The plasma concentrations of isosorbide 5-mononitrate (5-ISMN) administered in an extended-release form to patients with acute myocardial infarction

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Eighteen patients with acute myocardial infarction (AMI) followed the same extended-release isosorbide 5-mononitrate dosage regimen as was used in the Fourth International Study of Infarct Survival (ISIS-4). Plasma drug concentrations, blood pressure and heart rate were measured over 5 to 7 days following acute and repeated administrations. After the initial 30 mg dose on the first day of infarction, mean $\pm$ standard deviation $C_{\max}$ was 1237 ± 284 nmol l⁻¹ with a median $t_{\max}$ of 4 h (range 1 to 10 h). Following the last 60 mg dose, $C_{\max}$ was 2685 ± 497 nmol l⁻¹ with a median $t_{\max}$ of 4 h (2 to 7 h). The plasma concentrations of this extended-release 5-ISMN in patients with acute myocardial infarction were similar to those seen in studies with healthy volunteers. However, drug absorption following the acute dose was protracted in some patients, possibly due to the concomitant administration of morphine. The kinetics of 5-ISMN at steady state were similar for all patients, and none showed protracted 5-ISMN absorption.

Keywords acute myocardial infarction extended-release isosorbide 5-mononitrate morphine

Introduction

Nitrates may have some benefit in the setting of acute myocardial infarction [1–3]. By inducing dilatation of capacitance vessels (peripheral veins) and pulmonary arteries, they allow venous pooling to reduce the preload, and therefore cardiac oxygen demand. Second, in dilating coronary conduit arteries, and any pre-existing collaterals, they may increase coronary blood flow and help to limit infarct size [4]. Third, nitrates provide effective relief of cardiac pain.

To test the value of oral nitrate therapy in patients with acute myocardial infarction, the Fourth International Study of Infarct Survival (ISIS-4) selected an extended-release formulation (Durules®) of isosorbide 5-mononitrate (Imdur®) for the trial [5].

5-ISMN Durules® (60 mg) is given once each morning for prophylaxis against angina pectoris. The tablet is divisible, permitting dose titration for those patients in whom it is appropriate. Previous trials with 5-ISMN Durules®, a formulation which allows high concentrations throughout the day which fall gradually to low levels during the night, have already yielded information about its plasma concentrations in healthy subjects [6–11]. The 5-ISMN Durules® has been shown to have reproducible pharmacokinetics between subjects and patients, even when the tablet is halved [6, 7].

The purpose of this study was to describe the plasma profiles of 5-ISMN, given in Durules® to patients with acute myocardial infarction. The formulation and dosing strategy in this study matched that chosen for the ISIS-4 trial so that information about plasma concentrations could be interpreted in the context of the ISIS-4 clinical results.

Methods

Study design and patients

The protocol was reviewed by the ethics committee of Göteborg University (Göteborg, Sweden). The study aimed to collect a full set of data from 12 patients. Following conventional therapy for acute myocardial infarction, patients were enrolled in the study if they met all of the inclusion, and none of the exclusion criteria as used in the ISIS-4 trial [5].

During the first study day, patients were given one half of a 60 mg 5-ISMN Durules® tablet (30 mg), and the second half 10 to 12 h later (as in ISIS-4). Starting at least 24 h after the acute dose, one whole 60 mg 5-ISMN Durules® tablet was administered

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1.5 h after breakfast each day for 4 to 6 days. Long-acting nitrates (other than the study medication) were not permitted for the duration of the study.

Plasma 5-ISMN concentration, blood pressure and heart rate measurements following the acute 30 mg and the steady state 60 mg doses were made just before dosage, then every 0.5 h for the first 2 h after dose, every hour for the next 6 h, and at 10, 12, 14 (steady state only), and 24 h after dose. For the days in between the acute dose and steady state assessments (4–6 days after the first dose), measurements were taken at the end of each dosing interval. Blood pressure and heart rate were recorded just before the collection of samples for determination of plasma 5-ISMN concentration. Heart rate was determined from the ECG recordings, while blood pressure was measured using the cuff method with a mercury sphygmomanometer.

A full clinical examination was performed prior to and on completion of the study. Clinical chemistry determinations for blood haemoglobin, sodium, potassium, creatinine, and the myocardial band isomer of creatine kinase (CKMB) were made on the first study day. These determinations, except for CKMB, were repeated on the fourth study day.

For patients not completing the study, all data collected up to their withdrawal were used for mean calculations.

