CLINICAL DIFFERENCIATION OF NIFEDIPINE AND OTHER CALCIUM ANTAGONISTS

FRANZ EBNER, MANFRED DONATH, KARI-DIETRICH RAMSCH

Calcium antagonists have a common biochemical basis mechanism. This mechanism is the inhibition or reduction of transmembrane calcium influx [1] in the stimulated cells of the smooth muscles of the arterial vessels, the myocardium, the uterus and the pacemaker-Cells [2-5]

In European literature they are called "calcium-antagonists", in Anglo-American literature, they appear as "slow-channel-blocker" [6,7].

Here, however we are concerned with a group of pharmaceutical agents, which differ from each other considerably. Prenylamine and fendiline are from one chemical group, verapamil and gallopamil from an other. But verapamil, nifedipine, diltiazem and perhexiline show significant differences in their chemical structures (table I).

Because of the location of the smooth muscle cells, calcium antagonists could have several sites of action (left) and depending from this they should have influences on systems or organs, listed on the right side of table II

Though, in general, the predominant sites of clinico-pharmacological action are coronary arteries, aorta and peripheral resistance vessels, myocardium, sinus-node, AV-mode, pulmonary artery and peripheral veins However, it has been shown clinically that the up until now known calcium-antagonists have differences in organ selectivity and in sites of action.

Pharmacokinetic aspects

Some of the clinical differences are caused by differences in pharmacokinetics: nifedipine and the other substances are absorbed to more than 80 or 90%, in other words, the absorption is almost complete [8-11] (table III)

However, this is not the only decisive factor, other important parameters are bioavailability, protein-binding, distribution in the various compartments, metabolism and excretion.Nifedipine [12] belongs to those substances having a low firstpass effect. As a result it has a high bioavailability of approximately 70%. In contrast, the bioavailability of verapamil and diltiazem are low and in the range of 10-20%.

The first-pass metabolism greatly influences the bioavailability. After oral administration the origi-

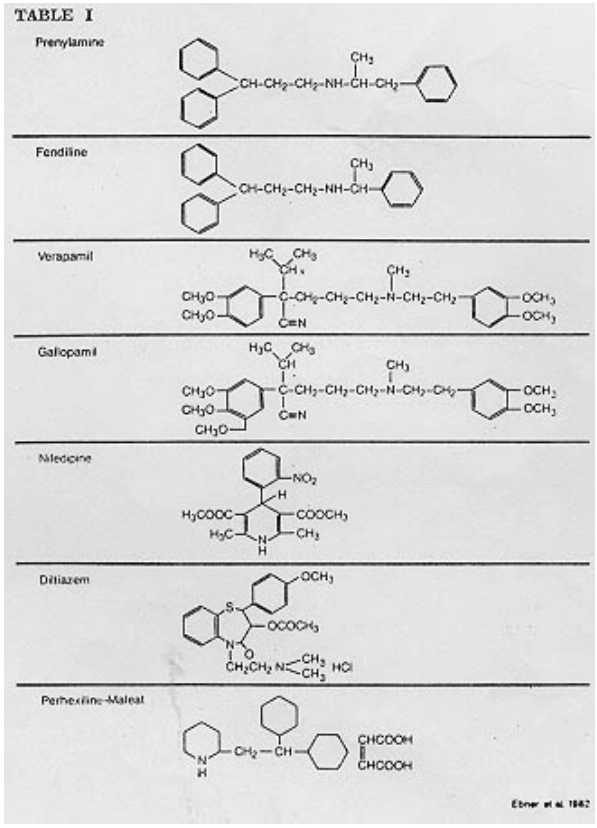

TABLE II - Ca^{++} - Antagonists.

SITE OF ACTION	CLINICAL CONSEQUENCE
Coronary arteries	Global/poststenotic flow/spasm
Aorta	Compliance/Windkessel
Periph. Res. vessels	Change of resistance/Decrease in blood pressure/Afterload-reduction
Myocardium	Negative inotropism Cardioprotective/cardioplegic
Sinus-node	Decrease/increase
AV-node	AV-conduction
Pulmonary Artery	
Peripheral veins	Venous pooling Preload-reduction

Apresentado no 2º Simpósio Brasileiro sobre Nifedipina, São Paulo, 1983.

TABLE III - Kinetics of Ca $^{++}$ - Antagonisis.

Absorption			
90% (ore more)			
First passe effect		Bioavailability	
low	high	low	high
Nifedipine (25-30%)	Verapamil (80-90%) Diltiazem (>80%)	Verapamil (10-20%) Diltiazem (<20%)	Nifedipine (65-70%)

TABLE IV - Kinetics of Ca $^{++}$ - antagonists

Protein-bindling		MetaboMites	
Low	High	Effectiv	Uneffectiv
	Nifedipine (90%) Verapamil (90%) Perhexiline (90%) Prenylarnine (80%) Diltiazem (80%)	Verapamil (4)	Nifedipine (2)

nal substance passing through the liver for the first tine is metabolized to a varying degree and as a result this portion is no longer available. If the metabolites are pharmacologically ineffective a reduction in efficacy occurs.

