Pharmacokinetic parameters and haemodynamic actions of midodrine in young volunteers

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In two groups of volunteers pharmacological parameters of the antihypotensive drug midodrine have been investigated. The first group of 12 male healthy volunteers received 2.5 mg midodrine hydrochloride intravenously, as drinking solution or as tablet according to a randomized cross-over design. Plasma and urine samples were analyzed for midodrine and its main metabolite ST 1059 by high-performance liquid chromatography. The mean maximum concentration in plasma for midodrine was 10 ng/ml 20-30 min after oral administration, for ST 1059 5 ng/ml after 1 h. Midodrine was eliminated with a terminal half-life of 0,5 h, ST 1059 with a half-life of 3 hrs. The mean area under the plasma-level vs. time curve (AUC) of ST 1059 after administration of 2.5 mg midodrine i.v. was 28.7 ng×h/ml, and similar for the other formulations which are considered to be bioequivalent. In a second group of 15 volunteers with postural hypotension midodrine (M) as α-sympathomimetic drug and oxilofrine (O) as β-sympathomimetic drug was given i.v. in a randomized double blind study against placebo (P). Blood pressure (BP), heart rate (HR) and circulating catecholamines (CA) were determined before and after injections of the drugs as well as before and during 10 min of tilting. Echocardiographic parameters were obtained at rest before and after the administration of the drugs. Blood pressure remained unchanged at rest and during orthostasis after all agents injected. After oral administration of midodrine heart rate was decreased and systolic blood pressure increased significantly and dose-dependently. M lowered circulating noradrenaline. Echocardiographic parameters were changed after administration of M (increase in end-diastolic volume index and SVI) and O (increase in SVI, EF and cardiac index). The observed changes in sympathetic and cardiovascular parameters are in agreement with the sympathomimetic actions of the drugs investigated and allow a differential therapeutic classification: M is suitable for patients with sympathotonic orthostatic reaction; O should be recommended for patients with asympathotonic orthostatic reaction.

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In the past decade among the sympathomimetic drugs used for therapeutic intervention in orthostatic hypotension, midodrine (Fig. 1) as a potent and selective peripherally acting as α-receptor agonist hast been established.[1] Pharmacological properties, therapeutic trials, adverse effects, dosage, and administration were reviewed recently.[2]

The aim of this paper is to summarize the investigations from our laboratory concerning pharmacodynamic properties and pharmacokinetic parameters of midodrine in young patients with orthostatic dysregulation and in healthy volunteers, respectively.

Patients volunteers and methods

Study 1

Haemodynamic effects. The study was performed in 15 young patients (i.v. administration)

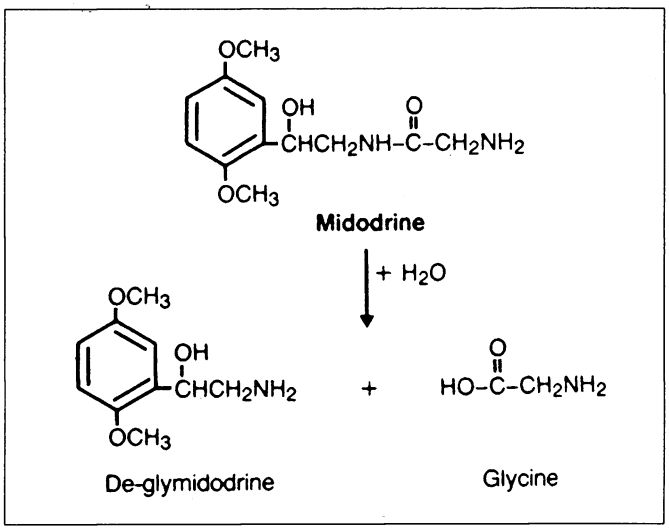

Fig. 1.—Conversion of midodrine to its active metabolite, deglymidodrine, via enzymatic hydrolysis in vivo.

or five volunteers for oral administration (Table I). The following parameters should be fulfilled twice by the volunteers prior to the study:

1. Systolic blood pressure after 30 min supine <130 mmHg.

2. Decrease in systolic blood pressure during passive orthostase after tilting with feet lowered at 90°: >15 mmHg (this method for inducing orthostatic hypotension is described by de Marees *et al.*, 1975); when collapse occurred, this requirement was regarded as fulfilled.

