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Effect of Alkylxanthines on Gentamicin-induced Acute Renal Failure in the Rat

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Abstract—Adenosine antagonists have been previously shown to be of benefit in some ischaemic and nephrotoxic models of acute renal failure (ARF). In the present study, the effects of three alkylxanthines with different potencies as adenosine antagonists 8-phenyltheophylline, theophylline and enprofylline, were examined in rats developing acute renal failure after 4 daily injections of gentamicin (200 mg kg^{-1}). Renal function was assessed by biochemical (plasma urea and creatinine), functional (urine analysis and [^{3}H]inulin and [^{14}C]*p*-aminohippuric acid clearances) and morphological (degree of necrosis) indices. The various drug treatments produced improvements in some, but not all, measurements of renal function. However, any improvement produced by drug treatment was largely a result of a beneficial effect exerted by its vehicle (polyethylene glycol and NaOH). The lack of any consistent protective effect noted with the alkylxanthines tested in the present study indicates that adenosine plays little, if any, pathophysiological role in gentamicin-induced ARF.

Studies in the rat have demonstrated that administration of theophylline, as aminophylline, can reduce the severity of glycerol-induced acute renal failure (Bidani & Churchill 1983) and recently, we have demonstrated that 8-phenyltheophylline (8-PT) is also beneficial in this model of renal failure (Bowmer et al 1986). Churchill & Bidani (1982) and ourselves (Bowmer et al 1986) have suggested that the beneficial effects of theophylline and 8-PT are due to their ability to block adenosine receptors. The adenosine antagonism hypothesis is attractive because in the initial stage of glycerol-induced acute renal failure (ARF) renal blood flow is reduced (Stein et al 1978) and the resultant ischaemia is likely to evoke release of adenosine (Miller et al 1978). This hypothesis is further supported by the observation that the alkylxanthine enprofylline, which has a low affinity for adenosine receptors (Collis et al 1986), affords no protection in glycerol-induced ARF (Yates et al 1987). In addition, ARF is associated with a fall in glomerular filtration rate (GFR) which may be due to preglomerular arteriolar constriction and postglomerular arteriolar dilation, an effect which is also produced by an infusion of adenosine (Churchill 1982).

Theophylline has also been shown experimentally to reduce the impairment in renal function following the administration of amphotericin B (Heidemann et al 1983) and radiocontrast media (Arend et al 1987). In these instances the acute impairment of renal function is associated with renal ischaemia. In addition, theophylline can reduce the severity of ARF produced in rats by the nephrotoxin cisplatin (Mertins et al 1984) which directly produces proximal tubular necrosis (Garnick et al 1983), accompanied by an early reduction in renal blood flow (Winston & Safirstein 1985). These beneficial effects of an adenosine antagonist in ARF induced by nephrotoxic agents imply a role for adenosine in the pathogenesis of these disorders.

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In the present study we have investigated the development of gentamicin-induced ARF in the rat. Gentamicin directly produces tubular cell necrosis and may also cause a fall in renal blood flow (Coggins & Fang 1983). In this model of ARF kidney ATP content is also decreased (Simmons et al 1980) which could be associated with elevated adenosine levels (Woods et al 1970). In order to investigate the role of adenosine in this form of ARF we have examined the effect of three alkylxanthines: 8-PT, theophylline and enprofylline on the impairment of renal function following a series of gentamicin injections. The alkylxanthines studied have differing potencies as adenosine antagonists; 8-PT is a more potent adenosine antagonist than theophylline (Collis et al 1984), whilst enprofylline has a low affinity for adenosine receptors (Collis et al 1986). Thus if adenosine plays a major role in the pathogenesis of gentamicin-induced ARF there should be a good correlation between the protective effect of alkylxanthines on renal function and their ability to block adenosine receptors. This investigation should give some indication of whether adenosine antagonists can protect renal function during clinical treatment with gentamicin.

Materials and Methods

Materials

Gentamicin sulphate, theophylline and 8-PT were obtained from Sigma Chemical Co. and enprofylline was a gift from Draco, Lund, Sweden. [^{3}H(G)]Inulin (180–215 mCi g^{-1}) of stated radioactive purity 98–99% and *p*-[glycyl-1-^{14}C]amino hippuric acid (46·4–57·6 mCi $mmol^{-1}$) of stated radioactive purity 97·5–98% were both obtained from New England Nuclear Ltd and were used without further purification. Kits for the assay of creatinine, urea and *N*-acetyl-β-D-glucosaminidase (NAG) were obtained from Pierce and Warriner, BDH Ltd and Boehringer Mannheim Biochemica, respectively.

