Acute effect of low dose theophylline on the circulatory disturbances of cirrhosis

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Abstract

Background—Adenosine is a potent vasoactive substance that may be responsible for mediating the altered haemodynamics found in patients with cirrhosis.

Aim—The administration of oral theophylline was used to investigate the effect of adenosine receptor antagonism upon the circulation of patients with cirrhosis.

Methods—Twenty eight patients were given oral theophylline and intravascular haemodynamic measurements obtained over approximately one hour.

Results—After 240 mg of oral theophylline elixir the hepatic venous pressure gradient mean fell from 21.8 (2.1) to 19.9 (2.4) mm Hg ($p < 0.01$), and azygos blood flow fell from 481 (94) to 375 (83) ml/min ($p < 0.05$). There were no changes in cardiac output or systemic vascular resistance despite a fall in mean arterial pressure (92.2 (2.0) to 89.2 (1.8) mm Hg; $p < 0.05$) and a rise in heart rate (78.3 (3.0) to 82.4 (3.2); $p < 0.001$). Left renal vein flow measured by a reverse thermodilution catheter rose from 387 (91) to 601 (119) ml/min ($p < 0.05$). The proportion of cardiac output perfusing the left kidney rose from 5.0 (1.3) to 9.7 (2.8)%.

Conclusions—These changes indicate a significant role for adenosine in the renal vasoconstriction and a more minor role in the maintenance of portal hypertension.

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Keywords: theophylline, adenosine, cirrhosis, portal hypertension, renal circulation.

The circulatory disturbances associated with cirrhosis are the cause of many of the complications of this condition. Some of these changes are paradoxical: portal hypertension is found together with systemic hypotension and peripheral vasodilatation, but with renal vasoconstriction. Thus a unifying hypothesis concerning their aetiology is not obvious.

Most hypotheses suggest that a circulating or a locally produced vasoactive substance(s) is responsible for the hyporesponsiveness of vascular tissue to vasopressor stimuli. The resulting vasodilatation contributes to the 'forward' component of portal hypertension as well as producing the typical hyperdynamic circulation of cirrhosis with its low systemic vascular resistance and high cardiac output. By the peripheral vasodilatation hypothesis, the reduction in effective circulating plasma

volume stimulates renal vasoconstriction and sodium retention.¹

Among putative mediators of the vasodilatation are glucagon, prostacyclin, vasoactive intestinal peptide, and most recently nitric oxide.^{2,3} However none has yet been demonstrated to be solely responsible for the changes seen. A drawback of ascribing a purely vasodilating substance to account for these changes is that it would not explain why the renal circulation is exempt from the hyporesponsiveness to vasoconstrictors seen elsewhere in the vascular tree. It is perhaps more likely that there is an imbalance of locally produced vasoactive substances, which modify regional vascular response to systemic stimuli.

Adenosine is one such substance. It is produced locally often in response to tissue hypoxia and acts to reduce local oxygen utilisation.⁴ Systematically it acts through adenosine-2 receptors that predominantly vasodilate. Indeed this is the basis of the hepatic artery buffer response, mediated by adenosine, which regulates total liver blood flow.⁵ However in the kidney it vasoconstricts afferent arterioles through adenosine-1 receptors, dilates efferent arterioles, and redistributes blood from the renal cortex to the medulla.^{6,7}

Studies in animal models of cirrhosis have shown differing effects of non-specific adenosine receptor blockade upon the splanchnic circulation.^{8,9} No beneficial effect was seen on the portal circulation in one study of patients with cirrhosis.¹⁰ However in patients with cirrhosis intravenous theophylline and aminophylline have been shown to have beneficial effects on the systemic and renal circulations respectively.^{11,12} Theophylline is a non-specific adenosine antagonist,¹³ but this may only be evident at low concentrations in the plasma as at higher concentrations phosphodiesterase inhibition may mediate its actions.¹⁴

The purpose of this study was to assess the circulatory effects of low plasma concentrations of theophylline after oral administration, to assess the role of adenosine in the haemodynamics of patients with cirrhosis.

