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Haemodynamic evaluation of two regimens of molsidomine in patients with chronic congestive heart failure

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Abstract We investigated the extent and duration of the haemodynamic effects of two regimens of molsidomine, i.e. two tablets of a standard regimen consisting of 4 mg given 6 h apart and one tablet of 16 mg in sustained-release form once daily in 13 patients with chronic congestive heart failure using a placebo-controlled, randomized, double-blind and crossover protocol over a period of 12 h. Both regimens significantly affected systolic, mean and diastolic pulmonary arterial pressure (reductions of up to 15%), right atrial pressure (reductions of up to 35%) and total pulmonary resistance (reductions of up to 18%). The lower dose achieved its maximum action after about 1 h and remained effective for 2 h, whereas the higher dose in sustained-release form showed maximal efficacy at 2 h and remained active even at 12 h. In contrast, only minor changes in arterial blood pressure, systemic vascular resistance and cardiac output were observed on both regimens, almost exclusively at 2 h. Heart rate was not affected by either of the regimens tested. Neither regimen led to any untoward adverse effects. Thus, molsidomine is a potent vasodilating agent which, apart from its effects on preload, also acts on pulmonary arterial and right atrial pressures, leaving systemic circulation largely unaffected on the regimens tested. Administered on its own, it is therefore suitable for treatment of congestive heart failure.

Key words Congestive heart failure, Molsidomine; haemodynamics, sustained released formulation

Vasodilators such as angiotensin converting enzyme (ACE) inhibitors and nitrates (and sydnonimines) have a well-established role in the treatment of chronic congestive heart failure since they not only provide relief of symptoms through improvement of haemodynamics but they have also been shown to improve prognosis [1–4].

Vasodilatation is effected through relaxation of vascular smooth muscle cells. Nitrates and sydnonimines share the common mechanism of guanylate cyclase stimulation [5], which, in the case of nitrates, requires the presence of thiol groups [5–7]. In spite of their favourable haemodynamic effects, the use of nitrates is encumbered by the necessity of incorporating a sufficiently long dose-free interval [8–10] to circumvent tolerance [6–8, 11], which in turn, precludes therapeutic coverage throughout a 24-h treatment cycle [12–15].

In contrast, the nitrate-like sydnonimines represent a class of compounds that also liberate NO^-, but, as opposed to nitrates, their actions are independent of intermediary enzymatic steps [16–18]. Consequently, plasma concentrations can remain within their therapeutic range without the development of tolerance, thus rendering sydnonimines at least theoretically suitable for treating heart failure on a 24 h a day basis. Since, however, the duration of action of molsidomine is only about 5 hours [5, 19, 20] the drug requires administration at least 4 times daily. Accordingly, it was the aim of the present study to compare the extent and duration of the haemodynamic effects of a standard regimen of molsidomine consisting of 4 mg-tablets given 6 h apart and one tablet of 16 mg in sustained-release form administered to patients with chronic congestive heart failure and to assess the dose-dependent impact of molsidomine on parameters of pulmonary as well as systemic circulation.

Patients and methods

Patients

The study group consisted of 13 men, 44–80 years old (average 60 years), with chronic, stable heart failure. All but three had undergone diagnostic cardiac catheterization. The heart failure was due

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to coronary artery disease in eight patients, dilated cardiomyopathy in two, hypertensive heart disease in two and valvular heart disease in one. Mean left ventricular ejection fraction was 26% (range 16%–38%). All patients had given their informed written consent before entering the study.

All patients had been hospitalized in fluid balance with no changes in weight for ≥ 2 days before the study. They were given a metabolically standardized diet and were administered fixed regimens of digitalis and diuretic compounds (average daily dose of furosemide 158 mg, in some cases in combination with a thiazide) that were kept constant throughout the study. Any vasoactive medication was withdrawn at least 5 half-lives prior to the study. The average sodium concentration was 138 mmol · l^{-1} (range 130–144 mmol · l^{-1}).

