Cardiovascular Parameters and Catecholamines in Volunteers During Passive Orthostasis

Influence of antihypotensive drugs

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Summary

To evaluate the therapeutic value of various antihypotensive agents we investigated amezinium (AMZ; CAS 30578-37-1), dihydroergotamine (DHE; CAS 511-12-6), midodrine (MDD; CAS 42794-76-3), and oxilofrine (OXF; CAS 365-26-4) in volunteers during passive orthostasis in a randomized double-blind study against placebo (PCB). Blood pressure, heart rate, and circulating catecholamines were determined before and after i.v. injections of the mentioned agents before and during 10 min of passive orthostasis. Echocardiographic and venous plethysmographic data were obtained during resting before and after the administration of the drugs. Resting heart rate decreased after injection of PCB, AMZ, DHE, and MDD. During tilting no significant changes in heart rate could be observed. Blood pressure remained unchanged at rest and during orthostasis after all agents injected. DHE and MDD lowered circulating noradrenaline. Echocardiographic parameters were changed after administration of AMZ (increase in stroke volume index (SVI) and ejection fraction (EF)), MDD (increase in enddiastolic volume index and SVI), and OXF (incease in SVI, EF, and cardiac index). The venous capacity of the left lower leg was only significantly decreased after injection of DHE, indicating an increased venous tone of the leg veins. The observed changes in sympathetic and cardiovascular parameters are in agreement with their sympathomimetic actions and allow a differential therapeutic classification: DHE and MDD are suitable agents for patients with sympathotonic orthostatic reaction; if asympathotonic orthostatic reaction occurs MDD, AMX and OXF should be recommended to those patients.

Zusammenfassung

Kardiovaskuläre Parameter und Katecholamine bei freiwilligen Probanden während passiver Orthostase / Wirkung antihypotensiver Substanzen

Bei freiwilligen Probanden wurden in einer randomisierten Doppelblindstudie gegen Plazebo die 4 antihypotensiv wirksamen Substanzen Amezinium (AMZ; CAS 30578-37-1), Dihydroergotamin (DHE; CAS 511-12-6), Midodrin (MDD; CAS 32794-76-3) und Oxilofrin (OXF; CAS 365-26-4) während passiver Orthostase untersucht, um ihren therapeutischen Wert zu bestimmen. Während 10minütiger passiver Orthostase wurden Blutdruck, Herzfrequenz und zirkulierende Katecholamine vor und nach i.v. Injektion der oben erwähnten Substanzen bestimmt. Echokardiographische Parameter und Venenplethysmographie wurden in Ruhe vor und nach Gabe der Substanzen bestimmt. Die Ruhe-Herzfrequenz nahm nach Injektion von Plazebo, AMZ, DHE und MDD ab. Während passiver Orthostase konnten keine signifikanten Veränderungen der Herzfrequenz beobachtet werden. Der Blutdruck blieb unter Ruhebedingungen und während passiver Orthostase nach Gabe aller Substanzen unverändert. DHE und MDD verminderten zirkulierendes Noradrenalin. Die echokardiographischen Parameter wurden nach Gabe von AMZ (Anstieg des Schlagvolumenindex (SVI) und der Auswurffraktion (EF)), Midodrin (Anstieg des enddiastolischen Volumenindex und des Schlagvolumenindex) und Oxilofrin (Anstieg des Schlagvolumenindex, der Auswurffraktion und des Herzindex) verändert. Die Venenkapazität des linken Unterschenkels wurde nur nach Injektion von DHE signifikant vermindert, was auf einen erhöhten Venentonus schließen läßt. Die beobachteten Veränderungen des Sympathikustonus und der kardiovaskulären Parameter stimmen mit den sympathomimetischen Wirkungen der Substanzen überein und erlauben eine differentialtherapeutische Klassifizierung: DHE und MDD können bei Patienten mit sympathotoner orthostatischer Reaktion eingesetzt werden, während bei Patienten mit asympathotoner orthostatischer Reaktion AMZ und OXF bevorzugt werden.