Methods

A total of 28 patients with biopsy confirmed cirrhosis were studied. None of the patients had received vasoactive medication within 72 hours of the study and patients were fasted for 12 hours. Caffeine containing beverages were avoided for 24 hours before the study. Each study assessed the effect after 240 mg oral theophylline elixir (Neulin Liquid, 3M Health

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Care Ltd) over a one hour period. Patients were studied in the supine position and an 8.5 FG introducer (Baxter Healthcare Corporation, USA) was inserted into the right femoral vein after local infiltration with 2% lignocaine. The vascular catheters were positioned under fluoroscopic control.

All patients gave informed consent and the study was approved by the Lothian Medicine and Oncology Ethics Committee.

Assessment of the portal circulation

Through the introducer a Sidewinder II torque balloon catheter (Cordis Corporation, USA) was positioned in the right hepatic veins of 18 patients. Free and wedged hepatic venous pressures (FHVP and WHVP) were recorded. Hepatic venous pressure gradient (HVPG) was calculated as WHVP minus FHVP. In six of these patients hepatic blood flow (HBF) was also calculated by the indocyanine green (ICG) method.¹⁵ An intravenous infusion of 0.2 mg/min of ICG was commenced after a bolus of 10 mg. An equilibration period of 40 minutes was allowed before three blood samples at two minute intervals were taken simultaneously from the right hepatic vein and the right femoral vein each. Patients with an ICG extraction of <10% were excluded from the analysis. HBF was calculated as follows:

$$\text{HBF} = (\text{ICG clearance} / \text{ICG extraction}) / (1 - \text{haematocrit})$$

Hepatic vascular resistance (HVR) was calculated as follows:

$$\text{HVR} = 79.96 (\text{WHVP} - \text{FHVP}) / \text{HBF}$$

All hepatic vein measurements were made at baseline and 60 minutes after theophylline administration.

Azygos blood flow (AzBF) was measured in 11 of these patients. A double thermistor catheter (Webster Laboratories, California) was positioned in the azygos vein. Its position remained constant throughout the study. The thermistor signals were transferred through a custom built interface (B55724 type CF) and processed in an IBM model PS2-286 micro-computer system as described previously.¹⁶ Mean blood flows were recorded over a 30–40 second period. Recordings were made before and 30 and 60 minutes after theophylline administration. Previous studies have shown that theophylline levels peak in patients with cirrhosis at this time after oral administration.¹⁷

A control group was not used in the study of the portal circulation as it has been established that these haemodynamic parameters are constant during such studies.

Assessment of the systemic and pulmonary circulations

Automatic heart rate (HR) and blood pressure recordings (A+D Company, model UA-743) were at 10 minute intervals throughout each study.

Through the right femoral vein introducer a Swan-Ganz catheter (Baxter Healthcare Corporation) was positioned in the right pulmonary artery after measurement of RAP in 10 patients. Pulmonary artery pressure (PAP) and pulmonary capillary wedged pressure (PCWP) were measured directly. Cardiac output (CO) was measured by the thermodilution technique. Systemic vascular resistance (SVR) was calculated as:

$$\text{SVR} = 79.96 (\text{MAP} - \text{RAP}) / \text{CO}$$

where mean arterial pressure (MAP) is:

$$\text{MAP} = (\text{pulse pressure} / 3) + \text{diastolic blood pressure}$$

Pulmonary vascular resistance (PVR) was calculated as:

$$\text{PVR} = 79.96 (\text{PAP} - \text{PCWP}) / \text{CO}$$

Measurements were made at baseline and immediately after the final renal vein flow measurement.

Assessment of the renal circulation

Through the right femoral vein introducer a reverse thermodilution catheter was positioned in the left renal vein of 10 patients after cardiac output studies had been carried out. Its position remained constant throughout the study. Renal vein blood flow (RVF) was recorded in a similar manner to that of AzBF. Recordings were made before and 30 and 60 minutes after theophylline administration in 10 patients. In four additional patients RVF and CO measurements were taken and used as controls without theophylline administration. Recordings were made at the same time points.

Only one intravenous introducer was inserted in any one patient, and so only one catheter was in position at any one time. In all patients the reverse thermodilution catheter was kept in same position throughout the course of the study. After the 60 minute study period the Swan-Ganz catheter or the hepatic venous catheter, or both, were repositioned to obtain final measurements. These final recordings were made within 10 minutes of the reverse thermodilution catheter removal.