Substances having a high first-pass effect are verapamil [8], diltiazem [9] and perhexiline [13]. As a result 80-90% of the administered quantity is no fonger available. This data, concerning first-pass metabolism- is not yet known for all the substances.

To achieve effects, in particular acute effects after oral administration, relatively high doses must be given: for example, a 240 mg dose of verapamil induces a very slight increase in load-tolerance; only and only after 320 mg is a satisfactory result achieved [l4]. Accordingly, the daily dose for the treatment of angina pectoris is somewhere between 360 mg [15] and 480 mg [16].

A single high dose may overcome the first-pass effect. However, it is not possible to predict the individual biological reaction of the individual patients. Thus the effective quantity passing through the liver without becoming ineffective varies greatly 8.

A high first-pass metabolism indicates at the same tine a low bioavailability if ineffective metabolites occur and also a greater degree of uncertainty An drug therapy because of the greater interindividual scatter.

It seems most difficult to find an effective acute dose in some Ca++-antagonists. Thus no effective acute single doses are given for diltiazem and perhexiline, only doses for long-term treatment.

According to Kaltenbach, 240 mg of prenylamime [14] and 300 mg of fendiline are ineffective in angina pectoris. A 4-week therapy with 3 x 50 mg per day of fendiline showed no definite antianginal effect [17.]

However there is another aspect of high firstpass metabolism e.g. in the case of verapamil: in patients suffering from liver insufficiency the bio-availability increases [l8], the substance is suddenly more effective and the excretion is delayed [19] due to the almost exclusive metabolism in the liver.

All substances from nifedipine to prenylamime have a protein-binding of 80% or 90% [8,9,20-22]. A high protein-binding indicates that only a smaller portion of the substance is free and as a result, effective The metabolites of nifedipine are ineffective. Only the original substance is pharmacologically effective (table IV).

The metabolism of verapamil is extremely complex and pharmacological effectivity of the cleavage products is only 5-10% of the original substance. The cleavage products are produced in large quantities and their half lives are more than 24 hours. As a result, during long-term therapy plasma concentrations occur which are almost at the same level as that of intact verapamil [8,23].

Most metabolites of diltiazem [9,24], perhexiline [20] and fendiline [25] are known, however, as far as we know their pharmacological efficacy is not.

This kinetic data explain partly, why a single dose of 20 mg of nifedipine is approximately equieffective to 240 or 360 mg of verapamil respectively in acute load tests. And also it needs approximately 4 weeks of verapamil and a dose of 3 tines 120 mg per day, to find significant differences to placebo in patients suffering from angina pectoris, according to Livesley.

In figure 1, we summarized the onset of the plasma levels, the maxima, the ß and y-phases of the excretion and the duration of detectable plasma levels based on the tine of the administration but without taking into account the absolute peaks.

Nifedipine appears most rapidly 26 All the others appear 15 to 30 minutes after administration927 except perhexiline, which appears after 1 hour [20] .The peaks of nifedipine, verapamil and prenylamine occur between 30 minutes and 2 hours after administration. Those of diltiazem, fendiline and perhexiline occur after 2 to 3 hours.

It is important to say, that certainly tissue levels and possibly a binding on local receptors are more important than phasma levels, because the onset, maxima and duration of clinical effects of the individual calcium antagonists are not always identical to the course of the plasma concentration.

The clinical effect of nifedipine begins 3 to 5 minutes after administration and shows a slight increase in load tolerance after 25 to 30 minutes for example. This is not identical with heights of the serum level. The duration of clinical effect in load tolerance is 65 to 7 hours after a single dose of 20 mg[28]. Effective single doses of 5-20 mg are found.

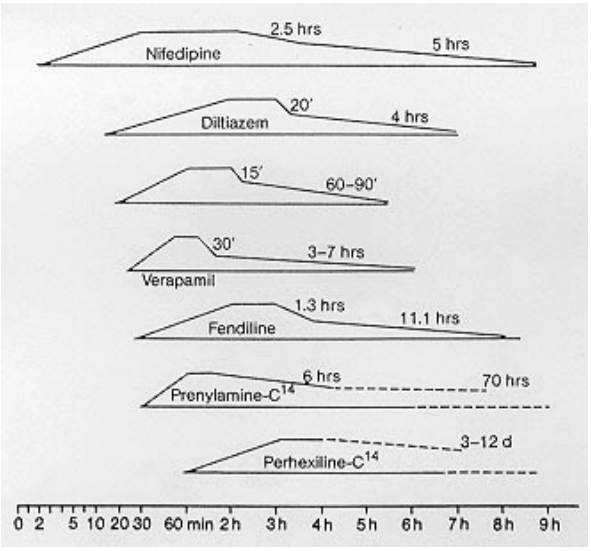

Fig.1 - Kinetics of Ca++ antagonists (s.l.-oral).