Key words: *Amezinum · Antihypotensive drugs · CAS 365-26-4 · CAS 511-12-6 · CAS 30578-37-1 · CAS 42794-76-3 · Dihydroergotamine · Midodrine · Oxilofrine*

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1. Introduction

Changes of body position from lying to standing lead to circulatory readjustments, counteracting the tendency for blood to pool into the legs or the splanchnic region. These adjustments are accompanied by a decrease in cardiac output, an increase in heart rate, and an increase in total peripheral resistance, thus maintaining arterial blood pressure approximately constant [14, 15]. Since circulating noradrenaline is almost doubled during erection [4], and sympathetic ganglionic blockade causes orthostatic hypotension, it is clear that sympathetic mechanisms are responsible for some reflex adjustments. In orthostatic dysregulation reflex adjustments seem to be impaired. A variety of drugs are administered during treatment of postural hypotension, mainly interfering with sympathetic mechanisms in the cardiovascular system.

Prior to the study, the drugs investigated can be characterized as follows:

Amezinium is probably an indirect acting sympathomimetic drug. In addition it has direct effects on α-adrenoceptors [8];

Dihydroergotamine is an ergot alkaloid which possesses serotonergic and α-adrenergic activities [12];

Midodrine, a prodrug, which is converted in vivo to an α-sympathomimetic agent [13], and

Oxilofrine has predominantly β-adrenergic effects on the myocardium [1].

Therefore it was the aim of the present study to investigate the effectiveness and mode of action on cardiovascular system and sympathetic activity of these antihypotensive drugs injected i.v. in young volunteers with different grades of postural hypotension, induced by tilting.

2. Patients and methods

2.1. Patients and drugs

The study was performed in 15 healthy volunteers (Table 1). They were informed about the nature and risks of the study and had given their written consent. The volunteers were allowed to withdraw of any time without giving reasons. 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 orthostasis after tilting with feet lowered at 90 °: > 15 mmHg (this method for inducing orthostatic hypotension in described by de Mareés et al. 1975 [11]); 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 study was performed in volunteers receiving acute equieffective doses, equieffective with respect to the blood pressure, of 5 mg amezinium (CAS 30578-37-1), 0.5 mg dihydroergotamine (CAS 511-12-6), 5 mg midodrine (CAS 42794-76-3) and 20 mg oxilofrine (CAS 365-26-4) intravenously (i.v.) within 2 min versus placebo. Between the drug administrations 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 h abstinence from alcohol and caffeine. Further informations to the products, e.g. names and Galch numbers are available from the authors.

Table 1: Data of patients.

Number of patients Male Female	15 5 10
Age (years)	22.4 ± 3.1
Weight (kg)	60.9 ± 8.5
Height (cm)	171.9 ± 6.6

The values are given as mean ± standard deviation.

2.2. Blood pressure and heart rate

Prior to investigation, an indwelling catheter was inserted into an antecubital vein of each volunteer. After 30 min supine, samples of 5 ml blood were taken for assay of curculating catecholamines (noradrenaline and adrenaline).

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 min of passive orthostasis (tilting table, feet lowered at 90 ° as described by [11]), blood pressure and heart rate were taken at 1-min intervals, and blood samples for plasma catecholamine assay were taken after the 1st, 2nd, 5th, and 10th minute.

2.3. Echocardiography

Cardiac parameters were estimated by 2-D-echocardiographic sonography (Sonotron Diasonics LV 3400 R) and evaluated by Cardio 80 system (Kontron; Chapman's biplane method). ECG-triggered enddiastolic and endsystolic 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.

2.4. Venous capacity

The pressure-dependent venous capacity of the left lower leg was measured by using a plethysmograph (VVP 300; Boucke, Tübingen, FRG). Stepwise increase of the pressure in the left lower leg from 40 up to 100 mmHg causes an enlargement in the venous volume of this leg. The pressure-volume curve thus obtained was used to determine the venous capacity for a height-corrected pressure of 70 mmHg.

2.5. Plasma catecholamines

To determine the plasma catecholamine concentrations, 5 ml blood were taken through the venous catheter and placed in ice cold PP tubes containing EGTA/glutathione (20 µl/ml blood). Immediately after mixing, the blood samples were centrifuged for 10 min at 4 °C and 5000 × g and the plasma stored at −70 °C until assay. Noradrenaline and adrenaline were determined by high pressure liquid chromatography (HPLC) (Waters, West Lafayette, USA) and electrochemical detection as described previously [5].