Theophylline and caffeine measurement

Theophylline and caffeine were measured by high performance liquid chromatography using a modified method to that already described.¹⁸ Blood was collected into tubes containing 5% EDTA. A Waters NOVA-PAK C18 column (250 mm × 4.6 mm) was used. Twenty µl of plasma was loaded onto the column with a flow rate of 1 ml/min. Detection was at 275 nm (Perkin Fulmer Diode Array Detector).

Statistical analysis

Results are expressed as mean (SEM). For parametric data paired Student's *t* test and Pearson's correlation were used. Wilcoxon signed ranked test and Spearman's correlation were used for non-parametric variables (RVF and HBF).

Results

Patients studied

The mean age of theophylline treated patients was 57 years (range 41–70). Mean Child's score was nine (6A, 11B, 7C). Fourteen patients had ascites and 19 had oesophageal varices. The four control patients had a mean Child's score of 11 (2B, 2C). All four had ascites or oesophageal varices, or both.

All patients tolerated the theophylline well without side effects.

Effects on portal haemodynamics

There was a significant, although variable fall in HVPG (21.8 (2.1) to 19.9 (2.4) mm Hg; $p<0.01$), accounted for by reductions in the

WHVP (24.1 (2.3) to 22.4 (2.5) mm Hg; $p<0.01$). However the mean fall in HVPG was only 10.4 (4.1)% with only 35% of the patients having falls greater than 10% (Fig 1). No significant change in HBF was seen (Table I). However there was a significant reduction in AzBF from 481 (94) to 375 (83) ml/min (Fig 2). A reduction was seen in all but one patient and the change in AzBF correlated with the rise in plasma theophylline after one hour ($r=0.699$, $p<0.05$).

Effects on systemic and pulmonary haemodynamics

There was a statistically significant rise in HR, and a fall in MAP. There were no changes in CO or SVR (Table II). Changes in portal haemodynamic variables did not correlate with any change in CO. However there were significant falls in PAP and PVR.

Effects on renal haemodynamics

The RVF rose from 387 (91) to 601 (119) ml/min ($p<0.05$) (Figs 3 and 4). This rise was significant 30 and 60 minutes after theophylline administration. After one hour the mean rise in RVF was 72 (28)% (Fig 5). The percentage of CO perfusing the left kidney at baseline was 5.0 (1.3)%. One hour after theophylline administration it rose to 9.7 (2.8)% ($p<0.05$). Six of 10 patients studied had ascites and these patients tended to have lesser rises in RBF in response to theophylline (119 (69) in comparison with 356 (132) ml/min in those without ascites). The control subjects showed no significant change in RVF or systemic haemodynamics (Table III).

The haemodynamic responses to theophylline did not vary with the severity of liver disease as determined by Childs-Pugh grade.

Methyl xanthine values

The plasma concentrations of theophylline and caffeine are shown in Table IV. Baseline caffeine value correlated with prothrombin time ($r=0.717$, $p<0.001$).

Discussion

The cause of the circulatory disturbances of cirrhosis remains elusive. The systemic vasodilatation may be due in part to excessive nitric oxide production, but portal hypertension does not seem to be affected by nitric oxide synthase inhibition.¹⁹ The vascular reactivity of the renal circulation seems to be different to that elsewhere in the body. Whereas systemic and splanchnic vessels are hyporeactive to a variety of endogenous vasoconstrictors^{20–22} renal blood flow correlates well with plasma noradrenaline values.²³

Adenosine is formed from the degradation of ATP by 5'-nucleotidase often in response to local tissue hypoxia. It modifies local vascular responses to systemically acting vasoactive substances. In the hepatic artery adenosine may inhibit the vasoconstrictor action of

Figure 1: Percentage change in HVPG after theophylline.

TABLE I Effect of theophylline on portal haemodynamics

	Number	Baseline	60 minutes
FHVP (mm Hg)	18	2.4 (0.8)	2.4 (0.7)
WHVP (mm Hg)	18	24.1 (2.3)	22.4 (2.5)**
HVPG (mm Hg)	18	21.8 (2.1)	19.9 (2.4)**
HBF (ml/min)	6	1377 (428)	1268 (141)
HVR (dynes-s/cm ⁵)	6	7804 (2138)	6195 (999)
AzBF (ml/min)	11	481 (94)	375 (83)

Mean (SEM); ** $p<0.01$ compared with baseline.