3. Pressure-dependent venous capacity of one leg at 70 mmHg pressure: 4.5-5.5 ml/100 ml soft tissue.

In a double blind, intraindividual and randomized order, the i.v. study was performed in volunteers receiving acute aequieffective doses, aequieffective with respect to the blood pressure, 5 mg midodrine* and 20 mg oxilofrine** intravenously (i.v.) within 2 minutes versus placebo. Between the drug administration an interval of 7 days was maintained. Haemodynamic measurements were performed in the morning in a room with a temperature of 24°C after at least 12 hours abstinence from alcohol and caffeine. Increasing doses of midodrine were administered orally in a controlled open study: 2.5 mg, followed by 7.5 mg and 15 mg.

Blood pressure and heart rate.—Prior to investigation, an indwelling catheter was introduced into an antecubital vein of each volunteer. After 30 min supine, samples of 5 ml blood were taken for assay of circulating catecholamines (noradrenaline and adrenaline after i.v. injection of the drugs). Pressure-dependent venous capacity and resting values for blood pressure (RR=combined Riva Rocci/Korotkoff method) and heart rate (via ECG) were determined. Resting blood pressure refers to the value taken immediately before tilting.

Resting blood pressure after injection of the drugs investigated was obtained 30 min after i.v. administration, immediately before tilting. During the subsequent 10 minutes of passive orthostase (tilting table, feet lowered at 90°; as described by de Marees *et al.*, 1975), blood pressure and heart rate were taken at l-minute intervals and blood samples for plasma catecholamine assay were taken after 1st, 2nd, 5th, and 10th minute. In the study with oral administration of midodrine heart rate and blood pressure were determined after each dose in 10-minute intervals.

Echocardiography.—Cardiac parameters were estimated after i.v. injection of the drugs by 2-D-echocardiographic sonography (Sonotron Diasonic LV 3400 R) and evaluated by Cardio 80 (Fa. Kontron; Chapman's biplane method).

ECG-triggered end-diastolic and end-systolic

*Gutron®.
**Carnigen®.

TABLE I.—*Data of patients.*

	i.v. administration	Oral treatment
Number of patients	15	5
-- male	5	5
— female	10	—
Age (years)	22.4±3.1	37.6±11.2
Weight (kg)	60.9±8.5	71.6±8.2
Height (cm)	171.9±6.6	179.2±9.7

The values are given as mean±standard deviation.

TABLE II.—*Initial values of cardiovascular data (blood pressure and heart rate).*

Substance i.v.	Before medication			After medications		
	SBP (mmHg)	DBP (mmHg)	HR (b/min)	SBP (mmHg)	DBP (mmHg)	HR (b/min)
Placebo	113.0±6.6	70.6±5.0	74.9±12.8	112.6±7.4	73.9±7.0	70.9±11.6*
Midodrine	111.5±9.3	71.1±7.0	74.7±11.2	112.9±9.3	73.9±8.5	64.3±10.5**
Oxilofrine	111.9±7.7	70.5±8.1	73.3±12.4	116.6±10.1	72.3±10.1	73.9±12.0

Abbreviations: SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate.
The values are given as mean±standard deviation.
Significance: *=$p<0.05$, **=$p<0.001$.