Induction of acute renal failure

Acute renal failure was induced using a modification of the

dosage regimen described by de Rougemont et al (1981). Male Wistar rats (200–250 g) were injected with gentamicin (200 mg kg^{-1} s.c.) and control rats received an equal volume of sterile saline (0·9% w/v NaCl; 1 mL kg^{-1} s.c.). Following injection the rats were deprived of drinking water for 24 h and further s.c. injections of gentamicin (200 mg kg^{-1}) or saline (1 mL kg^{-1}) were made at 24, 48 and 72 h after the initial injection.

Treatment with alkylxanthines

Immediately after the initial injection of gentamicin or saline, rats received either an i.p. injection of 8-PT (10 mg kg^{-1}), theophylline (7·0 mg kg^{-1}), enprofylline (7·6 mg kg^{-1}) or vehicle (1·0 mL kg^{-1}) which consisted of 50% v/v polyethylene glycol 400 in 0·1 M NaOH. The doses of theophylline and enprofylline were equal to the dose of 8-PT on a mole basis. Further injections of alkylxanthine or vehicle were made 12 h later and then twice daily for 3 days. A separate group of rats that was given a course of gentamicin injections, received 8-PT (10 mg kg^{-1} i.p.) twice daily for the 4 days following the last gentamicin injection.

Collection of urine and blood samples

The day before the initial injection of gentamicin or saline, rats that had been starved overnight, but with free access to water, were orally dosed with saline (25 mL kg^{-1}) and placed in metabolism cages for 6 h without food and water and then returned to their stock cages. Urine was collected from the metabolism cages, its volume recorded and then stored at −20°C until required for the analysis of electrolytes, NAG activity and osmolality. On the sixth day after the last gentamicin injection this procedure of saline dosing and urine collection was repeated.

Immediately before the first injection of gentamicin or saline, a blood sample (0·7 mL) was taken from the tail vein. Further blood samples were taken from the tail vein on the 3rd and 5th days following the completion of the gentamicin or saline injections, with a final blood sample taken on the 7th day from the carotid artery of anaesthetized rats. The plasma samples were stored at −20°C until required for the analysis of plasma urea and creatinine.

Determination of [^{3}H]inulin and [^{14}C]p-aminohippuric acid clearances

On the 7th day after the last gentamicin or saline injection, rats were anaesthetized with sodium pentobarbitone (60 mg kg^{-1}) and cannulae placed in the left jugular vein and right carotid artery. The single-injection method of Hall et al (1977) was then used to simultaneously measure the clearances of [^{3}H]inulin (100 mg kg^{-1}; 20 μCi kg^{-1} i.v.) (C_{IN}) and [^{14}C]*p*-aminohippuric acid (40 mg kg^{-1}; 4 μCi $^{-1}$ i.v.) (C_{PAH}). At the end of the experiment the animals were killed with an overdose of pentobarbitone and the kidneys removed, weighed, bisected longitudinally and placed in formal-saline (BDH Ltd).

Urine analysis

The activity of NAG was determined by reaction with 3-cresol-sulphophthalein-*N*-acetyl-β-D-glucosaminide to release 3-cresosulphophthalein which was measured photometrically at 580 nm. The total number of units of enzyme activity were determined for each urine collection where 1 unit is equivalent to 1 mmol of product formed per minute. Urine osmolality was determined by freezing point depression using an Advanced Instruments Digimatic Osmometer, Model 3D11.

Table 1. Plasma urea in saline (1·0 mL kg^{-1} s.c.) and gentamicin (200 mg kg^{-1} s.c.)-injected rats on days following the last of 4 daily injections. Gentamicin-injected rats were treated by i.p. injection with either vehicle (1.0 mL kg^{-1}), 8-phenyltheophylline (8-PT, 10 mg kg^{-1}), theophylline (7·0 mg kg^{-1}) or enprofylline (7·6 mg kg^{-1}), twice daily for 4 days during the course of gentamicin injections.