Plasma levels of nifedipine are measurable 2-3 minutes after sublingual administration, clinical effects are relevant after 5 minutes 29. After oral administration the plasma-levels are measurable 10-15 minutes later, depending on when the capsule opens.

Peaks are ranging from 50-180 µg/l. However, there are no significant differences in plasma levels after the oral or sublingual administration of nifedipine.

In hypertensive patients the blood pressure tends to agree with the course of plasma level. However, a statistically significant drop in blood pressure is only detectable for a period of up to approximately 4 hours after a single dose, when using the capsule, although the plasma levels are detectable for considerably longer.

Clinical differences

I want to focus mow more on the clinical differences of the 3 most important substances and, in addition, on newer results of clinical findings about nifedipine.

Table V summarizes effects of verapamil This agent clearly has anti-arrhvthmic and negative inotropic properties [30]. The effects, in particular the electrophysiological effect, starting approximately 2 hours after an oral dose and lasting for several hours.

The hemodynamics show less pronounced effects on total peripheral resistance and marked influences on myocardial contractility, on sinus-node and on AV-node. This is of clinical relevance

Higher oral doses have effects in angina at rest, variant angina and effort angina.

With regard to the anti-hypertensive, effect of verapamil the ix route is recommended for hypertensive crisis. However, after approximately 1 hour the diastolic pressure has returned to the initial value [31,32].

TABLE V - Ca ++-Antagonists - clinical efficacy.

VERAPAMIL	
Eff. dose: 240-320-480 mg daily 5-10 mg i.v.	
Onset 2 hrs Duration > 5 hrs [2 min. > 15 min.]	
Hemodynamics: TPR (↓) AOP ↓ POSTSTFL (↑) GLOBFL (↑)	
SV ↓↑ HR(↓)VRET?	
PAP ↑ PCP ↑ LVEDP ↑ LVVOL ↑ VPOOL?	
Contract. ↓↓ Sinus-node ↓ AV-node ↓↓	
Angina at rest/Variant	Effective
Stable Angina/Effort	Effective
Unstable Angina	?
Antihypertensive e.	Possibly
Antiarrhythmic e.	Effective
Cardioprot/Cardiopl.	Possibly
Acute myoc. inf.	Effective
Heart failure	Contraindication
HOCM	Effective
Main effect:	Antiarrhythmic (supraventricular), negativ inotrop
Main side effects:	Bradycardia (Sick-Sinus Syndrom), AV Prolongation Constipation

In chronic oral therapy, the anti-hypertensive effect of 320 or 640 mg daily over a period of 6 weeks appears to be only slightly pronounced[33]. In the treatment of hypertrophic cardiomyopathy is verapamil of value. Therefore, one can consider as main effects of verapamil anti-arrhythmic properties, especially against supra-ventricular arrhythmies and re-entrytachycardia, and negative inotropic effects.

In patients with and without sinus-node disfunction marked differences between the two groups were observed[34]. Patients having normal sinus-node recovery periods showed only a slight and insignificant prolongation of the corrected sinus-node recovery time.

In contrast, the patients with sinus-node dysfunction showed a very different effect under the influence of verapamil. The corrected sinus-node recovery tine increased in 11 of 16 patients and in it became critical (fig 2).

The onset of the hemodynamic effect of diltiazem after an oral dose of 30 to 90 sets in after approximately 30 minutes This effect is maintained in most cases for approximately 3 hours [35]. However, in angina at rest the effect could last longer (table VI).

Hemodynamics in most cases show a drop in. heart rate, a slight reduction in stroke work index in peripheral resistance and in blood pressure and a slight increase in global coronary circulation.

The onset of the negative chronotropic effect is significantly delayed compared with the reduction in the afterload [36]. No negative inotropic effect was observed.