Figure 2: Effect of theophylline on azygos blood flow.

TABLE II *Effect of theophylline on systemic, renal, and pulmonary haemodynamics*

	Number	Baseline	30 minutes	60 minutes
HR (bpm)	24	78.3 (3.0)	83 (3.8)	82.4 (3.2)***
MAP (mm Hg)	24	92.2 (2.0)	91.1 (2.2)	89.2 (1.8)*
CO (l/min)	10	7.22 (0.76)	—	7.15 (0.70)
SVR (dynes-s/cm ²)	10	1179 (152)	—	1149 (139)
PAP (mm Hg)	10	11.2 (2.2)	—	8.1 (1.8)†
PCWP (mm Hg)	10	4.3 (1.6)	—	4.0 (1.6)
PVR (dynes-s/cm ²)	10	82 (11)	—	45 (7)†
RVF (ml/min)	10	387 (91)	552 (134)	601 (119)*

Mean (SEM); †p<0.005, ***p<0.001, *p<0.05 compared with baseline.

Figure 3: Recording of real time unilateral RVF after theophylline administration in a patient with cirrhosis.

Figure 4: Effect of theophylline on unilateral renal vein flow.

Figure 5: Percentage change in unilateral RVF after theophylline.

vasopressors,²⁴ and local 'wash out' of adenosine by portal venular flow allows for rapid variations in hepatic arteriolar tone to maintain total hepatic blood flow homeostasis (the 'hepatic artery buffer response').⁵ These actions are mediated by adenosine-2 receptors, which may act through adenylate cyclase.²⁵ Adenosine-2 receptor activation on endothelial cells may increase nitric oxide production, but adenosine can also act directly on these receptors present on vascular smooth muscle cells to cause vasodilatation.²⁶

In the renal circulation adenosine-1 receptors are present particularly on the afferent arterioles. These receptors have a variety of intracellular effects including the inhibition of adenylate cyclase activity resulting in vasoconstriction.²⁵ In animal models adenosine causes renal cortical vasoconstriction but preserves medullary perfusion – similar to that which occurs in the kidneys of patients with cirrhosis.²⁷ Inhibition of the cellular uptake of adenosine by dipyridamole augments adenosine action. In patients with cirrhosis this causes a further deterioration in renal plasma flow especially in those with increased plasma renin activity.²⁸ Therefore adenosine may be responsible for the continued responsiveness of the renal circulation to vasopressors. We measured fasting caffeine values to see if this had any effect upon the action of theophylline. It has previously been recognised that fasting caffeine values are high in patients with cirrhosis and that these values are an indicator of the severity of liver disease. The fasting caffeine values that we found are similar to those which have been previously described in patients with cirrhosis. Normal subjects have fasting caffeine values of approximately 1 mg/l.²⁹ This shows the difficulty of discounting the effect of plasma caffeine in such patients. Such chronically high concentrations of caffeine may upregulate adenosine receptors.³⁰

In this study we have shown that theophylline significantly improves renal perfusion in patients with cirrhosis. We used the reverse thermodilution technique to measure unilateral RVF. This has previously been used in humans and found to correlate very well with the renal plasma flow as determined by para-aminohippuric acid.³¹ It is a safe and rapid method of evaluating total renal blood flow, although its main limitation is its inability to assess the glomerular filtration rate. The increase in RVF occurred independently of any effect on the systemic vasculature and therefore is probably mediated by adenosine-1 receptor antagonism. The rise in renal blood flow is different from that seen in normal controls in whom a transient rise may be observed followed by a fall in renal plasma flow.³² This implies a significant role for adenosine in the renal vascular disturbance of cirrhosis. Previous studies carried out in animals and patients with cirrhosis have indicated that adenosine is most potent as a renal vasoconstrictor in the presence of an activated renin-angiotensin-aldosterone system. It is perhaps surprising that the patients with ascites, and presumably therefore increased

TABLE III Renal and systemic haemodynamics in controls

	Number	Baseline	60 minutes
HR (bpm)	4	80.0 (7.9)	76.8 (7.0)
MAP (mm Hg)	4	85 (2.0)	87.2 (4.1)
CO (l/min)	4	7.4 (1.4)	7.3 (1.4)
SVR (dynes-cm ⁻⁵)	4	972 (162)	1017 (172)
RVF (ml/min)	4	386 (191)	352 (187)

Mean (SEM).

