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Portal and systemic haemodynamic action of *N*-acetylcysteine in patients with stable cirrhosis

A L Jones, I H Bangash, I A D Bouchier, P C Hayes

Abstract

The effects of intravenous *N*-acetylcysteine on hepatic and systemic haemodynamics were investigated in 11 patients with stable cirrhosis (eight alcohol; two primary bilary cirrhosis; one cryptogenic). *N*-acetylcysteine administration had no effect on the mean heart rate or mean arterial blood pressure despite a significant fall in systemic and pulmonary vascular resistance. Cardiac index increased but estimated liver blood flow and portal venous pressure did not change significantly. Administration of *N*-acetylcysteine resulted in increased oxygen delivery to the tissues because of the increased cardiac index but this was not accompanied by a rise in either arteriovenous oxygen extraction ratio or mean tissue oxygen consumption. Therefore *N*-acetylcysteine administration seems to confer no haemodynamic benefit to patients with cirrhosis.

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N-acetylcysteine (NAC), a sulphurated amino acid, has been reported to increase cardiac output, tissue oxygen delivery, and utilisation in fulminant hepatic failure.[1] As some of the haemodynamic changes seen in patients with cirrhosis are similar to those with fulminant hepatic failure, *N*-acetylcysteine may also increase tissue oxygen use and delivery in patients with cirrhosis. The aim of this study was to determine the haemodynamic effects of this agent in cirrhosis with particular reference to oxygen delivery and consumption.

Methods

Eleven cirrhotic patients proved by biopsy (eight men; three women; mean age 61.5 years; range 43–74) with a range of disease severity (4A, 3B, 4C Child's-Pugh grades) and aetiology (two primary biliary, one cryptogenic, and eight alcoholic cirrhosis) were studied. Exclusion criteria included known myocardial infarction or ischaemic heart disease, valvular heart disease, pregnancy, vasoactive treatment, current viral hepatitis B, C, or D or bleeding diathesis with prothrombin time ratio (PTR) greater than 2.5:1. The eight alcoholic cirrhotic patients had no evidence of alcoholic cardiomyopathy and were not actively drinking or withdrawing from alcohol as monitored by liver function tests, breath alcohol concentration, and clinical state. All patients gave witnessed informed consent and ethical permission was obtained from Lothian Health Board medical ethics subcommittee.

Each patient fasted after a light breakfast on the day of the study. In the catheter laboratory a 7·5 F introducer (Edwards, Critical Care Division, Irvine, USA) was placed in the right femoral vein under local anaesthesia (2% lignocaine). A Swan-Ganz catheter (7 F Edwards, Irvine, USA) was inserted under fluoroscopic screening and continuous pressure recording into the pulmonary artery. The tip of the catheter was positioned in a major branch of the pulmonary artery. The mean heart rate (from ECG monitor, Hewlett Packard HP monitoring system, Germany) and mean arterial blood pressure (manual syphygomomanometer) were checked every five minutes initially until all patients had achieved haemodynamic stability for at least 20 minutes. Simultaneous femoral artery, pulmonary artery, and femoral vein blood gas samples were then taken into heparinised blood gas syringes and analysed immediately for oxygen saturation (Co-Oximeter 282, Instrumentation Laboratory, Lexingham, MA, haemoglobin, and oxygen tension (Po_2) (ABL 2000, Radiometer, Copenhagen). The pulmonary artery free and wedge pressure and cardiac output (by Swan-Ganz thermodilution method using 10 ml of cold 5% dextrose as injectate) were estimated. Cardiac output was measured in quadruplicate and the results expressed as a mean value. Cardiovascular pressures were measured with reference to the mid axillary line. *N*-acetylcysteine (Parvolex, Duncan Flockhart, Greenford, UK) was infused intravenously by accurate infusion pump (Gemini 2, IVAC, USA) at 150 mg/kg in 200 ml 5% dextrose over 15 minutes followed by 15 minutes infusion at 125 ml/h of 50 mg/kg in 500 ml 5% dextrose. The blood gas analysis, pulmonary artery pressures, mean arterial blood pressure, cardiac output, and heart rate were remeasured 30 minutes after the start of *N*-acetylcysteine (NAC) infusion – that is, during infusion. Derived haemodynamic variables for each patient were calculated according to standard formulas.[2]

The O_2 content was calculated according to the formula;

$$(Hb \times 1{\cdot}34 \times sat\ \% + O_2\ tension \times 0{\cdot}0031).$$

The delivery of oxygen to tissues was calculated as the product of the cardiac index and the arterial oxygen content. Oxygen consumption was calculated from the reverse Fick

Department of Medicine, Royal Infirmary of Edinburgh, Edinburgh
A L Jones
I H Bangash
I A D Bouchier
P C Hayes

Correspondence to:
Dr A L Jones, Department of Medicine, Royal Infirmary of Edinburgh, 3 Lauriston Place, Edinburgh, EH3 9YW.