A few controlled clinical studies have been carried out according to literature. The number of patients in each is small: the effective doses required

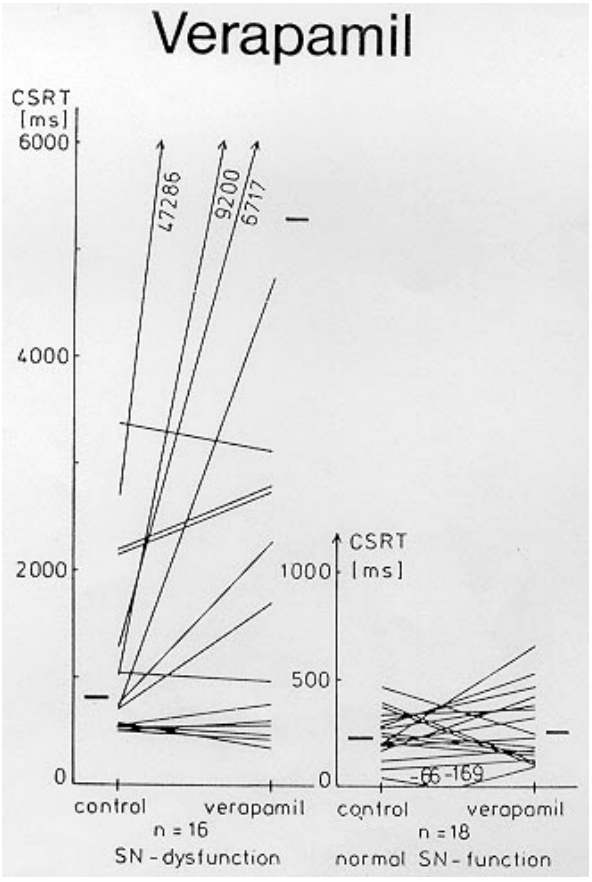

Fig.2 - Sinus node recovery time corrected for heart rate (CSRT) before and after veparamil administration (0.1 mg/Kg IV) in patients with and without clinical signs of sinus node disfunction (from Seipel et al, 1980).

to reduce the number of anginal attacks are between 120 and 480 mg per day. A period of 7 to 14 days is required to achieve effects [37].

Diltiazem also appears to be effective in the variant form of angina pectoris The daily dose varies between 240 and 480 mg [38-40].

A whole series of investigators showed the efficacy of nifedipine in variant angina, the so-called "Prinzmetal angina" [41-44] and even in refractory cases [44-51], as it will be discussed later on.

Numerous controlled and double blind studies have been carried out in stable angina, demonstrating the efficacy of nifedipine. But besides from the clear effects in stable and unstable angina pectoris as well, there are additional effects of nifedipine, of interest (table VII).

Through a reduction of smooth muscle tone the peripheral resistance decreases significantly and therefore the peripheral resistance decreases significantly and therefore the peripheral blood pressure falls to different extends depending on initial values. In normotensive patients slightly [52-54] and in hypertensive patients to a therapeutically relevant extent. Thus

TABLE VI - Ca $^{++}$ - antagonists - clinical efficacy.

DILTIAZEM	
Eff. dose: 30 - 90 mg	120 - 480 mg/daily 10 mg/i.v.
onset: 30 min	Duration: 3 hours
Hemodynamics: TPR (↓)	AOP (↑) r
SV (↑)	HR ↑
PAP (↓)	PAP =
Contract? Sinus node (?)	AV-node?
Angina at rest/variant :	240 - 480 mg/daily
Stable angina/effort:	effective (90 mg = 0,3 mg NTG)
Unstable angina:	unknown
Antihypertenisve e. :	possibly
Anti-arrhythmic e. :	Possibly
Cardioprot/cardioplegic:	(possibly)
Acute myoc. inf.:	unknown
Heart failure:	unknown
HOCM:	unknown
Main effect:	coronary dilation? Reduction of heart rate?
Main side effect:	Dizziness, asthenia, bradycardia

TABLE VII – Ca $^{++}$ antagonists - clinical efficacy.

NIFEDIPINE	
Eff. dose: 5/10/20 mg 30-60 mg daily (- 120 mg) 1 mg iv.	
Onset 2-3 min s. I- Duration 6-7 hours (11 hrs)	
Hemodynamics: TPR ↓↓ AOP ↓ POSTSTFL ↑	
SV ↑HR (↑) VRET ↑	
PAP ↓ (L) PCP ↓ (L) LVEDP ↓ (L) VPOOL =	
↓↑ Sinus-node AV-node	
Angina at rest/variant	Very effective
Stable angina/effort	Effective
Unstable angina	Effective
Anti hypertensive e.	Effective
Antiarrhythmic e.	None?
Card iprot-/Card iopleg ic	Effective
Acute myoc. inf.	Possibly
Heart failure	Possibly
HOCM	Possibly
Chron. Airw. Obstr. (Bronch. Asthma)	Possibly
Morbus Raynaud	Possibly
Main effect : Antianginal effect (afterload + antiischemic)	
Main side ef.: Flush, headache	

nifedipine shows clear anti-hypertensive properties both in acute [55-59] and in long-term trials [60].