	Saline-injected	Gentamicin-injected				
Plasma urea (mg dL^{-1})	No treatment	No treatment	Vehicle	8-PT	Theophylline	Enprofylline
Day 0	41 ± 1	41 ± 2	38 ± 3	42 ± 1	40 ± 1	37 ± 2
Day 3	40 ± 2	141 ± 18[b]	103 ± 11*	83 ± 7***	81 ± 6***	95 ± 10**
Day 5	39 ± 2	213 ± 27[b]	141 ± 20**	96 ± 10***†	101 ± 10***	120 ± 13***
Day 7	36 ± 2	206 ± 41[a]	119 ± 20**	64 ± 8***†	106 ± 15**	77 ± 9***

Results are given as mean ± s.e. mean: n = 12 for each group
[a] $P < 0.01$; [b] $P < 0.001$ relative to saline-injected no treatment group (Student's *t*-test)
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ relative to gentamicin-injected no treatment group (ANOVA)
† $P < 0.05$ relative to vehicle treated group (ANOVA)

Table 2. Plasma creatinine in saline (1·0 mL kg^{-1} s.c.) and gentamicin (200 mg kg^{-1} s.c.)-injected rats on days following the last of 4 daily injections. Gentamicin-injected rats were treated by i.p. injection either vehicle (1.0 mL kg^{-1}), 8-phenyltheophylline (8-PT, 10 mg kg^{-1}), theophylline (7·0 mg kg^{-1}) or enprofylline (7·6 mg kg^{-1}), twice daily for 4 days during the course of gentamicin injections.

	Saline-injected	Gentamicin-injected				
Plasma creatinine (mg dL^{-1})	No treatment	No treatment	Vehicle	8-PT	Theophylline	Enprofylline
Day 0	0·51 ± 0·04	0·51 ± 0·03	0·58 ± 0·03	0·57 ± 0·04	0·51 ± 0·03	0·62 ± 0·03
Day 3	0·47 ± 0·04	2·03 ± 0·22[b]	1·63 ± 0·19	1·26 ± 0·12**	1·19 ± 0·12**†	2·11 ± 0·24†
Day 5	0·50 ± 0·05	3·26 ± 0·47[b]	2·10 ± 0·31**	1·46 ± 0·17***	1·50 ± 0·19***	2·18 ± 0·21**
Day 7	0·49 ± 0·05	2·72 ± 0·44[b]	1·90 ± 0·33*	1·14 ± 0·15***†	1·45 ± 0·20**	1·83 ± 0·23**

Results are given as mean ± s.e. mean: n = 12 for each group
[b] $P < 0.001$ relative to saline-injected no treatment group (Student's *t*-test)
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ relative to gentamicin-injected no treatment group (ANOVA)
† $P < 0.05$ relative to vehicle treated group (ANOVA)

Measurement of plasma urea and creatinine

Standard spectrophotometric assays were used: creatinine by reaction with alkaline picrate solution and urea by reaction with diacetylmonoxime (Henry et al 1974).

Kidney histology

A longitudinal section was cut from one kidney of each rat and stained with haemotoxylin and eosin. Sections were examined by a pathologist who was unaware of the treatment the donor animal had received and the extent of renal damage was assessed according to a scoring system previously reported (Bowmer et al 1986). The degree of necrosis and presence of casts were each scored out of 5. The two scores for each kidney were added to give the total damage score (maximum 10).

Analysis of results

Results are expressed as mean ± s.e. mean. Statistical comparisons of data were made where appropriate by either a non-paired Student's *t*-test or one-way analysis of variance (ANOVA) after which the means were compared by the Method of Least Significant Difference (Snedecor & Cochran 1967). There was no significant correlation between kidney weight and body weight, so kidney weight was not expressed as a fraction of body weight. Statistical analysis of the histological damage score was made by a one-sided Mann-Whitney test.