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TABLE I *Effect of* N-*acetylcysteine (NAC) infusion on mean haemodynamic parameters in 11 patients with stable cirrhosis (eight alcohol; two PBC; one cryptogenic)*

Variable	*Before NAC*	*After NAC*	*p Value*
HR	78·3 (3·2)	79·2 (2·7)	NS
MABP	88 (2·7)	85·8 (3·3)	NS
SVRI	1902 (195)	1645 (193)	p<0·02
PVRI	169·2 (28)	127 (21)	p<0·01
O_2 delivery	1086 (136)	1214 (140)	p<0·01
LVSWI	60·3 (7·3)	65·9 (10·3)	p<0·05
CI	3·85 (0·35)	4·36 (0·36)	p<0·01
O_2 consumption	240 (18)	240 (14·5)	NS
OER	23·6 (2·1)	21·3 (1·7)	NS (p>0·05)

NAC infusion was at 150 mg/kg body weight in 200 ml 5% dextrose for 15 minutes followed by 15 minutes of 50 mg/kg in 500 ml 5% dextrose (set at 125 ml/h). Mean values (SEM) are shown. HR is heart rate in beats per minute, MABP is mean arterial blood pressure in mm Hg, SVRI and PVRI are systemic vascular resistance index and pulmonary vascular resistance index respectively in dynes $\times sec/cm^5 \times m^2$. O_2 delivery and consumption are measured in ml/min. CI is cardiac index in $l/min/m^2$ and LVSWI is left ventricular stroke work index in $g \times m/m^2$. OER is the oxygen extraction ratio expressed as a percentage. Statistical significance is taken at the 95% value.

TABLE II *Effect of* N-*acetylcysteine infusion at 150 mg/kg body weight for 15 minutes in 200 ml 5% dextrose followed by 15 minutes of 50 mg/kg in 500 ml 5% dextrose (set at 125 ml/h) on mean blood gas values in 11 patients with cirrhosis (eight alcohol; two PBC; one cryptogenic)*

	Before NAC	*After NAC*	*p Value*
Femoral artery Po_2 (kPa)	11·25	10·32	NS
Femoral artery O_2 saturation (%)	94·3	93·7	NS
Pulmonary artery Po_2 (kPa)	5·35	5·37	NS
Pulmonary artery O_2 saturation (%)	72·1	73·8	NS
Femoral vein Po_2 (kpa)	5·15	5·70	NS
Femoral vein O_2 saturation (%)	67·9	74·9	NS

Statistical significance is taken at the 95% value.

TABLE III *Effect of* N-*acetylcysteine infusion on estimated liver blood flow, wedged, and free hepatic pressures and hepatic venous pressure gradient in six of the 11 (randomly selected) patients with cirrhosis*

Variable	*Units*	*Before NAC*	*After NAC*	*p Value*
ELBF	ml/min	1161 (167)	1283 (92)	NS
WHVP	mm Hg	20·7	22·2	NS
FHVP	mm Hg	7·3	8·5	NS
HVPG	mm Hg	13·3	13·7	NS

N-acetylcysteine infusion was initially at 150 mg/kg body weight in 200 ml 5% dextrose for 15 minutes followed by 50 mg/kg in 500 ml 5% dextrose (at 125 ml/h). Figures are expressed as means. A significance value of more than 95% is taken. ELBF is estimated liver blood flow, WHVP is wedged hepatic venous pressure, FHVP is free hepatic venous pressure, and HVPG is hepatic venous pressure gradient.

TABLE IV *Control data. The haemodynamic response of five of 11 patients with cirrhosis to 5% dextrose infusion only*

	Baseline	*After 5% dextrose alone*	*p Value*
Heart rate (bpm)	74·4 (4·6)	73·2 (41)	NS
MABP (mm Hg)	91 (3·3)	89·2 (3·1)	NS
RAP (mm Hg)	3·8 (0·37)	3·8 (0·37)	NS
CI ($l/min/m^2$)	3·46 (0·30)	3·54 (0·26)	NS
SVRI ($dynes \times sec/cm^{-5}$)	2064 (184)	2008 (183)	NS
LVSWI ($g \times m/m^2$)	59·0 (7·8)	60·2 (5·3)	NS
PVRI ($dynes \times sec/cm^{-5}$)	188 (44)	184·7 (48·5)	NS

Values are expressed as mean (SEM). MABP is mean arterial blood pressure, RAP is right atrial pressure, CI is cardiac index, SVRI and PVRI are systemic and pulmonary vascular resistance index respectively. LVSWI is left ventricular stroke work index. Statistical significance is taken at the 95% value.

equation (cardiac index x a-v O_2 difference); this technique has been validated against the direct method of calculation of O_2 consumption by analysis of respired gas.[3] The oxygen extraction ratio was calculated by dividing the difference between the arterial and venous O_2 content by the arterial O_2 content.