TABLE III.—*Route of application.*

Parameter	Route of application		
	i.v.	Oral	
		Solution	Tablet
t_{max} (h)	—	1.1±0.5	1.1±0.5
C_{max} (ng/ml)	—	4.6±1.0	5.0±1.6
$t\frac{1}{2}$ (h)	3.1±0.5	3.0±0.4	3.0±0.5
AUC (ng×h/ml)	28.7±6.6	25.7±6.6	25.6±6.2
Cl (ml/min)	1200±229	1392±278	1378±319
V (!)	319±61	355±81	353±80
$U_{0\text{-}24\ h}$ (% der Dosis)	39.8±3.8	34.4±2.6	34.4±4.5

v=distribution volume.

silhouettes of the heart were determined after freezing, and stroke volume, ejection fraction and cardiac output were calculated and depicted as the indices (ml/m^2).

The volunteers were then given the scheduled drug and the sequence of investigations described above was repeated 30 min later.

Plasma catecholamines.—To determine the plasma catecholamine concentrations, 5 ml blood were taken through the catheter and placed in ice cold PP tubes containing EGTA/glutathione ul. Immediately after mixing, the blood samples were centrifuged for 10 min at 4°C and 5000×g, and the plasma was stored at −70°C until assay. Noradrenaline and adrenaline were determined by high pressure liquid chromatography (HPLC) and electrochemical detection.

Study 2

Pharmacokinetic parameters.—Volunteers, methods and material has been described extensively elsewhere.[3]

Results

Study 1

Haemodynamics and circulating (Table II) noradrenaline as biochemical index of sympathetic tone.

Blood pressure and heart rate.—The initial values for blood pressure and heart rate were comparable in the different groups, and resting

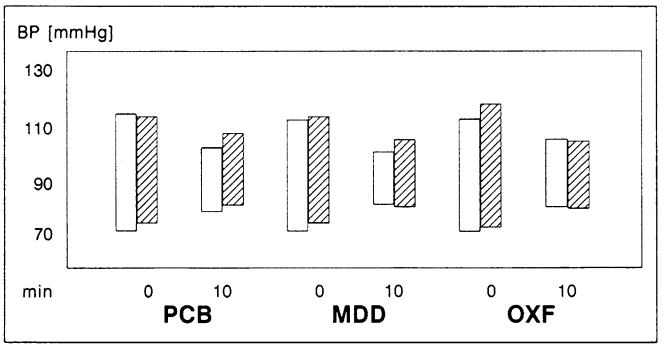

Fig. 2.—Blood pressure (BP) using passive orthostasis before (open columns) and after (hatched columns) i.v. injection of the various antihypotensive agents. Abbreviations: PCB=placebo, MDD=midodrine, OXF=oxilofrine.

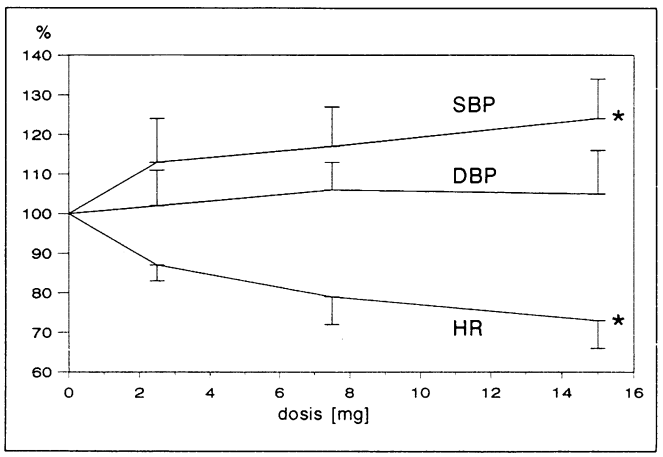

Fig. 3.—Blood pressure (BP) and heart rate (HR) during oral administration of midodrine. After increasing doses BP and HR are depicted as percent of basic values from 5 volunteers. Before treatment=100% (mean±SEM, N=5). Significance: *=$p<0.01$.

blood pressure was not influenced by administration of the different antihypotensive agents and placebo.

However, the resting heart rate decreased significantly by 10.5 and 11.6 beats/min, respectively, after injection of midodrine and placebo. Oxilofrine did not change the heart rate.