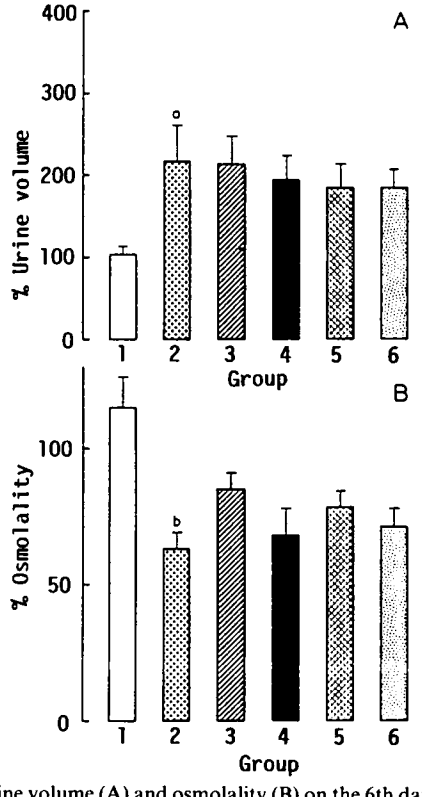

FIG. 1. Urine volume (A) and osmolality (B) on the 6th day after the last of 4 single, daily injections of saline (1 mL kg^{-1}; unshaded columns, group 1) or gentamicin (200 mg kg^{-1}; shaded columns, groups 2–6). Urine was collected for 6 h following an oral saline load (25 mL kg^{-1}). Urine volume and osmolality were expressed as a % of the values recorded after a control saline loading given 24 h before any injections. Columns show mean values and vertical bars s.e. means: n = 12 for each group. Key to the treated gentamicin-injected groups is as follows: (2) no treatment, (3) vehicle (1 mL kg^{-1}), (4) 8-phenyltheophylline (10 mg kg^{-1}), (5) theophylline (7·0 mg kg^{-1}) and (6) enprofylline (7·6 mg kg^{-1}).

(a) $P < 0.01$; (b) $P < 0.001$ relative to group 1 (Student's *t*-test). There were no significant differences between groups 2–6 (ANOVA).

Results

Plasma urea and creatinine concentrations

Gentamicin given to untreated rats resulted in large increases in plasma urea and creatinine concentrations when compared to saline-injected controls (Tables 1, 2). With the exception of plasma creatinine concentrations on day 3, treatment with vehicle, 8-PT, theophylline or enprofylline resulted in significantly lower urea or creatinine levels compared with untreated gentamicin-injected rats. By contrast to dosage with either theophylline and enprofylline, 8-PT treatment in a number of instances resulted in concentrations of urea and creatinine which were significantly lower than the values obtained in the vehicle group i.e. urea on days 5 and 7 and creatinine on day 7 (Tables 1, 2).

Urine analysis

The mean volume of urine excreted in 6 h after oral saline dosing in the group of rats destined for saline injections (s.c.) and no drug treatment was 1·84 ± 0·16 mL $100g^{-1}$b.w. (n = 12). There were no significant differences ($P > 0.05$) between any of the groups of rats in the mean volumes of urine excreted after the saline loading period before treatment (ANOVA). For each group the volume of urine excreted after the second oral saline load (given 6 days after the last s.c. injection of gentamicin or saline) was expressed as

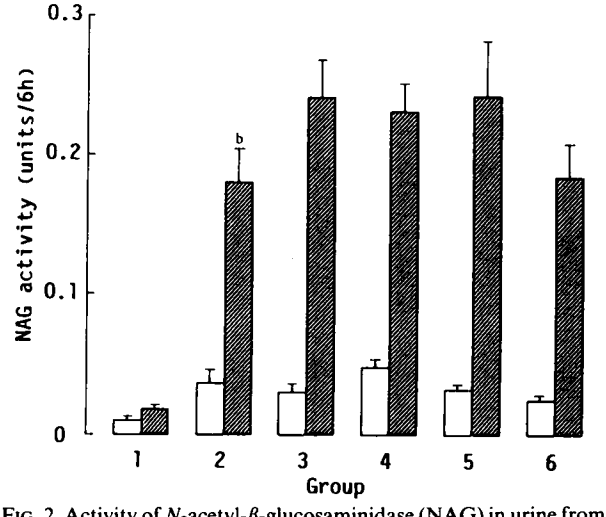

FIG. 2. Activity of *N*-acetyl-β-glucosaminidase (NAG) in urine from saline and gentamicin-injected rats. Urine was collected for 6 h after oral administration of saline (25 mL kg^{-1}) 24 h before any injections (unshaded columns) and on the 6th day after the last of 4 single daily saline or gentamicin injections (shaded columns). Columns represent mean values and vertical bars s.e. means: n = 12 for each group. Group 1 is the saline-injected, no treatment group and the key to the treated gentamicin-injected groups is as follows: (2) no treatment, (3) vehicle (1 mL kg^{-1}), (4) 8-phenyltheophylline (10 mg kg^{-1}), (5) theophylline (7·0 mg kg^{-1}) and (6) enprofylline (7·6 mg kg^{-1}).