The hepatic venous pressure gradient (wedged hepatic venous pressure – free hepatic venous pressure) and estimated liver blood flow (ICG, Cardiogreen Hynson, Westcott and Dunning Inc, Baltimore, MD – continuous infusion method[4 5]) were measured immediately before and after NAC infusion randomly in six of 11 patients with cirrhosis. For hepatic pressure measurements a sidewinder II catheter (Cordis, USA) was inserted into the main right hepatic vein under fluoroscopic control. Inflating and releasing the balloon permitted repeated consistent measurements of wedge and free hepatic pressure respectively to be made. The intravenous infusion of indocyanine green was made up in saline and infused at a rate of 0·20 $mg/m^2/min$ after a priming dose of 0·20 mg/kg body weight. After a 30 minute equilibration period three simultaneous samples of peripheral and hepatic venous blood were drawn into heparinised syringes for the determination of estimated liver blood flow. The indocyanine green concentrations in the serum and infusion fluid were estimated by spectrophotometry at 810 nm in a Zeiss PMQ II spectrophotometer against a blank serum sample. The estimated liver blood flow was derived from the equation estimated liver blood flow=R/(A-H) (1-PCV), where R is the rate of infusion of indocyanine green in mg/min; A and H are the concentrations of dye in peripheral and hepatic venous blood in mg/l; and PCV is the packed cell volume.[4–7]

As the systemic haemodynamic effect of NAC has been assessed previously in patients without liver disease it was felt that inclusion of normal healthy controls in an invasive study such as this was unethical.[8 9] The haemodynamic response, however, to infusion of the same volume of 5% dextrose as above but not containing *N*-acetylcysteine to five (randomly selected) patients with cirrhosis was assessed to investigate any potential volume loading effect of the infusion.

STATISTICAL ANALYSIS OF HAEMODYNAMIC VARIABLES

The results after the infusion of NAC were compared with the baseline haemodynamic values before infusion. All results were expressed as mean (SEM) with statistical analysis by a two tailed paired Student's *t* test.

Results

Administration of *N*-acetylcysteine had no effect on mean heart rate or arterial blood pressure (Table I). Infusion of NAC resulted in vasodilatation with a significant reduction in both mean systemic vascular resistance index and pulmonary vascular resistance index (Table I). No significant changes in right atrial pressure, pulmonary artery free and wedge pressure occurred.

Administration of NAC resulted in a significant increase in mean oxygen delivery resulting from an increase in the mean cardiac index (Table I). This was associated with a significant increase in left ventricular stroke work index (Table I). Both arteriovenous oxygen extraction ratio and the mean oxygen consumption

did not rise in response to NAC (Table I).

The effect of *N*-acetylcysteine on mean blood gas values showed a minor fall in arterial oxygen tension and increase in venous oxygen tension after NAC administration (Table II).

There was no significant statistical correlation between Child's score variables – that is, serum albumin, bilirubin, and prothrombin ratio – and degree of change in response to NAC of cardiac index, oxygen delivery, oxygen consumption, oxygen extraction ratio or blood gases.

Mean estimated liver blood flow increased in response to NAC infusion; but did not achieve statistical significance (Table III). Wedged hepatic venous pressure, free hepatic venous pressure, and portal pressure showed no significant change after *N*-acetylcysteine infusion (Table III).

The control group of five patients who received intravenous dextrose alone showed no significant change in haemodynamic parameters (Table IV).

Discussion

We have shown that NAC acts as a vasodilator in patients with cirrhosis, similar to the effect shown in fulminant hepatic failure.[1] This has not occurred in patients with cardiac failure, with symptoms of chest pain or in those fully recovered from acute liver failure.[1 8 9] NAC is not known to possess direct relaxant activity in normal vascular smooth muscle[10] and given to pigs, both healthy and with septic shock produced no significant haemodynamic changes.[11 12] There is thus convincing evidence that NAC has no haemodynamic action in healthy controls. As NAC given to our 11 cirrhotic patients clearly conferred no haemodynamic benefit we felt that to study more patients would be unethical.