2.6. Statistical analysis

During orthostasis the systolic and diastolic blood pressure values circumscribe areas above and/or below the respective resting pressure curves. These were calculated with the trapezoidal formula and their absolute values added. The heart rate curve was evaluated during the orthostasis, the values recorded immediately before discontinuation were continued until the end of the test.

The values of the random samples are given as mean ± SEM and were compared statistically by means of analysis of variance (ANOVA) and Student's t-test for paired differences.

3. Results

3.1. Blood pressure and heart rate

The initial values for blood pressure and heart rate were comparable in the different groups (Table 2). Resting blood pressure was not influenced by administration of the different antihypotensive agents and placebo (Table 2). However, the resting heart rate decreased significantly by 9, 8, 11, and 4 beats/min, respectively, after

Table 2: Initial values of cardiovascular data.

Substance	Blood pressure and heart rate					
	Before medication			After medication		
	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*
Amezinium	113.3±7.7	71.4±7.4	73.9±12.8	116.9±10.1	76.0± 9.3	65.3±12.0***
Dihydroergotamine	112.1±7.0	71.9±7.0	70.4±12.8	112.9± 7.7	77.4± 7.4	61.9±10.8**
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

Abbrevations: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate. The values are given as mean ± standard deviation. Significance: * $p < 0.05$, ** $p < 0.01$, *** < 0.001.

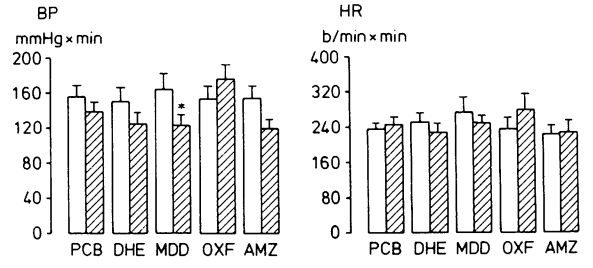

Fig. 1: Blood pressure (BP) and heart rate (HR) during passive orthostasis before (open columns) and after (hatched columns) i.v. injection of the various antihypotensive agents. The columns represent the area criterions of the BP or HR curves (× min) during orthostasis (see methods). Abbreviations: PCB = placebo, DHE = dihydroergotamine, MDD = midodrine, OXF = oxilofrine, AMZ = amezinium. *$p < 0.05$, in comparison to the respective control.

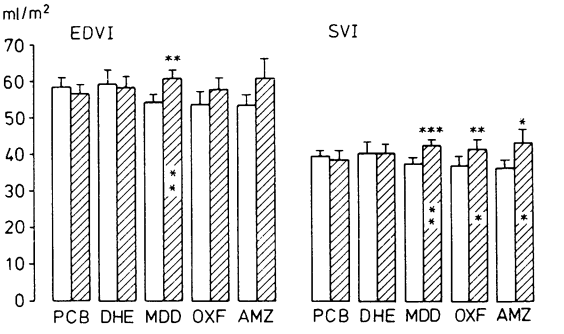

Fig. 2: Enddiastolic (EDVI) and stroke volume index (SVI) as determined by cardio-sonographic measurements before (open columns) and after (hatched columns) i.v. injection of the various antihypotensive agents. Abbreviations see Fig. 1. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. The asterisks above the columns represent the significance versus the respective control, the asterisks within the columns show the significance versus placebo.

injection of amezinium, dihydroergotamine, midodrine, and placebo. Oxilofrine did not change the heart rate (Table 2).

Also the changes in blood pressure observed during orthostasis are comparable for the different groups before administration of the drugs (Fig. 1). Only midodrine lowered significantly the area criterion of blood pressure when compared to the respective control, but not versus placebo (Fig. 1).

Heart rates were also comparable before administration of the antihypotensive agents. After injection of the drugs and tilting no significant changes were observed (Fig. 1).

3.2. Echocardiography

Enddiastolic volume index was significantly enhanced against control and placebo by midodrine only. Also for amezinium and oxilofrine, a tendency for an increase in enddiastolic volume index in comparison to controls could be observed (Fig. 2). Stroke volume index was increased by midodrine, oxilofrine and amezinium, when compared to the respective controls and placebo (Fig. 3). We did not observe any changes in endsystolic volume index (ESVI); therefore the ESVI-values are not depicted.