5-ISMN assay

Blood samples for determination of plasma 5-ISMN concentration were drawn into heparin-containing tubes (Venoject®). Samples were stored in a refrigerator for several hours until they were centrifuged for 10 min at +4°C and 3000 rev min⁻¹. The supernatant was removed and kept frozen (-20°C) until analysis. Plasma (0.25 ml) was mixed for 10 min with a 1 ml mixture of ethyl acetate and toluene (35:65 v/v) containing 500 nmol l⁻¹ of isomannide mononitrate (IMMN) as internal standard. After centrifugation, the organic phase was transferred to a clean test tube and reacted with 20 µl of N,O-bis(trimethylsilyl)acetamide for 1 h at 60°C before it was transferred to autosampler vials for gas chromatographic analysis.

A capillary gas chromatograph equipped with a ⁶³Ni electron capture detector and a split/splitless detector was used. The 25 m fused silica column had a 0.32 mm internal diameter, and was coated with SE-54 or similar methylphenyl polysiloxane phase (film thickness 0.5 µ, phase ratio 150). The helium carrier gas linear flow was 0.65 m s⁻¹ (1.5 bar inlet pressure). One microlitre was injected in split mode (split flow 25 ml min⁻¹). The column was held at 140°C during injection and elution of 5-ISMN (7.7 min) and IMMN (8.6 min), after which the temperature was raised to 220°C before the next run. Injector and detector block temperatures were 200°C and 220°C, respectively.

The extraction efficiency was 85–90% for both 5-ISMN and IMMN. The derivatisation yield was better than 90%. The intra-assay coefficient of variation was

better than 4% at the 2000 nmol l⁻¹ level and better than 10% at 200 nmol l⁻¹. The limit of quantitation was set to 100 nmol l⁻¹.

Plasma concentrations

To confirm that steady state was reached by the end of the study, mean values of plasma 5-ISMN concentration taken at the end of each study day were compared. Values of $C_{\max}$ and $t_{\max}$ were noted directly from the data. The area under the curve (AUC) was calculated using the linear trapezoidal method. The average plasma 5-ISMN concentration (C_{average}) following the last 60 mg dose was calculated from AUC(0,24 h)/24 h. Using the plasma 5-ISMN concentration measured 24 h after the last 60 mg dose as $C_{\min}$, a fluctuation index (FI) was calculated from:

$$FI = \frac{C_{\max} - C_{\min}}{C_{\text{average}}}$$

The elimination rate constant, λ_z , was estimated by linear regression of the logarithmic values of three consecutive concentrations in the last 12 h of the dosing interval after dosage to steady state. Half-life ($t_{1/2}$) was calculated from $\ln 2/\lambda_z$.

Results

Eighteen patients (17 men and 1 woman) entered the study. Thirteen patients (12 men and 1 woman) completed both the acute and steady state study days. Eight patients suffered a Q-wave infarction, and one patient's ECG was non-interpretable due to a bundle branch block (patient 7). The mean age was 64 years (range 39–86), with a mean weight of 77 kg (58–100). There were six current and nine former smokers. Drug treatment during the infarction included β -adrenoceptor blockers (15 patients), morphine (11), nitroglycerine (11), thrombolytics (10), diuretics (4), antiarrhythmics (2), and calcium antagonists (1).

The individual drug concentrations after initial and continuous dosing are shown in Figure 1. Following the acute dose, more than half of the patients (10) showed a plasma drug concentration-time curve comparable with that observed in healthy volunteers [6], peaking within 4 h. Of these 10 patients, three were given morphine during the first study day. The eight remaining patients either did not reach a peak 5-ISMN concentration until 6 to 8 h after dosing (patients 3, 4, 11), or did not reach a peak at all within 10 h of the initial dose (patients 10, 12, 13, 15, 17). All eight of these patients were given morphine during the first study day. The median 5-ISMN $t_{\max}$ for those patients given morphine was 8 h, compared with 3 h for those patients not receiving morphine. Patient 10 suffered from nausea, and may have lost the tablet through vomiting shortly after administration of the 30 mg dose.

By contrast, all patients had similar plasma drug profiles following steady state administration of 60 mg 5-ISMN, with $C_{\max}$ values around 3 to 5 h. None of the patients received morphine on the final day when steady state measurements were taken. Mean pharmacokinetic parameters for both the acute and steady state doses are shown in Table 1. Comparisons of the

plasma 5-ISMN trough values indicated that steady state had been reached. Patient 10 was excluded from the calculation of mean parameters following the 30 mg dose because no plasma 5-ISMN concentrations were detected.