The cardioprotective effect of nifedipine as an additive in cardioplegic solution recently was reported [6l,62]. In open heart surgery a large group of approximately 100 patients, most of them risk cases were treated by nifedipine. It was found that the incident of severe myocardial post-ischemic injury, resulting in either hospital death or survival, after intensive treatment was 29% for the group receiving cardioplegia alone and only 20% for the group receiving nifedipine cardioplegia.

Figure 3 published by Clark, St Louis [63] and coworkers shows the influences of nifedipine during

heart surgery. As one can see, the substance increases left ventricular performance over a period of 48 hours.

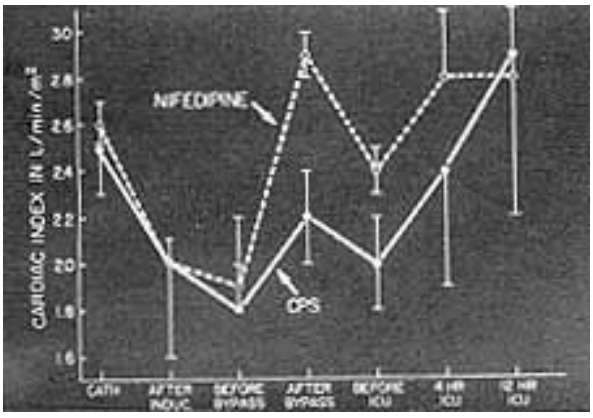

Fig.3

As seen in figure4, CK-MB values were significantly lower in the nifedipine - treated group, compared with cardioplegia alone. This also reflects in a better myocardial state due to reduced ischemia.

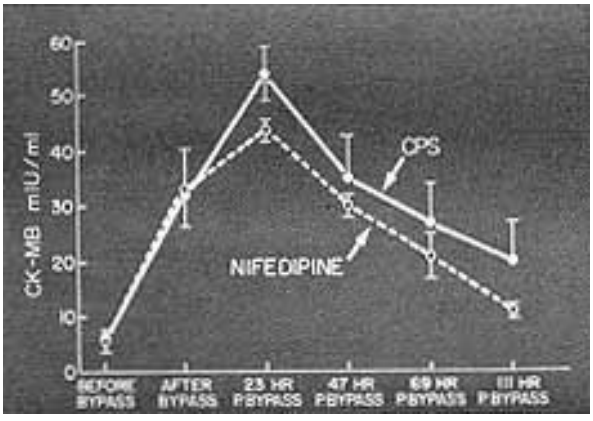

Fig.4

Experiences in acute myocardial infarctions and in heart failure without hypertension are small,and have to be continued.

Recently, an inhibition of hypoxic, pulmonary vasoconstriction by nifedipine was published. Thirteen patients with acute respiratory failure were studied within 48 hours of their admission to the respiratory care unit (fig 5).

One hour after administration of oral nifedipine, pulmonary arterial pressure had fallen from 38 to 31 mmHg and the driving pressures had fallen in every patient significantly. Because of the fall in pulmonary vascular resistance there was an increase in cardiac output in an average of 46 litres per minute.

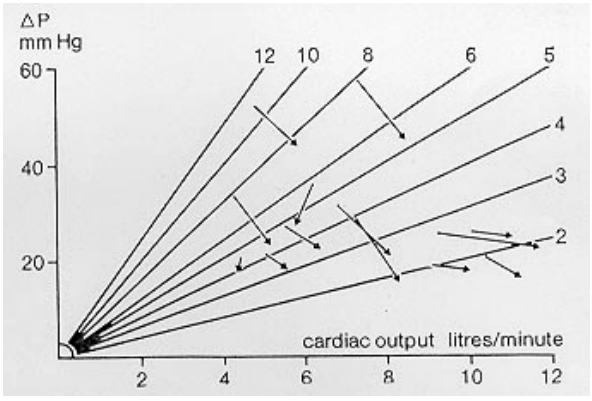

Fig.5 - Changes in pulmonary vascular resistance in response to nifedipine in 13 patients with acute respiratory failure. From Sinoneau et al, New England Journal of Medicine, June 25th, 1981.

It could be demonstrated, that the more severe the hypoxic vaso-constriction, the greater the effect of nifedipine on the pulmonary circulation.

May I say some additional words to contra-indications, precautions on use and main side-effects of calcium antagonists.

Contra indications for verapamil are: AV-block, sick-sinus syndrome, cardiogenic shock, complicated myocardial infarction and cardiac insufficiency.

Contra-indications for diltiazem and nifedipine are pregnancy (table VIII).

Precautions on use: in the case of verapamil, in particular of the using the i-v route, it should riot be combined with P-blockers or anti-arrhythmic agents, because it may cause intensified conduction disturbances. Nifedipine, however, in combination with 9-blockers could intensify the decrease in blood pressure, but usually a beneficial effect was observed. I will discuss this more in detail in my second presentation.