Also the changes in blood pressure observed during orthostasis are comparable for the different groups before administration of the drugs (Fig. 2).

After oral administration of midodrine in increasing doses from 2.5 mg up to 15 mg with an interval of 1 hour we could observe a dose-dependent significant decrease of heart rate and simultaneously a significant increase of systolic blood pressure (Fig. 3).

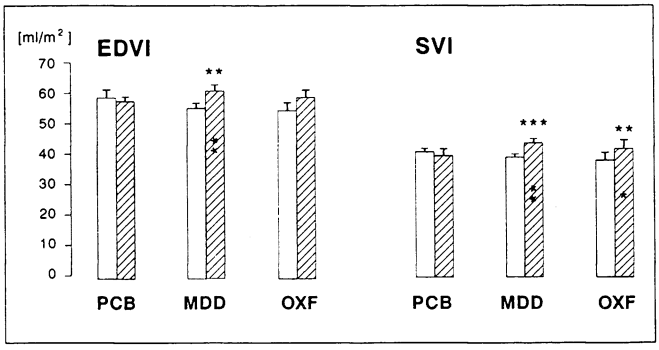

Fig. 4.—End-diastolic (EDVI) and stroke volume index (SVI) as determined by cardiosonographic measurements before (open columns) and after (hatched columns) i.v. injection of the various antihypotensive agents. * = p < 0.05, ** = p < 0.01, *** = p < 0.001. The asterisks above the columns represent the significance versus the respective control, the asterisks within the columns show the significance versus placebo.

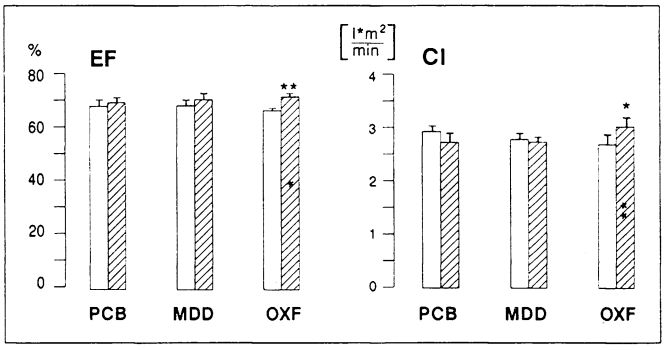

Fig. 5.—Ejection fraction (EF) and cardiac index (CI) as calculated from end-diastolic and end-systolic silhouettes or from stroke volume and heart before (open columns) and after (hatched columns) i.v. injection of the various antihypertensive drugs. * = p < 0.05, ** = p < 0.01, *** = p < 0.001. The asterisks above the columns represent the significance versus the respective control, the asterisks within the columns show the significance versus placebo.