The five patients in our control group showed no vasodilation in response to dextrose infusion alone (Table IV). Thus the postulate that the haemodynamic changes in the 11 patients given *N*-acetylcysteine infusion were caused by the effects of volume loading or patients relaxing after the initial invasive procedures can be ruled out.

In patients with cirrhosis, unlike those with fulminant hepatic failure,[1] the mean arterial pressure did not change and the oxygen extraction ratio and O_2 consumption did not rise in response to NAC infusion (Table I). The cardiac index, systemic vascular resistance index, pulmonary vascular resistance index, stroke work index, and O_2 delivery % changes were, however, similar between cirrhotic and fulminant hepatic failure patients (Table 1).

As most drugs that primarily cause afterload reduction increase cardiac index without affecting left ventricular stroke work index (or rate pressure product, or other measures of myocardial consumption) the rise in cardiac index in association with left ventricular stroke work index seen here is suggestive of a positive inotropic response rather than purely peripheral vasodilation and reduction in left ventricular afterload.

Interestingly, there were no reported changes in arterial Po_2, calculated a-v tension gradient, and shunt in hepatic failure patients in response to NAC.[1] Errors in estimation of mixed venous O_2 saturation and tension could occur if the blood is drawn rapidly or if the catheter is positioned peripherally within the pulmonary artery because of contamination of the mixed venous pulmonary blood with arterialised blood drawn from the pulmonary capillaries and veins. We are confident that sufficient care was taken to prevent this error occurring in our study. This is supported by the increasing Po_2 trend seen in peripheral vein samples after NAC infusion, parallelling the increase in pulmonary artery Po_2 after the infusion (Table II).

We believe that the difference between the action of NAC to increase O_2 delivery in cirrhosis but not tissue O_2 consumption (compared with fulminant hepatic failure) may be because patients with cirrhosis have established pulmonary shunts[13] and NAC acts as a vasodilator to increase pulmonary shunting. This hypothesis is supported by the finding that pulmonary vascular resistance (Table I) fell in response to NAC infusion. The exact nature of such shunting is controversial.[14–18] The multiple inert gas elimination technique[19] has also shown V/Q mismatching in some patients with cirrhosis. Patients with lower pulmonary vascular resistance have greater V/Q mismatch.[13] Our data suggest that cirrhotic patients, unlike hepatic failure[1] and cardiac failure[20] patients, are not dependent on supply of oxygen to increase consumption. This may, however, just reflect the well compensated liver disease in most of these patients and it might be necessary to evaluate a group of grade C patients alone before a beneficial effect of NAC can be excluded.

Differences between fulminant hepatic failure patients and our cirrhotic patients may also result from the fact that some of the fulminant patients had encephalopathy (with and without neurohumoral factors) and were on mechanical ventilation (volume controlled) with continuous intravenous infusion of muscle relaxant (atracurium 50 mg/h).[1] Pulmonary capillary wedge pressure had to be stabilised at 8–14 mm Hg by infusion of 4·5% human albumin solution before the study.

Sulphydryl groups are required for the relaxation of vascular smooth muscle. Packer's data[8] support the hypothesis that sulphydryl depletion plays a part in the development of tolerance to nitroglycerin and as NAC, and other sulphydryl donors, can reverse this tolerance we postulate that in cirrhotic patients who are known to be deplete in sulphurated amino acids[21] NAC acts by sulphydryl repletion to cause vasodilatation. NAC may be acting directly on vasculature or indirectly by nitric oxide by sulphydryl donation.[22] As partial tolerance to organic nitrates (used to reduce portal hypertension in cirrhotic patients) has been reported[23] we would speculate that should longterm tolerance be a problem NAC or its oral derivative methionine might reverse this tolerance and thus be of therapeutic value.

It should be appreciated that not all vasodilators have the same haemodynamic effect in patients with cirrhosis, for example, nitrates cause vasodilatation but cause a fall in liver blood flow, cardiac output, and mean arterial blood pressure and an increase in systemic vascular resistance[24]; this presumably reflects different mechanisms or sites of action of vasodilating agents.

N-acetylcysteine given to patients with cirrhosis is probably not of haemodynamic value. This study illustrates that extrapolation of drug use between patients with fulminant hepatic failure and chronic liver disease is not always justifiable. We would still advocate its use, however, in paracetamol poisoning, particularly in patients with chronic alcohol intake (as such patients have increased susceptibility to paracetamol).[25 26]

This work has been presented in part at the British Society of Gastroenterology meeting 24–26th March 1993 and appears in abstract form in *Gut* 1993; **34** (suppl): S43.

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