Haemodynamic measurements

One day before the study, a semifloating, balloon-tipped catheter was positioned in the pulmonary artery for determinations of right atrial pressure (RAP), pulmonary artery pressure (PAP) and cardiac output (CO) using the thermodilution technique. Cardiac output measurements were carried out in triplicate. A precordial electrocardiographic lead was used for recording heart rate, and systemic arterial pressure was measured by cuff and mercury column sphygmomanometer. Mean right atrial and mean pulmonary artery pressures were obtained by electronic integration. Mean arterial pressure (MAP) was calculated as diastolic plus one third of the pulse pressure. Systemic vascular resistance (SVR), pulmonary arteriolar resistance (PAR) and total pulmonary resistance (TPR) were expressed as dyn · s · cm^{-5} and calculated as SVR = 80 × (MAP - RAP)/CO, PAR = 80 × (PAPmean - PAPdiastolic)/ CO and TPR = 80 × PAPmean/CO, respectively [21, 22].

Study protocol

The study was carried out using a randomized, placebo-controlled, double-blind, crossover protocol. The extent and duration of action were assessed on the next 3 consecutive days, on which, every morning, immediately after baseline measurements of haemodynamic parameters were taken, either two tablets of placebo identical in appearance to the respective regimens were given or placebo + either one tablet of 4 mg molsidomine or placebo + one tablet of 16 mg molsidomine in sustained-release form. Six hours later, again immediately after haemodynamic measurements were taken, either two tablets of placebo identical in appearance to either dosage form were administered or, on the day on which 4 mg molsidomine was tested, another tablet of 4 mg molsidomine + placebo identical in appearance to the sustained-release 16 mg dose, respectively. Before (= 0 h) as well as at 1, 2, 6 and 12 h after morning ingestion of active substance/placebo on the respective days of treatment, haemodynamic measurements were performed.

Values shown are means with SEM. Statistical analysis was carried out with a repeated analysis of variance, subjected to multiple comparison according to the Friedman test. A P value < 0.05 was considered statistically significant.

Results

Systolic pulmonary arterial pressure (Table 1)

Four milligrams molsidomine 6-hourly. Reductions of 12% ($P < 0.034$), 10% ($P < 0.038$) and 3% (NS) were found at 1, 2 and 6 h after the first tablet. At 12 h, i.e. at 6 h after the second tablet, the change amounted to −3% (NS).

Sixteen milligrams molsidomine sustained-release. Reductions of 5% (NS), 12% ($P < 0.014$), 9% ($P < 0.05$) and 5% (NS) were measured at 1, 2, 6 and 12 h after tablet intake, respectively.

Comparison of both active treatment forms revealed no statistically significant differences at any point in time.

Mean pulmonary arterial pressure (Table 1)

Four milligrams molsidomine 6-hourly. This parameter was reduced by 11% ($P < 0.05$), 10% ($P < 0.05$) and 5% (NS) at 1, 2 and 6 h after the first tablet, and by 4% (NS) at 12 h, i.e. at 6 h after another 4 mg molsidomine.

Sixteen milligrams molsidomine sustained-release. High-dose administration reduced this parameter by 6% (NS), 14% ($P < 0.005$), 13% ($P < 0.009$) and 6% ($P < 0.05$) at the corresponding points in time.

At 6 h after the morning dose, the difference between the effects of both active tablets achieved statistical significance ($P < 0.05$).

Diastolic pulmonary arterial pressure (Table 1)

Four milligrams molsi-domine 6-hourly. Reductions of 10%, 7% and 0% were found at 1, 2 and 6 h after the first tablet. At 12 h, the observed change was 8%. None of these reductions was significantly different from placebo values.

Sixteen milligrams molsidomine sustained-release. Reductions of 10% (NS), 11% (NS), 19% ($P < 0.007$) and 17% ($P < 0.03$) were measured at 1, 2, 6 and 12 h after tablet intake, respectively.