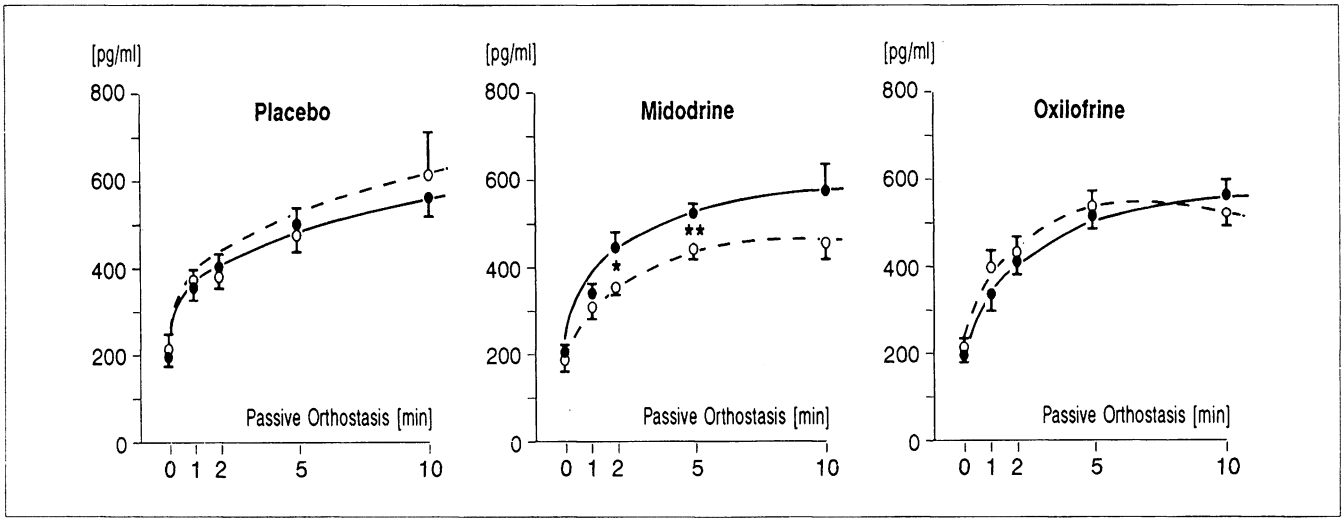

Fig. 6.—Plasma noradrenaline concentrations before (0) and during 1, 2, 5 and 10 minutes of passive orthostasis. Before treatment = solid lines and black circles, after i.v. injection of the various drug = broken line and open circles. 0 = p < 0.05, 0* = p < 0.01, *** = p < 0.001).

Echocardiography.—End-diastolic volume index was significantly enhanced against control and placebo by midodrine. Stroke volume index was increased by midodrine and oxilofrine when compared to controls and placebo (Fig. 4). We did not observe any changes in end-systolic volume index (ESVI).

As a parameter for myocardial contractility the ejection fraction was calculated. Oxilofrine but not midodrine increased significantly the ejection fraction. In addition, cardiac index was enhanced, but only after injection of oxilofrine (Fig. 5).

Plasma catecholamines.—During resting in supine position mean circulating noradrenaline (NA) in the volunteers before medication was approximately 200 pg/ml and was comparable for the 5 groups (Fig. 6). After tilting noradrenaline concentrations showed a typical pattern, obtaining saturation curves reaching 490-570 pg/ml after 5 to 10 min. The noradrenaline curves after oxilofrine and placebo showed no changes when compared to curves before medication. However, midodrine decreased NA significantly ($p < 0.1$) during the 2nd, 5th and 10th minute of tilting

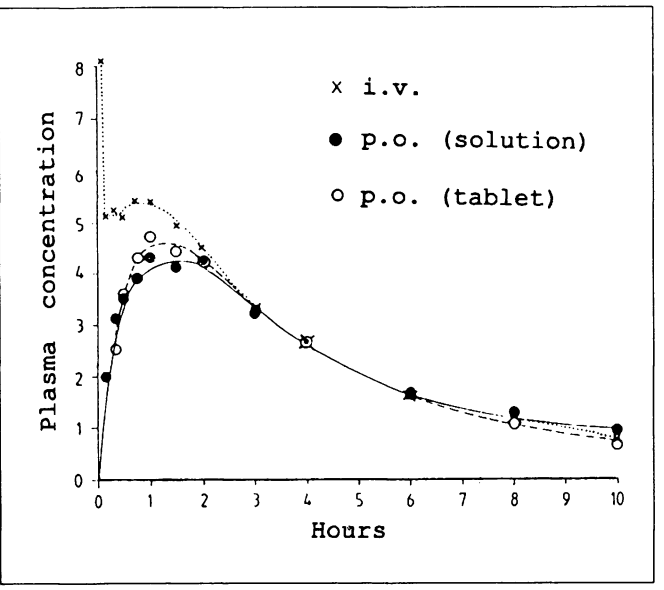

Fig. 7.—Mean concentrations of ST 1059 in plasma of volunteers after oral application of 2.5 mg midodrine as hydrochloride n = 10.

(Fig. 6). Circulating adrenaline did not change under all experimental conditions.