(b) $P < 0.001$ relative to the second urine collection from group 1 (Student's *t*-test).

There were no significant differences between the second urine collections from groups 2–6 (ANOVA).

a percentage of the volume collected in the first test before treatment. Gentamicin administration to untreated rats resulted in a twofold increase ($P<0.01$) in urine volume and Fig. 1A shows that the volume of urine excreted in all gentamicin-injected rats was similar irrespective of any treatment.

Mean urinary osmolality from the first saline load in rats which were to receive saline s.c. was 636 ± 51 mOsm kg^{-1}. There were no significant differences ($P>0.05$) in urine osmolality between any of the groups before treatment (ANOVA). In a manner similar to urine volume, osmolality of the urine excreted in the second test was expressed as a percentage of the osmolality of the urine produced after the control saline loading. Gentamicin given to untreated rats resulted in a significant decrease ($P<0.001$) in osmolality compared with saline-injected rats (Fig. 1B). However, as with urine volumes, Fig. 1B shows that urinary osmolality was similar for all rats which received gentamicin irrespective of their treatment. Thus treatment with alkylxanthines did not increase osmolality or reduce polyuria.

NAG activity in the urine increased fourfold ($P<0.001$) in rats which received gentamicin (Fig. 2). The NAG activity in each of the gentamicin groups treated with vehicle or an alkylxanthine was not significantly different ($P>0.05$) from the activity recorded in the urine of untreated rats given gentamicin.

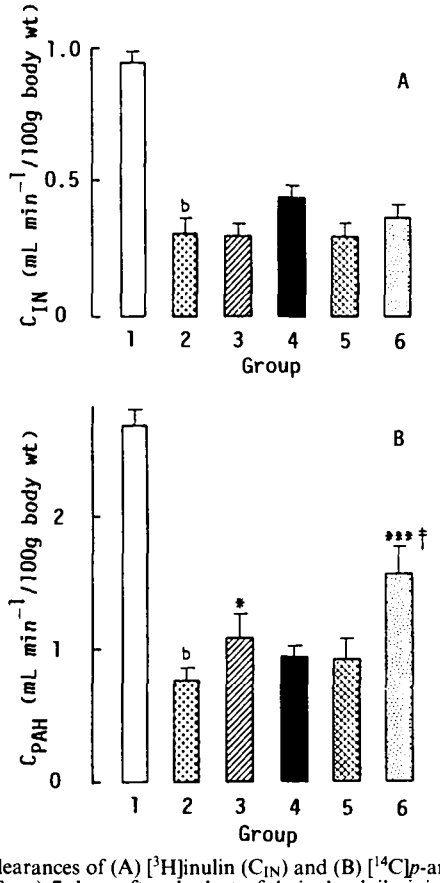

FIG. 3. Clearances of (A) [^{3}H]inulin (C_{IN}) and (B) [^{14}C]*p*-aminohippurate (C_{PAH}) 7 days after the last of 4 single, daily injections of saline (unshaded columns, group 1) or gentamicin (shaded columns, groups 2–6). Columns represent mean values with vertical bars showing s.e. means: n = 12 for each group. Key to the treated gentamicin-injected groups is as follows; (2) no treatment, (3) vehicle (1 mL kg^{-1}), (4) 8-phenyltheophylline (10 mg kg^{-1}), (5) theophylline (7·0 mg kg^{-1}) and (6) enprofylline (7·6 mg kg^{-1}).

(b) $P<0.001$ relative to group 1 (Student's *t*-test).
* $P<0.05$; *** $P<0.001$ relative to group 2; ‡ $P<0.01$ relative to group 3 (ANOVA).