Mean systolic blood pressure ranged from 108–124 $\pm$ 15–20 mm Hg over the acute study day, and from

Figure 1 Individual plasma 5-ISMN concentrations following administration of an initial 30 mg dose (○) and steady state 60 mg dosage (▲). X axis = Time (0 to 24 h post-dose); Y axis = Plasma 5-ISMN concentration (0 to 3500 nmol l⁻¹).

Table 1 Pharmacokinetics of 5-ISMN administered as Durules® to AMI patients (mean $\pm$ s.d.)*

	Acute 30 mg dose (n = 17)	Steady state 60 mg dose (n = 13)
$C_{\max}$ (nmol l ⁻¹)	1237 $\pm$ 284	2685 $\pm$ 497
$C_{\min}$ (nmol l ⁻¹)		518 $\pm$ 237
C_{average} (nmol l ⁻¹)		1446 $\pm$ 349
$t_{\max}$ (h)	4 (1–10)	4 (2–7)
$t_{1/2z}$ (h)		8.7 $\pm$ 3.3
AUC(0,10 h) (nmol l ⁻¹ h)	8858 $\pm$ 2533	
AUC(0,24 h) (nmol l ⁻¹ h)		34707 $\pm$ 8368
FI		1.5 $\pm$ 0.4

*Median (range) reported for $t_{\max}$.

115–133 $\pm$ 11–18 mm Hg over the steady state study day. Mean heart rate ranged from 65–74 $\pm$ 13–22 beats min^{-1} over the acute study day, and between 63–68 $\pm$ 6–11 beats min^{-1} over the steady state study day.

The clinical chemistry values were typical for infarct patients both at entry and on the fourth study day. Mean CKMB was 173 $\mu\text{g l}^{-1}$ (range 3 to 610) during the first day of infarction (only patient 10 showed a normal CKMB of 3 $\mu\text{g l}^{-1}$).

Discussion

Following acute administration of one half (30 mg) of a 60 mg 5-ISMN Durules[®], the maximum concentration of 5-ISMN in plasma was comparable in healthy subjects [6] and patients who were in the acute stages of myocardial infarction. Previous studies of this formulation of 5-ISMN in healthy subjects indicated mean t_{max} values from 3.6 to 4.5 h with standard deviations ranging from 0.6 to 1.7 h [7]. The median t_{max} in this study was 4 h, but the particularly large range (1–10 h) compared with that seen in healthy subjects suggested an effect of either myocardial infarction or drug interaction. A similar lengthening of t_{max} times was seen in a study using immediate-release 5-ISMN tablets in patients with elevated central venous pressure following acute myocardial infarction [12], though none of the patients in our study showed outward signs of heart failure. Even so, oral preparations of β -adrenoceptor blockers such as atenolol and metoprolol can be associated with delayed absorption during acute myocardial infarction [13, 14]. The same may be said for oral antiarrhythmic drugs such as procainamide, aprindine, mexiletine and disopyramide [15–18].

Morphine delays gastric emptying [19] which may

slow the absorption of drugs [20]. All patients in this study with a t_{max} longer than that seen in healthy subjects had also received morphine during the first day of their infarction. The mean t_{max} is longer in the patients who received morphine. The concomitant administration of morphine possibly slowed absorption of 5-ISMN in these patients. t_{max} values ranged from 1 to 10 h for patients given concomitant morphine (compared with a 1 to 4 h range for the other patients), but this variation may have more to do with the timing and dosage of the morphine administrations than any difference between patients in the effect of morphine on 5-ISMN absorption.

By the time that steady state measurements were made, 4 to 6 days after the acute dose, t_{max} , elimination half-life, AUC values and their variances were similar to those seen in healthy subjects [6, 9, 21] and angina patients [7]. This is consistent with a study of immediate-release 5-ISMN (80 mg) conducted in patients, 3 to 4 days following acute myocardial infarction, wherein plasma 5-ISMN concentrations were approximate to those seen in healthy subjects [22].

The clinical importance of the effect of morphine on the absorption of 5-ISMN in the hours following onset of acute myocardial infarction is unknown. Any effect that morphine may have on the plasma concentration of 5-ISMN is short-lived. Other parameters measured in this study were unremarkable and severe changes in haemodynamics were not observed. These results are consistent with those of the ISIS-4 study [23].

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