As a parameter for myocardial contractility the ejection fraction was calculated. Oxilofrine and amezinium increased significantly the ejection fraction. In addition, cardiac index was enhanced, but only after injection of oxilofrine (Fig. 3).

3.3. Venous capacity

The values of the pressure-dependent venous capacity before administration of the antihypotensive agents ranged between 4.0 and 5.02 ml/100 ml soft tissue (ST) and were comparable. Amezinium, midodrine, oxilofrine, and placebo did not influence the venous capacity. After dihydroergotamine, however, the venous capacity decreased significantly by 0.6 ml/100 ml ST (Fig. 4).

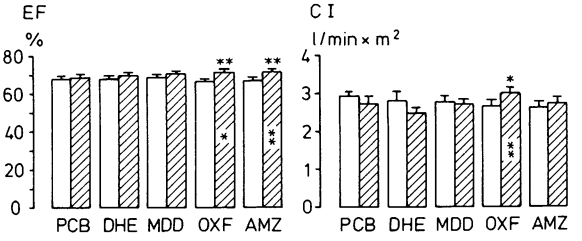

Fig. 3: Ejection fraction (EF) and cardiac index (CI) as calculated from enddiastolic and endsystolic silhouettes or from stroke volume and heart rate before (open columns) and after (hatched columns) i.v. injection of the various antihypotensive drugs. Abbreviations see Fig. 1. *$p < 0.05$, **$p < 0.01$. The asterisks above the columns represent the significance versus the respective control, the asterisks within the columns show the significance versus placebo.

3.4. 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. 5). After tilting noradrenaline concentrations showed a typical pattern, obtained saturation curves reaching 490 — 570 pg/ml after 5 up to 10 min

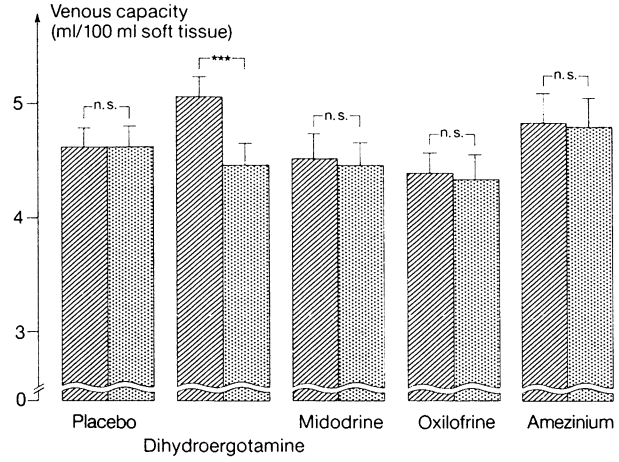

Fig. 4: Venous capacity of the left lower leg at height corrected venous pressure of 70 mmHg before (hatched columns) and after (dotted columns) i.v. injection of the various antihypotensive drugs. ***p < 0.001 versus control and placebo.

Table 3: Symptoms during orthostasis.

	PCB	AMZ	DHE	MDD	OXF
Vertigo	5+	4+	4+	5+	3+, 2–
Scotodinia	1+	1+	2+	2+	2+
Tinnitus	1+				
Palpitation	2+	1+	1+	2+	
Sweating stage	2+	3+	1+	3+	1+, 2–
Congestion in the head	1+	1+			1+

+ means improvement of the conditions under the respective drug. – means aggravation of the conditions. Abbreviations: PCB = placebo, AMZ = amezinium, DHE = dihydroergotamine, MDD = midodrine, OXF = oxilofrine.

(Fig. 5). The noradrenaline curves after amezinium, oxilofrine, and placebo showed no changes when compared to the respective curves before medication. However, dihydroergotamine reduced circulating noradrenaline significantly during all sampling times, whereas midodrine decreased NA significantly during the 2nd, 5th, and 10th (only $p < 0.1$) minute of tilting (Fig. 5). Circulating adrenaline did not change under all experimental conditions (not depicted).