[^{3}H]Inulin and [^{14}C]p-aminohippuric acid clearances

Gentamicin injections resulted in considerable falls in C_{IN} and C_{PAH} (Fig. 3). The C_{IN} values determined in rats treated with vehicle or an alkylxanthine were not significantly different ($P>0.05$) from the C_{IN} found in untreated gentamicin-injected rats. By contrast, in gentamicin-injected rats C_{PAH} in the vehicle and enprofylline groups was significantly higher than in the untreated group and the value in the enprofylline group was significantly greater than C_{PAH} in the vehicle treated rats.

Kidney weight and damage score

Kidney weight was significantly increased (by about 75%) as a result of gentamicin administration (Table 3). Treatment with either vehicle or each of the three alkylxanthines produced significant reductions ($P<0.05$) in kidney weight compared with the untreated group. The groups of rats treated with either theophylline or enprofylline had kidney weights which were significantly lower than in vehicle-treated rats. Data from the histological examinations of kidneys showed a large increase in damage score after gentamicin (Table 3) which was significantly reduced by the vehicle and all drug treatments. However, there was no significant difference in damage score between any of the alkylxanthine treatments and the vehicle treatment.

Effect of later administration of 8-PT

One group of gentamicin-injected rats received 8-PT (10 mg kg^{-1}) twice daily for 4 days following the last gentamicin injection as opposed to 8-PT treatment during the period of gentamicin injections, the data for which have been described. The overall effect of this later treatment was to

Table 3. Effect of treatment with alkylxanthines given twice daily for 4 days on the total kidney weight and renal damage associated with gentamicin (200 mg kg^{-1} s.c. daily for 4 days) induced-acute renal failure.

Group	Total kidney weight (g)	Damage score
Saline-injected no treatment	2·15±0·07	0·83±0·17
Gentamicin-injected no treatment	3·78±0·18[b]	5·25±0·28[b]
Gentamicin-injected +vehicle (1·0 mL kg^{-1})	3·34±0·18*	3·25±0·33**
Gentamicin-injected +8-PT (10 mg kg^{-1})	3·09±0·13**	2·92±0·08***
Gentamicin-injected +theophylline (7·0 mg kg^{-1})	2·68±0·14***‡	3·58±0·40*
Gentamicin-injected +enprofylline (7·6 mg kg^{-1})	2·90±0·15***†	3·08±0·19**

Results are given as mean±s.e. mean: n = 12. Maximum damage score = 10.
[b] $P<0.001$ relative to saline-injected group
* $P<0.05$; ** $P<0.01$; *** $P<0.001$ relative to untreated gentamicin-injected group
† $P<0.05$; ‡ $P<0.01$ relative to gentamicin-injected vehicle treated group.

potentiate the degree of renal failure as assessed by biochemical and functional indices. For instance on day 5 after the last gentamicin injection plasma urea and creatinine concentrations were 354 ± 63 and $4{\cdot}25 \pm 0{\cdot}63$ mg dL^{-1} ($n = 12$), respectively (cf. data for untreated and 8-PT treated rats in Tables 1, 2). C_{IN} and C_{PAH} of rats treated later with 8-PT were $0{\cdot}07 \pm 0{\cdot}01$ and $0{\cdot}62 \pm 0{\cdot}11$ mL min^{-1} 100 g^{-1} body wt, respectively. It is clear that the values of C_{IN} and C_{PAH} are lower than the corresponding values shown in Fig. 3 for any other group of gentamicin-treated rats. In addition, later treatment with 8-PT produced a urine output which was 270% of the control volume and this represents a greater polyuria than that recorded in other rats injected with gentamicin (see Fig. 1).

Discussion

The results presented here provide a comprehensive characterization of the impairment of renal function following administration of high doses of gentamicin. Gentamicin administration resulted in large increases in plasma urea and creatinine concentrations, tubular necrosis and cast formation accompanied by a polyuria and a decrease in urine osmolality. These findings have been previously noted in rats when gentamicin was given at a dose of 200 mg kg^{-1} on three consecutive days (de Rougemont et al 1981). Our investigation also showed that following gentamicin injections there were marked reductions in [^{3}H]inulin and [^{14}C]PAH clearances together with a rise in the urinary excretion of NAG, an index of tubular cell damage (Lee et al 1987). Similar observations have been made in a study of rats given gentamicin at a dose of 40 mg kg^{-1} per day for 12 days (Lee et al 1987).