Pharmacokinetic parameters—The pharmacokinetics of midodrine (α-2.5-dimethoxyphenyl-β-glycinamidoethanol hydrochloride, ST 1085) and its main metabolite ST 1059 (α-2.5 dimethoxyphenyl-β-aminoethanol hydrochloride) have been investigated in 12 male healthy volunteers. 2.5 mg midodrine hydrochloride were applied intravenously, as drinking solution or as tablet (Gutron®) according to a randomized cross-over design. Plasma and urine samples collected up to 24 h after application were analyzed by high-performance liquid chromatography with fluorescence detection. The method of high pressure liquid chromatography used had a limit of sensitivity for detection of 1 and 0.5 ng/ml for midodrine and its active metabolite de-glymidodrine respectively.[3] The mean maximum concentration in plasma for midodrine was ca. 10 ng/ml 20-30 min after oral administration, for ST 1059 ca 5 ng/ml after 1 h. Midodrine was eliminated with a terminal half-life of 0.5 h. The half-life of ST 1059 was determined to be 3 h. The mean area under the plasma-level vs time curve (AUC) of ST 1059 after administration of 2.5 mg midodrine i.v. was 28.7 ng×h/ml, and as drinking solution or as tablet 25.7 and 25.6 ng×h/ml, respectively (Fig. 7 and Table III). The data of 10 volunteers could be used for the calculations of the bioavailability of ST 1059 by the AUC. Assuming an interval of equivalence of 0.75-1.25 because of the relatively small number of volunteers, the three formulations are considered to be equivalent).

Discussion

The aim of the present study was to estimate the therapeutic value after acute administration of different antihypotensive drugs on the basis of determination of cardiac parameters by 2-D-echocardiography, and assay of circulating catecholamines with the help of high pressure liquid chromatography (HPLC). Also blood pressure and heart rate were recorded, especially after establishing a dose response curve for orally administered midodrine. Both parameters can be used to estimate pharmacological effects of the drugs investigated on the cardiovascular system.

Pharmacodynamic investigations have classified *midodrine* as an α-sympathomimetic drug.[4] We were able to confirm these findings while observing effects, mainly classified as actions on post- and presynaptic α-adrenoceptors. After stimulation of postsynaptic α-adrenoceptors reflex bradycardia is induced in a dose dependent fashion. The reduced plasma noradrenaline concentrations observed during orthostasis indicated probably an action on presynaptic α-adrenoceptors and/or on baroreflex mechanisms.

Clinical pharmacology studies on *oxilofrine* [5] allow this compound to be classified as a β-sympathomimetic drug. β-sympathomimetic agents have a positive inotropic and chronotropic action on the heart. In accordance with this assumption, our results demonstrate an effect of oxilofrine on cardiac parameters i.e. increase in stroke volume, ejection fraction and cardiac index, parameters for myocardial contractility.[6 7]

The data available appear to allow a differential estimation of the therapeutic value of the drugs investigated for pharmacotherapy of orthostatic dysregulation. According to the scheme of Thulesius, 1976, for differential diagnosis of orthostatic dysregulation, the sympathotonic reaction (rise in heart rate, fall in systolic blood pressure, rise in diastolic blood pressure, reduc-

tion of stroke volume by about 51%) is the most frequent, i.e. about 70%, of all forms of postural hypotension. If this type of hypotension is present and associated with sequestration of blood volume in the leg veins, drugs like dihydroergotamine appeared to be most suitable. If, however, the blood volume is displaced more into the region of the splanchnic or thoracic region, treatment with midodrine should be recommended. The asympathotonic reaction according to Thulesius, 1986 (decreases in systolic and diastolic blood pressure, reduction of stroke volume by about 28%, heart rate remains unchanged) appeared to be an indication for midodrine and oxilofrine.

Because of their mechanisms of action, these drugs are able to increase the sympathetic tone by stimulating cardiovascular α- and β-adrenoceptors. However, it is not clear whether midodrine and its active metabolite stimulates α^1- or α_2-adrenergic receptors.

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