3.5. Side effects

Note on subjective symptoms of volunteers in the study: Before and after administration of the various antihypotensive drugs the volunteers were asked for the following symptoms during orthostasis: vertigo, scotodinia, tinnitus, palpitation, sweating stage and congestion in the head (Table 3). Moreover, the side effects during and after i.v. injection of the agents were observed: congestion in the head: placebo 1 ×, dihydroergotamine 8 ×, midodrine 2 ×; palpitation: amezinium 1 ×, oxilofrine 10 ×; tiredness: dihydroergotamine 2 ×, oxilofrine 1 ×, sensation of coldness: amezinium 2 ×, midodrine 2 ×, oxilofrine 1 ×; heat sensation: placebo 1 ×, dihydroergotamine 3 ×, midodrine 1 ×; dryness of the mouth: dihydroergotamine 1 ×; tingling of the scalp: dihydroergotamine 1 ×, midodrine 7 ×; analeptic effects: midodrine 1 ×, oxilofrine 1 ×; nausea: dihydroergotamine 4 ×; pilo-erection: midodrine 1 ×.

It should be noted that even injection of placebo caused side effects and was able to improve the conditions observed under tilting. Side effects only occurred during i.v. injections and lasted at the most for 30 min.

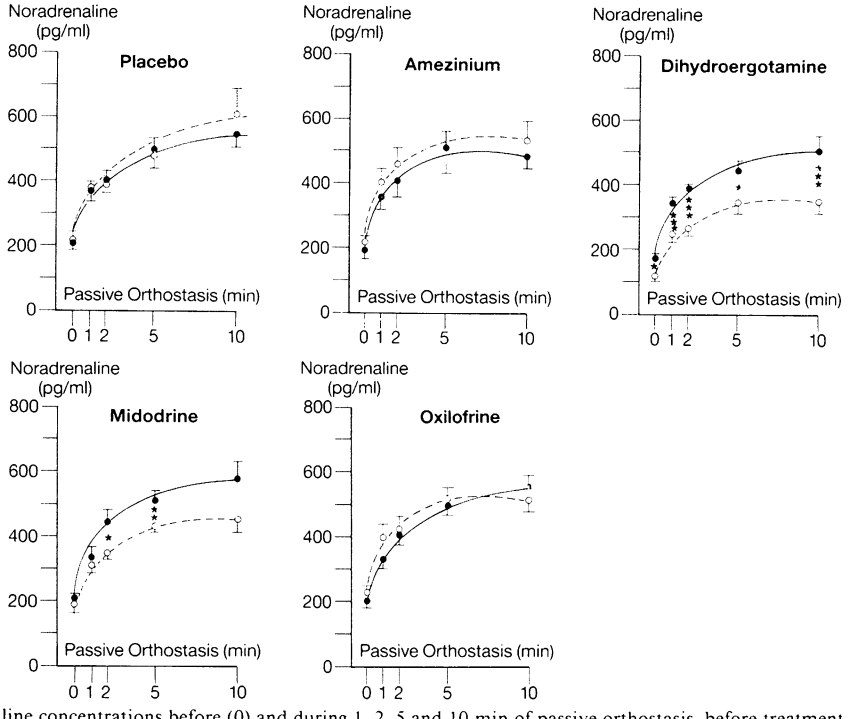

Fig. 5: Plasma noradrenaline concentrations before (0) and during 1, 2, 5 and 10 min of passive orthostasis, before treatment (●), after i.v. injection of the various drugs (○). *p < 0.05, **p < 0.01, ***p < 0.001.

4. 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, venous plethysmographic measurements, and assay of circulating catecholamines with the help of high pressure liquid chromatography (HPLC). Also blood pressure and heart rate were recorded. As we could demonstrate blood pressure and heart rate are not reliable parameters for establishing differences between the drugs investigated. Therefore, echocardiographic data, venous plethysmography, and catecholamines as an index of sympathetic tone [3] have been used in order to differentiate the pharmacological actions of the various antihypotensive agents.

The results of our study confirm earlier data for dihydroergotamine [9, 10]. Dihydroergotamine reduces the venous capacity of the lower leg indicating an increased venous tone. The decreased venous capacity is followed by an enhanced venous blood reflow to the heart and results in a possibly lower sympathetic tone in orthostasis (via baroreceptor reflex), clearly reflected by the reduced plasma noradrenaline concentration at all sampling times after injection of dihydroergotamine. The mechanism of action of dihydroergotamine was originally explained as an action at postsynaptically localized α-adrenoceptors of the veins. However, more recent in vitro studies have shown that tonicising of the leg veins in man after dihydroergotamine administration is induced almost exclusively by an excitation of postsynaptic serotonin receptors [12]. The decrease in circulating noradrenaline under resting conditions and in orthostasis could be explained as a consequence from both, stimulation of presynaptic α-adrenoceptors and of serotonin receptors, reducing noradrenaline release by a negative feed-back mechanism [16].