Treatment of rats with gentamicin-induced ARF with any of the alkylxanthines or their vehicle, produced significant reductions in plasma urea and creatinine concentrations, total kidney weight and renal damage score. Furthermore, treatment with a particular alkylxanthine produced an improvement in some indices of renal function that was significantly greater than observed with vehicle treatment e.g. 8-PT on plasma urea and theophylline and enprofylline with kidney weight. However, there was no consistent pattern of improvement in renal function with any drug beyond that produced by the vehicle. None of the treatments, either drug or vehicle alone, significantly reduced the polyuria after oral saline dosing and associated high NAG activity. In addition, no treatment reversed the low urinary osmolality or improved C_{IN}. The effect on C_{PAH} of the various treatments differed from the other measurements of renal function in that vehicle and enprofylline administration produced significant increases compared with untreated rats. The overall impression of these results is that any improvement in a particular index of renal function is not correlated with the drugs' potency in blocking adenosine receptors, but would appear to be largely a result of the beneficial effect of its vehicle.

In previous studies of the effect of alkylxanthines in glycerol-induced ARF (Bowmer et al 1986; Yates et al 1987) we found that this vehicle (polyethylene glycol and NaOH) also exerted a protective effect, as judged by improvements in a range of indices of renal function. We attributed this beneficial action to the polyethylene glycol component which by virtue of its hyperoncotic and impermeant nature may reduce cell swelling and oedema in damaged kidneys (Frega et al 1979; Leaf et al 1983). A problem with 8-PT is that it is poorly soluble in a range of aqueous and non-aqueous solvents and the current vehicle was the only one we could devise that could dissolve sufficient quantities of drug. A further salutary effect of the vehicle may be due to its alkalinity. The pK_a of gentamicin is 8·2 and any increase in proximal tubular fluid pH as a result of the vehicle would be expected to decrease the fraction of the gentamicin molecules in the cationic form. This would reduce its binding to anionic sites on the renal brush border membrane and its subsequent uptake into cells (Coggins & Fang 1983).

By contrast to the present results, we have found that 8-PT treatment ameliorates glycerol-induced ARF as shown by significant reductions in plasma urea and creatinine, a significant increase in C_{IN} and an improvement in kidney morphology. These effects were significantly greater than any beneficial effects afforded by the vehicle (Bowmer et al 1986; Yates et al 1987). In glycerol-induced ARF the deterioration in renal function is rapid being evident within 3 h of the i.m. injection of glycerol (Kurtz et al 1976) with a fourfold increase in plasma urea concentrations 12 h after glycerol administration (Yates et al 1983). In our previous studies with 8-PT and glycerol-induced ARF, the drug was administered twice daily for two days with the initial dose given immediately following glycerol injection. Consequently the drug was being administered during, what would be in the untreated animal, the period of rapid deterioration in renal function. In gentamicin-induced ARF the deterioration in renal function is slower and in the present study, judging by plasma urea and creatinine concentrations, renal dysfunction was present on the third day after the last of the four gentamicin injections and was maximal on the fifth day. Therefore, to investigate whether later administration of 8-PT would be beneficial, one group of rats was treated with the drug for four days following the last gentamicin injection as opposed to giving it during the period of gentamicin injections. 8-PT given in this manner, however, failed to produce any amelioration of ARF.

Gentamicin is taken up into cells of the proximal tubule where it is known to disrupt a number of cellular processes producing necrosis. The drug has been shown to produce an uncoupling of oxidative phosphorylation (Coggins & Fang 1983) which is likely to decrease cellular ATP content and Simmons et al (1980) have reported that rats given gentamicin (40 mg kg^{-1} per day for 7 days) had whole kidney ATP content reduced by 30%. A consequence of low ATP levels is activation of 5′-nucleotidase, the enzyme that converts AMP to adenosine (Woods et al 1970). Churchill & Bidani (1982) have proposed that adenosine may play an important role in the pathogenesis of various forms of ARF. However, the lack of any consistent protective effect noted with the adenosine antagonists tested in the present investigation indicates that adenosine does not play a major role in the pathophysiology of gentamicin-induced ARF. The results also indicate that the prophylactic administration of adenosine antagonists will be of little value in protecting renal function during the therapeutic use of gentamicin.

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