Patients suffering from sick-sinus syndrome or AV-block are automatically excluded from the combination β-blocker and nifedipine because of the contra-indication for the P-blocker (table IX).

Side effects (table X): The main side effects of calcium antagonists are vascular ones, i e. vasodilation.

In the case of verapamil and diltiazem. possible side effects are AV-block, asystoly and bradycardia These are relatively rare The possibility of such side-effects is increased in combination with digoxin or ß-blockade.

Nifedipine differs in this respect. Most observed side effects are headache, flush, dizziness and sometimes edema of the legs and in very rare cases, retrosternal pains.

In conclusion: calcium antagonists are a new approach to the therapy of angina pectoris especially. We can differentiate in principle between three types of agents, from the clinical point of view.

TABLE VIII – Ca $^{++}$ - antagonists contraindications.

	AV-Block Sick-Sinus-S.	Card. Shock Compl. A-M-I.	Heart Failure	Severe Hypotension	Liver-Renal-Dys.	Pregnancy
Verapamil	•	•	•			
Prenylamine	•	•				
Perhexiline					•	
Diltiazem						•
Nifedipine						•

TABLE IX - Ca $^{++}$ -antagonists precautions.

	AV-Cond. System Disturbances With		Hypotension if comb. With			Provoke Tachyar. with Salur.	Intensify Sedatives	Delayed Reactiv.	Estim. of Liver-Enz. under Long-T-T.	A.M.I.
	β-BL	Antiarrh	β-BL	Antihyp.	MAO					
Prenylamine	•	•	•	•	•	•	•			
Verapamil	•	•	•							
Nifedipine			•	•						
Pendiline			•							
Perhexiline								•	•	

TABLE X - Ca $^{++}$-antagonists side-effects.

	Vascular	Gastrointestinal	Central	Conductive-System	Peripheral Nervous System	Others
Perhex.	Dizziness Headache Collapse	Vomiting Liver-dist.			Paresthesia	Loss of weight Dist. of potency
Verap.	Hypotension Plush	Constipation		AV-Block Asystole		
Diltia.	Dizziness Hypotension PMush Heaftche	Disorders		Bradycardya AV-Block		
Nifed.	Headache Flush Dizziness Oed/Legs Retrost. Pains	Nausea	Tiredness			
Fendil Prenyl.	Headache	Vomiting	 Sedation			Restlessness, HypoykaMernia

Type 1 has predominantly effects on peripheral arteries and is therefore also effective on the coronary arteries, this results in a reduction in the afterload and in an increase in coronary flow. It seems, that there is a direct myocardial, anti-ischemic effect and no significant influence on conduction system or on the venous system. Most of dihydroperidines belonging to this type.

Type 2 has predominantly electrophysiological effects, i e a slowing down of the sinus-node, a prolongation of AV conduction tine and therefore owing anti-arrhythmic properties. On the other hand a small reduction in arterial resistance occurs or is completely absent, in most cases this type consists of small or negligible negative inotropic effects. Verapamil, diltiazem, perhexiline are belonging to this group.

Type 3 is predominantly effective on peripheral venoles and capacitance vessels, causing a reduction in preload, a so-called “venous pooling” and having no significant effect on arterial tone or conduction system. Fendiline belongs to this group.

REFERENCES

1. Fleckenstein, A. - Steuereung der myocardialen Kontraktilitat, ATP-Spaltung, Atmungsintensitat und Schrittmacher-Funktion durch Calcium-Ionen - Wirkungsmechanismus der Calcium-Antagonisten. In Fleckenstein, A.; Roskamm, H. -Cilciumantagonismus. Springer-Verlag, Berlin, Heidelberg, New York, 1980. p. 1.
2. Späh, F.; Fleckenstein, A. - Nachweis einer strengen quantitativen Korrelation swischen Hemmung des transmembranären Calcium-Influx und der mechanischen Spannungsentwicklung des Myocards unter dem Einflu β verschiedener Calciumantagonistein. In Fleckenstein, A.; Roskamm, H- - Calciurnantagonistein Springer Verlag, Berlin, Heidelberg, New York 1980 p 29.
3. Taira, N. et al - The effect of calcium-antagonists on atrio ventricular conduction. In Fleckenstein, A.; Roskamm, H.-

