Plasma profile and haemodynamic tolerance to isosorbide-5-mononitrate in controlled-release form

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- 1 Plasma concentrations and some haemodynamic parameters known to be affected by nitrates, were monitored in healthy volunteers who received three different dose regimens of isosorbide-5-mononitrate (5-ISMN) over 5 day study periods.
- 2 No haemodynamic tolerance was found in the 60 mg once-daily dose schedule which produced high plasma concentrations during the daytime but concentrations no greater than 100 ng ml^{-1} at night. In contrast, a dose regimen of 60 mg followed by 30 mg 12 h later and thereafter every 8 h until the fifth day induced complete haemodynamic tolerance. With this dose regimen the minimum plasma concentrations were never below 300 ng ml^{-1} . A significant attenuation of haemodynamic effects was also found with the third dose regimen, 60 mg followed by 30 mg 6 h later for 5 days, which produced minimum plasma concentrations of between 100 ng ml^{-1} to 300 ng ml^{-1} ; the degree of attenuation rose as trough plasma concentrations increased.
- 3 In conclusion, 60 mg 5-ISMN in a controlled-release (Durules®) preparation given once daily was the only dose regimen not inducing nitrate tolerance.

Keywords pharmacokinetics pharmacodynamics haemodynamic tolerance
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Introduction

The development of tolerance associated with the use of all organic nitrates and all routes of administration is a common problem and depends on the type of compound administered, the dose, and the dosing interval. It has been shown, however, that tolerance to nitrates can be circumvented by dose regimens which include a daily 'nitrate-poor' interval (Abrams, 1986; Parker, 1987; Rudolph *et al.*, 1983).

This study was designed to investigate the effect of three different dose regimens of the controlled-release (Durules®) preparation of isosorbide-5-mononitrate (5-ISMN), 60 mg per tablet, on some haemodynamic parameters known to be affected by organic nitrates and to relate these effects to plasma concentration profiles. The primary aim of the study was to determine whether the maintenance of a critical plasma level over a certain period of time would produce haemodynamic tolerance and, conversely, whether a lower plasma concentration during a certain period of time would circumvent the development of tolerance.

Methods

The subjects were healthy, male, volunteers aged 25 ± 3 (mean $\pm$ s.d.) years with a mean height of 181 ± 3 cm

and an average body weight of 77 ± 8 kg. Prior to the study these volunteers were selected based on the haemodynamic response to 0.8 mg glyceryl trinitrate (GTN) sublingually. Individuals in whom the a/b ratio of the finger pulse curve increased by less than 50% of the pretreatment value, or who did not tolerate GTN, were excluded from the study. Initially, all subjects received placebo for 24 h.

The first dose regimen, which consisted of a once-daily dose of 60 mg 5-ISMN, was given to six subjects for 5 days.

The second regimen was administered to four of the same subjects 2 weeks later. They received a dose of 60 mg followed by 30 mg given 12 h later and thereafter 30 mg every 8 h. The last dose on the fifth day was again 60 mg. In addition, after the second regimen, the effect of 0.8 mg sublingual GTN on the finger pulse curve was measured 12 h and 24 h after the last dose and compared with that obtained before the study.

Three months later, the third dose regimen was given to four of the original subjects who had already received the first two dose regimens plus two other subjects. This third regimen consisted of 60 mg 5-ISMN taken in the morning followed by 30 mg 5-ISMN 6 h later every day for 5 days.

Volunteers had to rest in the supine position for at least 30 min before each assessment. Finger pulse curves were measured using a photoelectric transducer fixed to the distal phalanx of the index finger. The a/b ratio, expressed as the mean of 10 consecutive digital pulse waves, was obtained by dividing the height of the systolic peak (a) by the height of the diastolic wave (b) (Schinz *et al.*, 1981). Changes in venous distensibility were determined by means of venous occlusion plethysmography using the upper thigh. All measurements were taken in the supine position. Blood pressure (standard cuff method) and pulse rate (finger pulse curve) were measured with the subjects in the supine position and 30 s after adoption of an upright posture. Plasma concentrations of 5-ISMN were measured frequently following the first and last dose of each treatment regimen.

Results

The a/b ratio of the finger pulse varied from 1.35 ± 0.16 to 1.45 ± 0.17 during the 24 h placebo period. The maximal deviation of the venous capacity observed 16 h after placebo was an increase of $4.9 \pm 6.2\%$. Systolic blood pressure and heart rate varied from 115 ± 6 to 120 ± 8 mm Hg and from 71 ± 7 to 75 ± 5 beats min^{-1} , respectively.

Dose regimen I

5-ISMN 60 mg once daily did not induce tolerance. All haemodynamic effects produced by the first dose of this regimen were maintained throughout the 5 days. The a/b ratio of the finger pulse curve increased $36.7 \pm 5.8\%$ after the first dose and was obtained after 5.2 ± 1.6 h (Figure 1a). These mean values were $46.6 \pm 16.1\%$ and 6.2 ± 2.1 h after the last dose on the fifth day. The standing systolic blood pressure decreased from a baseline value of 118 ± 6 to 102 ± 6 mm Hg after the first dose and from 121 ± 6 to 106 ± 7 mm Hg after the last dose. The heart rate increased from 73 ± 11 to 94 ± 7 beats min^{-1} following the first dose and from 73 ± 5 to 87 ± 7 beats min^{-1} following the fifth dose. The venous capacity increased to $36.2 \pm 23.6\%$ at 16 h and was maintained above the baseline value throughout the study period.