Again, only at 6 hours after the morning dose, the difference between the effects of both active tablets achieve statistical significance ($P < 0.004$).

Right atrial pressure (Fig. 1, Table 1)

Four milligrams molsidomine 6-hourly. Right atrial pressure was reduced by 37% ($P < 0.018$), 33% ($P < 0.005$) and 13% (NS) at 1, 2, and 6 h after the first tablet, and by 12% (NS) at 6 h after another 4 mg molsidomine.

Sixteen milligrams molsidomine sustained-release. High-dose administration reduced right atrial pressure by 23% ($P < 0.028$), 23% ($P < 0.01$), 22% ($P < 0.05$) and 19% ($P < 0.05$) at the corresponding points in time.

Table 1 Haemodynamic parameters. Values are mean ± standard error of the mean. b · min^{-1}, beats per minute, BP, blood pressure, CO, cardiac output, dias, diastolic, HR, heart rate, PAP, pulmonary arterial pressure, PAR, pulmonary arteriolar resistance, RAP, right atrial pressure, SR, sustained release, SVR, systemic vascular resistance, sys, systolic, 6 h, 6 h apart, TPR, total pulmonary resistance; *$P < 0.05$, **$P < 0.01$ (vs placebo)

		Time (h)				
		0	1	2	6	12
PAP_{sys} (mmHg)	Placebo	54.2 (4.2)	53.1 (3.3)	55.1 (3.8)	55.2 (4.2)	55.1 (4.3)
	4 mg molsidomine 6 h	53.5 (4.4)	46.9* (3.9)	49.8* (4.6)	53.5 (4.5)	53.3 (4.6)
	16 mg molsidomine SR	53.1 (5.3)	50.7 (4.8)	48.5** (4.6)	50.1* (4.2)	52.3 (4.3)
PAP_{mean} (mmHg)	Placebo	34.1 (2.7)	31.9 (2.2)	33.8 (2.9)	34.6 (2.6)	34.0 (3.0)
	4 mg molsidomine 6 h	33.0 (2.9)	28.4* (2.8)	30.1* (3.3)	32.7 (3.1)	32.8 (2.8)
	16 mg molsidomine SR	32.2 (3.5)	29.9 (3.1)	28.9** (3.1)	30.1** (2.8)	32.0* (2.8)
PAP_{dias} (mmHg)	Placebo	22.9 (2.2)	21.5 (2.0)	22.8 (2.1)	22.5 (2.4)	24.5 (1.9)
	4 mg molsidomine 6 h	21.8 (2.2)	19.3 (2.3)	21.2 (2.7)	22.5 (2.7)	22.6 (2.6)
	16 mg molsidomine SR	22.3 (2.7)	19.4 (2.7)	20.4 (2.7)	18.2** (2.5)	20.4* (2.2)
RAP (mmHg)	Placebo	6.1 (1.5)	7.1 (1.5)	7.8 (1.7)	7.6 (1.5)	7.5 (1.7)
	4 mg molsidomine 6 h	5.5 (1.5)	4.5* (1.4)	5.2** (1.3)	6.6 (1.6)	6.6 (1.6)
	16 mg molsidomine SR	5.9 (1.6)	5.5* (1.6)	6.0** (1.5)	5.9* (1.6)	6.1* (1.4)
CO ($l \cdot min^{-1}$)	Placebo	3.7 (0.2)	4.1 (0.2)	3.8 (0.3)	3.9 (0.2)	3.8 (0.2)
	4 mg molsidomine 6 h	3.7 (0.3)	4.0 (0.2)	4.2* (0.3)	3.7 (0.2)	3.9 (0.3)
	16 mg molsidomine SR	3.9 (0.3)	4.2 (0.2)	4.0 (0.3)	4.0 (0.2)	4.1* (0.2)
BP_{sys} (mmHg)	Placebo	124 (6.3)	123 (6.2)	126 (6.4)	121 (5.6)	123 (6.2)
	4 mg molsidomine 6 h	122 (5.8)	121 (5.1)	121* (6.2)	125 (4.9)	125 (5.2)