Calciumatagonismus. Springer-Verlag, Berlin, Heidelberg, New York, 1980. P. 42.
4. Adelstein, R. S.; Hathaway, D. R. - Role of calcium and cyclic adenosine 3':5'monophosphate in regulating muscle contraction. Am. J. Cardiol. 4: 783, 1972.
5. Schonz, H - Physiologische und pharmakologische Grandlagen der Therapie mit sogenannten Calcium-Antagonisten. Deutsch. Arzteball, 7: 381, 1980.
6. Antman, E. M. et al - Calcium channel blocking agents in the treatment of cardiovascular disorders. Basic and clinical electrophysiologic effects. Ann. Intern. Med. 93: 875.1980.
7. Stone, D. H. et al - Hemodynamic effects and clinical an applications of the calcium channel blocking agents. Ann. Intern. Med. 93: 886, 1980.
8. Schomerus, M.; Spiegenhalder B.; Stieren, B.; Eichelbaum, M. - Physiological disposition of verapamil in man. Cardiovasc. Res. 10: 605, 1976.
9. Kohno, K.; Tabeuchi, Y.; Etoh, A.; Node, K. - Pharmakinetcis and bioavailability of diltiazem (CRD-401) in dog. Drug Res. 27 (11): 1424 1977.
10. Vater et al - Zur Pharmakologie von 4-(2'-Nitrophenyl)-26dinethyM-14-dibydropyridin-3,5-dicarbonsäuredinethyles (Nifedipin) BAY a 1040). Arzneim. Forsch- (Drug Res.) 22: 1 n972.
11. Schmidt, H- A. E.; 1-idussMer, A-; Hoffmann W. - Resorption, Verteilung und Ausscheidung von 14C-markiertem N-(3'-prenylpropyl-(2')-1,1-diphnyl-propyl-(3)-amin(lactat)- Drug Res. 13: 173, 1963.
12. Raemsch, X. - Adalat- II Mediterranean Symposium, Madrid, 1980.
13. Leeson, G- A-; Lang, J- P-; Zeiger, A- V-; Hudak, W. J; Wright, G- J. - Excretion, blood levels and tissue retention of perhexiline-14 C maleate in dogs. Pharmacologist, 11: 280 1969.
14. Kaltenbach, M.; Kober, G-; Schulz, W.; Becker H. I.; Werner, R-; Hopf, R. - Antianginal activity of calciuminhibitive drugs on isosorbid-dinitrate coronary heart disease. In Kaltenbach et al - 3rd Int. Symp. Ff. Thieme Stuttgart 1978. p. 301.
15. Livesley, B.; Catley P. P.; Campbell, R. C.; Dram, S - Double blind evaluation of verapamil, propranolol and isosorbide dinitrate against a placebo in the treatment of angina pectoris- Br- Med. J. 17: 375, 1973.
16. Maseri, A.; Severi, S.; Parodi, O:; Distante, A.; Biagini, A. - Application of calcium-antagonists in patients with vasospastic angina pectoris. In Fleckenstein, A.; Roskamm, H. - calciumantagonismus Springer-Verlag, Berlin Heidelberg New York, 1980 p. 243.
17. Spies, H. F.; Schulz, W.; Werner, H.; Appel, E.: Becker, H. J.; Kaltenbach, M. - Einflu β der Calcium-antagonisten Verapamil, Nifedipin und Fendilin auf Blutdruck und Hersfrequenz. In Fleckenstein, A-; Roskamm H. Calciumantagonismus- Springer Verlag, Berlin, Heidelberg, New York, 1980. p. 252.
18. Eichelbaum, M. - Clinical Pharmacokinetics of Cacium Antagonists. International Conference on Calcium Antagonists in Cardiovascular Disease, Toronto, 1979.
19. Woodcock, B. G.; Kirsten R.; Rietbrock, I. Nelson K.; Vohringer, N. F.; Zilly, W. - Verapamil plasma concentration after a single dose in normal subjects and in patients with liver disease 85. Tag d. Dtsch. Ges. F. Innere Medizin, Wiesbaden, 1979.
20. Wright, G. J.; Leeson, G. N.; Zeiger, A. V.; Lang, J. F. - The absorption, excretion and metabolism of perhexiline maleate by the human. Postgr. Med. J. 49 (suppl. 3): 8. 1973.
21. Schlossmann, K.; Medenwald, H-; Rosenkranz, H. - Investigations on the metabolism and protein binding of nifedipine. In Lochner, W et al - 2nd Int. Adalat Symposium,. Springer Verlag, Berlin, Heidelberg New York, 1975. p. 33.
22. Dengler, H. J.; Eichelbaum, M.; Schomerus, M. - Pharmacokinetics of prenylamine in man. Clinico-pharmacological and therapeutical aspects of prenylamine, 26: 1970.
23. Eichelbaum, M Ende, M.; Remberg, G.; Schomerus. M; Dengler, H. J. - The metabolism of DL-(14C)-Verapamil in man Drug Metab Dispos 7: 145, 1979.