In contrast to the effects of sympathomimetic drugs like midodrine and oxilofrine, dihydroergotamine obviously did not change the cardiac parameters measured in our study. The diminished sympathetic tone (c.f. Fig. 5, reflected by decreased plasma noradrenaline concentrations) in combination with the tonicising action of dihydroergotamine on the α-adrenoceptors and serotonin receptors of the leg veins are probably responsible for the unchanged cardiac parameters.

Pharmacodynamic investigations have classified midodrine as an α-sympathomimetic drug [13]. We were able to confirm these findings while observing effects, mainly classified as actions on post- and presynaptic α-adrenoceptors. The stimulation of postsynaptic α-adrenoceptors is suggested by the reflex bradycardia. The reduced plasma noradrenaline concentrations observed during orthostasis indicated an action on presynaptic α-adrenoceptors. Midodrine had no influence on venous capacity. This finding could support further evidence that leg veins in man are tonicised mainly by stimulation of serotonin receptors [12]. The described increase in central venous pressure after midodrine could therefore be due to tonicising of the veins of the splanchnic or thoracic region, as observed after administration of etilefrine [2] (cf. also discussion on amezinium). The latter effects could be also responsible for the observed increase in enddiastolic volume and stroke volume (cf. Fig. 2).

Clinical pharmacology studies on oxilofrine [1] allow this compound to be classified as a β-sympathomimetic drug. β-sympathomimetic agents have a positive inotropic and chronotropic action on the heart. Non-specific β-sympathomimetic drugs (with β_1-/β_2-adrenergic effects) can moreover dilate arterioles and venoles by stimulating vascular β_2-adrenoceptors and therefore decrease the peripheral resistance.

Our results are compatible with this classification, showing a distinct action of oxilofrine on cardiac parameters, i.e. increase in stroke volume, ejection fraction, and cardiac index, parameters for myocardial contractility.

Amezinium is an indirect sympathomimetic drug which also acts directly on α-adrenoceptors [6, 8, 12]. However, indirect sympathomimetic effects (significant increase in circulating noradrenaline) have been observed after injection of 10 mg i.v. (Grobecker 1977, unpublished observations). After amezinium, a pronounced reflex decrease in heart rate occurred under resting conditions indicating an α-sympathomimetic activity. The results of the plasma noradrenaline assay could not confirm an indirect sympathomimetic effect of amezinium in the low dose injected (5 mg). However, cardiac parameters for contractility were increased (stroke volume and ejection fraction, cf. Fig. 2 and 3) probably indicating a release of myocardial noradrenaline by amezinium.

Since an increase in central venous pressure was observed after acute amezinium doses, it is conceivable that the blood volume required for this effect is mobilized from the veins of the splanchnic or thoracic region. This effect has recently been described for etilefrine [2].

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 [17] for differential diagnosis of orthostatic dysregulation, the sympathotonic reaction (rise in heart rate, fall in systolic blood pressure, rise in diastolic blood pressure, reduction 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, dihydroergotamine appeared to be the most suitable drug for therapy. 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 [17] (decrease in systolic and diastolic blood pressure, reduction of stroke volume by about 28 %, heart rate remains unchanged) appeared to be an indication for amezinium and oxilofrine. Because of their mechanisms of action, both drugs are able to increase the sympathetic tone by stimulating cardiovascular α-and β-adrenoceptors.

This study does not provide any data about the effect of the drugs investigated after chronic oral administration in patients with orthostatic dysregulation. In a forthcoming paper this issue will be investigated and the therapeutic value of the drugs reevaluated.

On the other hand we failed to observe reproducible orthostatic reactions in our volunteers, despite the subjects fulfilled the criteria of "orthostatic dysregulation" described under methods, when proofed prior to the investigation schedule. It is a well known physiological fact that orthostatic hypotension or dysregulation depends on room temperature, psychical behaviour, and climate conditions, etc.; those changes in external conditions could also contribute to a non-reproducible orthostatic reaction.

Therefore a careful selection of patients exhibiting orthostatic dysregulation is needed in studies concerning orthostatic dysregulations.

5. References

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