TABLE IV Plasma theophylline and caffeine values

	Theophylline (mg/l)	Caffeine (mg/l)
Baseline	0.80 (0.36)	6.48 (1.24)
30 minutes	4.03 (0.65)	—
60 minutes	5.37 (0.80)	—

Mean (SEM).

RAAS activity, had lesser rises in RVF after theophylline. This may be artefactual due to the small numbers of patients studied without ascites. However it may suggest that although adenosine has an important part to play in the renal hypoperfusion, other vasoconstrictors such as endothelin or locally produced prostanoids may be involved in patients with decompensated liver disease.

In addition adenosine may have a minor role in the maintenance of the splanchnic hyperaemia of cirrhosis – the so called 'forward' component of portal hypertension. It is possible that the small effect of theophylline upon HVPg is related to a reduction in splanchnic inflow mediated by adenosine-2 receptor antagonism. However these changes are relatively subtle and this is perhaps why the indirect ICG estimation of total hepatic blood flow did not change significantly. The effect upon AzBF, although significant on paired testing, was also highly variable and was directly related to the plasma concentrations of theophylline, perhaps reflecting the extent of adenosine blockade.

Despite these splanchnic and renal vascular changes no effect was seen on CO or SVR. The increase in heart rate is probably a direct effect of adenosine-1 antagonism on the chronotropic tissues of the heart.^{4 33} This implies that adenosine does not play a significant part in the peripheral vasodilatation of these patients. This dissociation of the splanchnic and systemic vasodilatation has been noted in animal models of portal hypertension.³⁴

The effects we have demonstrated differ from other studies that investigated the effect of methyl xanthines on the haemodynamics of cirrhosis. MacMathuna *et al* described an improvement in CO and SVR in patients with compensated cirrhosis after theophylline,¹¹ and Milani *et al* found only a 16% increase in renal blood flow after aminophylline.¹² Moreau *et al* did not demonstrate any effect of theophylline upon portal haemodynamics.¹⁰ However the first two of these studies used the intravenous route of administration and MacMathuna *et al* described plasma concentrations of 10 mg/l.¹¹ It is possible that higher plasma values of theophylline than those which we studied had effects beyond that of adenosine antagonism.

Alternatively differing concentrations of adenosine antagonist may result in a differing spectrum of adenosine receptor blockade as the K_d of adenosine-1 receptors is much lower than that of adenosine-2 receptors. In the study by Moreau *et al* intravenous aminophylline was also used. However at a dose of 3 mg/kg plasma values of theophylline reached approximately 7 mg/l, similar to those in this study. Although they demonstrated a rise in HR without any change in CO or SVR, no change was noted in AzBF or HVPg. The reasons for these differences are unclear. Certainly fewer patients were studied by Moreau *et al* at this dose (n=6) and all but one of them were Child's grade C. It may be that if more patients without such severe decompensated liver disease had been studied similar changes in the portal circulation might have been seen.

The lowering of PVR is similar to that seen in animal models.³⁵ The role of adenosine in the pulmonary circulation is uncertain. Adenosine vasodilates the pulmonary vasculature in normal subjects.³⁶ However in sheep adenosine has been noted to cause pulmonary vasoconstriction possibly through thromboxane A₂.³⁷ Whether theophylline is acting independently of adenosine antagonism in our patients, or there is an upregulation of adenosine-1 receptors in the pulmonary vasculature in patients with cirrhosis remains uncertain.

In conclusion we have demonstrated that adenosine has a major part to play in the renal circulation of cirrhosis and a lesser role in the maintenance of splanchnic hyperaemia. Antagonism of adenosine receptors by theophylline does not compromise systemic haemodynamics but improves renal blood flow. Such antagonism may also improve sodium excretion,³⁸ but this was not investigated in this study. Therapeutically theophylline is not an ideal drug for patients with cirrhosis as it is poorly cleared.¹⁷ However more specific adenosine-1 receptor antagonists may in the future have a role in the treatment of the renal abnormalities of cirrhosis.

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