	16 mg molsidomine SR	123 (3.3)	123 (6.1)	117* (5.0)	121 (7.6)	120 (5.3)
BP_{mean} (mmHg)	Placebo	96.8 (3.9)	94.6 (3.5)	97.3 (3.2)	94.3 (3.8)	98.0 (3.9)
	4 mg molsidomine 6 h	96.3 (3.1)	93.8 (2.9)	92.7 (3.4)	96.5 (3.0)	97.0 (3.2)
	16 mg molsidomine SR	97.2 (2.5)	94.9 (4.2)	93.5 (3.1)	93.1 (4.3)	94.2 (3.7)
BP_{dias} (mmHg)	Placebo	83.1 (2.9)	80.4 (2.6)	83.1 (2.2)	81.1 (3.2)	85.4 (3.1)
	4 mg molsidomine 6 h	83.5 (2.1)	80.4 (2.4)	78.5 (2.5)	82.3 (2.8)	83.1 (2.6)
	16 mg molsidomine SR	84.2 (2.5)	81.5 (3.9)	81.5 (2.5)	79.2 (3.1)	81.1* (3.4)
HR(beat · min^{-1})	Placebo	77.1 (4.7)	80.3 (3.7)	77.8 (3.4)	77.2 (4.0)	76.0 (3.8)
	4 mg molsidomine 6 h	77.1 (4.2)	77.6 (3.7)	76.9 (3.7)	77.5 (3.8)	76.4 (3.5)
	16 mg molsidomine SR	77.4 (4.3)	82.5 (4.7)	78.3 (4.2)	77.5 (3.6)	78.2 (4.5)
TPR(dyn · s · cm^{-5})	Placebo	805 (96)	650 (70)	771 (100)	780 (100)	779 (99)
	4 mg molsidomine 6 h	793 (120)	624 (96)	636* (107)	768 (108)	748 (108)
	16 mg molsidomine SR	719 (108)	622 (99)	632** (95)	652** (91)	664* (80)
PAR (dyn · s· cm^{-5})	Placebo	260 (34)	204 (22)	251 (36)	265 (29)	232 (33)
	4 mg molsidomine 6 h	252 (30)	185 (27)	198 (35)	225 (26)	219 (23)
	16 mg molsidomine SR	212 (31)	211 (27)	176** (26)	248 (29)	239 (30)
SVR(dyn · s · cm^{-5})	Placebo	2054 (133)	1720 (87)	1930 (90)	1860 (108)	1960 (96)
	4 mg molsidomine 6 h	2060 (146)	1810 (65)	1710 (97)*	1980 (85)	1930 (126)
	16 mg molsidomine SR	1950 (105)	1730 (81)	1800 (102)	1770 (71)	1740* (86)

Comparison both active treatment forms, no differences were found at any point in time.

Cardiac output (Table 1)

Four milligrams molsidomine 6-hourly. Only at 2 h was a significant increase by 11% ($P < 0.02$) observed. At the remaining points in time, this parameter remained left unaltered.

Sixteen milligrams molsidomine sustained-release. At 12 h, cardiac output increased by 8% ($P < 0.04$). Before then, no significant changes were detected.

Comparison of effects of both active tablets revealed a borderline superiority of the high-dosed tablet in sustained-release form at 6 h after the morning dose ($P < 0.05$).

Systolic, calculated mean and diastolic arterial blood pressure (Table 1)

Four milligrams molsidomine 6-hourly. Only at 2 h was a significant reduction by 4% ($P < 0.04$) of the systolic arterial pressure observed.

Sixteen milligrams molsidomine sustained-release. Likewise, this regimen decreased systolic arterial blood pressure significantly only at 2 h by 7% ($P < 0.05$). The remainder of the values were unaltered.

