administered pentoxifylline [21]. Vasodilating renal prostaglandins are associated with increased natriuresis. However, no changes in fractional reabsorption of sodium or renal sodium excretion were observed with pentoxifylline in either experimental model or untreated rats; thus, the mechanism of amelioration is most likely not mediated via prostaglandin or diuretic effects. Therefore, other factors, such as the disruption of the vicious cycle of vascular congestion, may be involved in the mechanism of amelioration.

In summary, beneficial effects were demonstrated with the co-administration of a single dose of pentoxifylline following induction of ARF by glycerol and mercuric chloride. Although unclear at present, the mechanism of amelioration may be due to prevention of vascular congestion. Supported by the experimental data, post-insult administration of pentoxifylline may provide benefit in the clinical setting.

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