The peak plasma concentrations after the first dose of this 60 mg dose regimen were 383 ± 83 ng ml^{-1} and were obtained at 4.3 ± 1.0 h (Figure 2a). Plasma concentration declined with an apparent half-life of 7.3 ± 1.1 h. Following the fifth dose, maximal plasma concentrations were 465 ± 112 ng ml^{-1} and occurred at 3.3 ± 0.8 h. Minimum plasma concentrations measured at 24, 48, 72, and 96 h after the first drug administration were 74 ± 27 , 55 ± 16 , 82 ± 32 and 73 ± 25 ng ml^{-1} , respectively.

Dose regimen II

5-ISMN 60 mg followed by 30 mg given 12 h later and thereafter 30 mg every 8 h with a final dose of 60 mg on the fifth day, was designed to maintain minimum plasma concentrations of about 300 ng ml^{-1} . This regimen induced a complete loss of the haemodynamic effects of the dose of 60 mg given on the fifth day. This was clearly

Figure 1 Time course of the a/b ratios of the finger pulse curves [mean (s.e. mean)] during one dosing interval on the first (left curve) and fifth (right curve) days following three different dose regimens. (From Wagner *et al.*, 1990).

demonstrated by the finger pulse curve (Figure 1b), the mean systolic blood pressure and the heart rate. Following the first dose, the a/b ratio of the finger pulse curve increased and a mean maximum value of $44.3 \pm 19.8\%$ was obtained after 5 h. Following the last dose of 60 mg, no increase above the baseline values was seen. The standing blood pressure fell from 128 ± 6 to 111 ± 5 mm Hg after the first dose but did not change after the last dose (124 ± 8 to 121 ± 6 mm Hg), and the heart rate increased from 69 ± 4 to 89 ± 5 beats min^{-1} following the first dose and from 75 ± 4 to 79 ± 2 beats min^{-1} following the last dose. Venous capacity increased $24.9 \pm 13.1\%$ at 24 h and to a similar level on the second day. The increases were of a similar order to that seen with dose regimen I. Thereafter the effect was attenuated and had completely disappeared on the fourth day. Before study, when the subjects were selected, the administration of GTN produced an increase of 50% or higher in the a/b ratio. Twelve hours after the last 60 mg dose, when GTN was given once again, no response was seen. However, 24 h after the last dose the effect was restored.

The peak plasma concentrations following the first

Figure 2 Plasma concentration-time curves of isosorbide-5-mononitrate (5-ISMN) following three different dose regimens. (From Wagner *et al.*, 1990).

dose of this second dose regimen were 392 ± 62.8 ng ml⁻¹ which was achieved 4.0 ± 1.2 h after dosing and had a half-life of 7.6 ± 1.0 h (Figure 2b). The trough concentrations were always higher than 275 ng ml⁻¹.

Dose regimen III

5-ISMN 60 mg in the morning followed by 30 mg 5-ISMN 6 h later every day for 5 days produced pronounced haemodynamic effects on the first day. The mean maximum increase in the a/b ratio of the finger

pulse was $90.1 \pm 44.9\%$ and was obtained 8 ± 3.3 h after the first dose (Figure 1c). The systolic blood pressure decreased from 123 ± 15 to 97 ± 8 mm Hg and the heart rate increased from 81 ± 10 to 103 ± 11 beats min⁻¹. However, a significant attenuation of the haemodynamic effects was measured on the fifth day when trough plasma concentrations were between 100 and 230 ng ml⁻¹ (Figure 2c). The mean maximum increase in the a/b ratio of the finger pulse was reduced to $38.6 \pm 13.0\%$ (Figure 1c: $P < 0.05$), the systolic blood pressure decreased from 123 ± 10 to 108 ± 9 mm Hg, and the heart rate increased from 80 ± 14 to 89 ± 10 beats min⁻¹. Peak plasma concentrations were 438 ± 91 ng ml⁻¹ on Day 1 and 628 ± 90 ng ml⁻¹ on Day 5. These occurred 8.8 ± 2.7 h and 7.8 ± 2.9 h after the first daily dose, respectively. There was a significant negative correlation ($r = 0.92$, $P < 0.01$) between the magnitude of haemodynamic effect remaining on the fifth day (measured by the area under the finger pulse curve) and the trough plasma concentration.

Conclusions

The results of this study show that the maintenance of minimum plasma concentrations of 5-ISMN of 300 ng ml⁻¹ or higher, produces a rapid development of haemodynamic tolerance. It appears that tolerance to 5-ISMN is linked to tolerance to sublingual GTN.

Dose regimens which produce minimum plasma concentrations between 100 and 300 ng ml⁻¹ may lead to a significant attenuation of haemodynamic effects. The degree of attenuation in this concentration range increased with increasing trough plasma concentrations.

The study further shows that haemodynamic tolerance can in all probability be avoided if the plasma concentrations of 5-ISMN are allowed to fall below 100 ng ml⁻¹ for a sufficient period of time before administration of the next dose. A dose regimen which will produce such minimum plasma concentrations is the once-daily administration of the 60 mg controlled-release (Durules®) formulation of 5-ISMN. The haemodynamic measurements very closely agree with antianginal efficacy. A dose of 60 mg 5-ISMN Durules® not only prevents tolerance, which was shown in this study, but also has an optimal antianginal effect (Kendall, 1990). A lower dose will not induce tolerance but may not offer sufficient antianginal protection. With higher dosages the risk of tolerance is obvious.

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