Neither of the active treatment forms was found to be superior to the other at any point in time.

Heart rate (Table 1)

Neither regimen tested affected heart rate at rest in a statistically significant manner at any point in time.

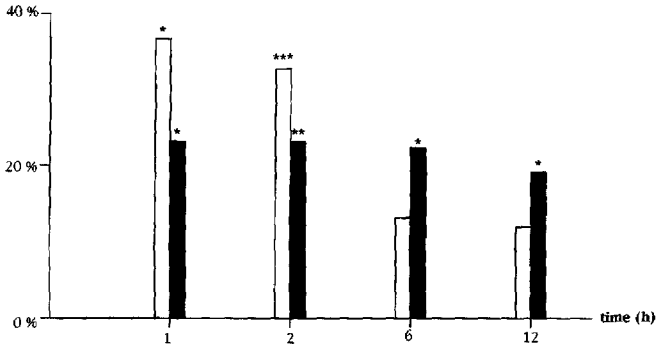

Fig. 1 Right atrial pressure (percentage change vs placebo) at 1, 2, 6 and 12 h after administration of the first of two tablets of 4 mg molsidomine (*open bars*) 6 h apart or after one tablet of 16 mg molsidomine sustained-release (*black bars*). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$ (vs. placebo)

Total pulmonary resistance (Fig. 2, Table 1)

Four milligrams molsidomine 6-hourly. Reductions were 4% (NS), 18% ($P < 0.05$) and 2% (NS) at 1, 2 and 6 h after the first tablet. At 12 h, i.e. 6 h after the second tablet, total pulmonary resistance was 4% (NS) below the placebo value.

Sixteen milligrams molsidomine sustained-release. On the higher dose, reductions by 4% (NS), 18% ($P < 0.01$), 16% ($P < 0.005$) and 15% ($P < 0.03$) were found at the corresponding points in time.

The differences between both active treatment forms achieved statistical significance only at 6 h after the morning dose ($P < 0.02$).

Pulmonary arteriolar resistance (Table 1)

Four milligrams molsidomine 6-hourly. Reductions of 9%, 21% and 15% were found at 1, 2 and 6 h after the first tablet, respectively. At 12 h after the morning dose, the reduction in pulmonary arteriolar resistance was 6%. None of these changes was significant.

Sixteen milligrams molsidomine sustained-release. On the higher dose, changes by 3% (NS), −30% ($P < 0.006$), −6% (NS) and 0% (NS) were found at the corresponding points in time.

In none of these effects was either active tablet found to be superior to the other.

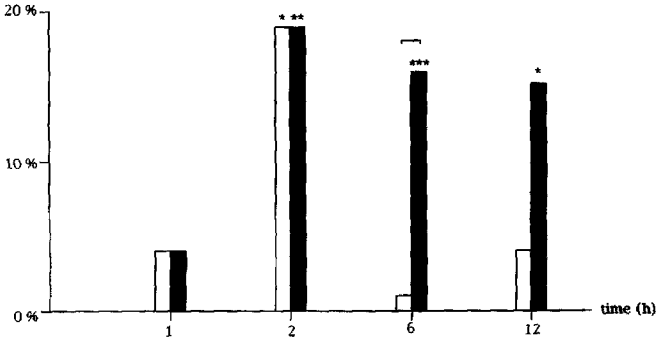

Fig. 2 Total pulmonary resistance (percentage change vs placebo) at 1, 2, 6 and 12 hours after administration of the first of two tablets of 4 mg molsidomine (*open bars*) 6 h apart or after one tablet of 16 mg molsidomine sustained-release (*black bars*). *Asterisks* as in Fig. 1. Bracket indicates a statistically significant difference between the two active treatment forms

Systemic vascular resistance (Table 1)

Four milligrams molsidomine 6-hourly: Reductions were 0%, 11% ($P < 0.03$) and 0% at 1, 2 and 6 h after the first tablet. At 12 h, systemic vascular resistance remained unaltered.

Sixteen milligrams molsidomine sustained-release. The higher dose reduced this parameter by 0%, 6% (NS), 5% (NS) and 11% ($P < 0.03$) at the respective points in time.

The active treatment forms did not differ with respect to this parameter at any point in time. Of note, the small number of few statistically significant reductions of this parameter always paralleled increases in cardiac output with both of the formulations tested.

Adverse effects

None of the patients complained about any untoward side effects at any point in time. Furthermore, no disabling side effects such as symptomatic hypotension were observed.

Discussion

This investigation was undertaken to determine the extent and duration of two different regimens of molsidomine on haemodynamic parameters in patients suffering from chronic congestive heart failure. Both dosage regimens led to statistically significant reductions of both pulmonary artery and right atrial pressures as well as total pulmonary resistance, thus affecting the functional parameters of the pulmonary, i.e. the low-pressure arm of circulation. On the other hand, arterial blood pressure, cardiac output and systemic vascular resistance were found to be significantly affected only at single points in time, otherwise there were only slight alterations in these parameters.

Haemodynamic effects identical to those demonstrated in the present study have been found with comparable dosage forms of molsidomine and SIN-1, its major metabolite [22–24]. The present study, therefore, using different methods, has confirmed the sydnon-

imines as being substances which act predominantly on preload [22–24]. Nevertheless, there have been some reports [22–25] of decreases in total vascular resistance and, consequently, in after-load, as could also be seen from the tendency for such decreases to occur in the present study, and which was paralleled by increases in cardiac output taking place exclusively at the same points in time (Table 1). Consequently, since this points to a possibly dose dependent influence of molsidomine on all types of vascular resistance, administration of an even higher dose in sustained-release form would seem justified for effective treatment of chronic congestive heart failure, this should also affect left ventricular afterload, i.e. reduce systemic vascular resistance and enhance both cardiac output and stroke volume, respectively [22–25].

Heart rate at rest was the only haemodynamic parameter which was not affected significantly by either of the regimens tested compared with the placebo or control groups, respectively, neither in the present study nor in other studies which have assessed the haemodynamic effects of sydnonimines [15, 22–26]. Altogether it can be assumed that changes in haemodynamic parameters brought about by molsidomine in the dosages tested do not lead to statistically significant changes in heart rate at rest, which, in turn, obviously is not augmented unless more marked reductions of systemic resistance and arterial blood pressure take place at higher dosages, e.g. comparable to the alterations brought about by nitrates [27].

With respect to duration of effects, a single dose of 4 mg molsidomine in non-sustained release form elicited significant effects lasting for no more than 2 h in the present study. Others have found a duration of action of up to 5 h post dosing [5, 19, 20], which, as a consequence, implies administration at least 4–5 times daily to cover the 24-h treatment cycle [19, 23]. In contrast, maintained effects lasting for up to 12 h can be derived from the higher dosage of 16 mg in sustained-release form such that administration twice daily appears to be sufficient, which, in addition, facilitates patient compliance. Possibly dosing frequency can be minimized to one single tablet per day by increasing the dosage of molsidomine even further, which would lead to further enhancement of the favourable haemodynamic effects of molsidomine.

In the present study there were no meaningful untoward adverse effects observed nor were there any reported on the part of the patients. Other studies [23, 28] have reported no clinically important adverse effects, apart from headaches, of molsidomine in therapeutically relevant doses [23, 28].

In summary, molsidomine is a cardiovascularly effective compound which, due to its beneficial haemodynamic actions and lack of clinically important adverse effects [22, 23, 25, 26, 28], can be used for treatment of both coronary artery disease [5, 15, 20] and heart failure. In future, the disadvantage of a comparably short duration of action might be overcome by the use of higher dosages in sustained-release formulations which can be expected to exert more pronounced effects on the arterial circulation and at the same time will also lead to better patient compliance.

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