24. Takahashi, T.; Kimura, T; Meshi, T.; Sato, Y. -Studies on the distribution of radioisotopes by whole body autoradiography. 1. Fate of 14-fluocinonone acetonide in mice. Chem Pharm. Bull. 19: 1971.
25. Benthe, H F; Thieme, R. - Metabolism of D-L-fendiline in man- Arch- Pharmacol. 308, R 21/1979.
26. Horster, F. A.; Patzschke K.; Wegner, L. A.; Wildmeister W. Zur - Resorption und Elimination von Adalat bei oraler und sublingualer Applikation- Munch- Med. Wochschr. 119 (suppl. 1): 98, 1977.
27. Eichelbaum, M; Birgel, P; Güntgemann U. von Uruk, YE. - Simultaneous determination of the kinetic parameters of D-L-verapamil following combined i-v- and oral administration using stable labelled techniques. Nauuyn Schimiedebergs. Arch- Exp. Path- Pharmakol. 307 (suppl. R): 71, 1979.
28. Henkeles U.; Blümchen G.; Ebner, F. - Zur Problematik von Belastungsprufungen in Abh1ingigkeit von der Tageszeit bei Patienten mit Konorarinsuffizienz Herz Kreislauf 9: 343 1977.
29. Wick, W.; Strödter, D. - Die Angina pectoris - Schwelle vor und nach Nifedipin (Adalat R). Munch. Med. wschr. 119 (suppl. 1): S 53, 1977.
30. Krikler, D. - Verapamil in cardiology. Eur. J. Cardiol. 2: 3 1974.
31. Brittinger, W. D.; Schwarzbeck, A.; Wittenmeier K. W.; Twillenhoff, W. D; Stegaru B.; Huber, W.; Ewand R. W.: Heining, G.; Fabricius, M.; Strauch, M. - Klinisch-experinentelle Untersuchungen uber die blutdrucksenkende Wirkung von Verapamil. Dtsch. Med. Wschr. 95: 1871, 1970.
32. Bender, F- - Die Behandlung der tachycarden Arrhythmien und der arteriellen Hypertonie mit Verapamil- Arzneim. Forrsch/ Drug Res. 9: 1310, 1970.
33. Lederballe Pedersen O. - Does verapamil have a clinically significant antihypertensive effect? Eur. J. Clin. Pharmacol. 13: 21 1978.
34. Seipel, L.; Breithardt V. G. - Effects of calcium antagonists on automaticity and conduction in man. In Fleckenstein, A.: Roskamm, H. - Calciumantagonismus. Springer Verlag Berlin, Heidelberg New York 1980. p. 85.
35. Theroux, P.; Debaisieux J. C.; Waters, D. D.; Bour, Mizgala H. F. - Effects hemodynamiques des antagonistes calciques dans l'infarctus aigu du myocarde. Eur. Congr. Cardion. Paris, 1980. p. 220.
36. Tubau J. F.; Cóte, P.; Bourassa, M. G. - Systemic and coronary hemodynamic effects of intravenous diltiazem in patients with coronary artery disease. Am J. Cardiol. 45: 439 1980.
37. Nakamurua, M.; Koiwaya, Y.; Mitsutake A.; Takeshita A. - Effects of diltiazem on angina pectoris. Eur. Congr. Cardiol. Paris, 1980. p- 111.
38. Rosenthal, S.; Ginsburg, R.; Lamb, I.; Baim, D.; Schroeder. J. - Efficacy of diltiazem in variant angina. Am. J. Cardiol. 45: 439, 1980.
39. Yasue, H.; Omote, S.; Takizawa, A. :Nagao M.; Miwa, K. Tenaka S. - Exertional angina pectoris caused by coronary arterial spasm: effect of various drugs. Am. J. Cardiol. 43: 647, 1979.
40. Waters D.: Theroux, P.; Dauwe, F.; Crittin, J.; Affaki, G.: Mizgala, H - Ergonovine testing to assess the effects of calcium antagonist drug in variant angina. Circulation 59-60 (suppl. II): 248, 1979.
41. Endo, M. et al - Prinzmetal's variant form of angina pectoris. Re-evaluation of mechanisms. Circulation, 52: 33, 1975.
42. Mizuno, K.; Tanaka, K.; Honda, Y.; Kimura, E. - Suppression of repeatedly occurring ventricular fibrillation with nifedipine in variant form of angina pectoris Jap. Heart i18: 736, 1977.
43. Kishida, H. - Application of calcium antagonists in patients with Prinzmetal angina pectoris. In Fleckenstein, A.; Roskamm, H. - Calciumantagonismus. Springer-Verlag, Berlin. Heidelberg, New York 1980. p. 246.
44. Heupler, A- F.; Proudfit, W. L. - Nifedipine therapy for refractory coronary arterial spasm. Am. J. Cardiol. 44: 798, 1979.

45. Gredberg, S.; Reichek, N.; Wilson, J.; Hirsfeld, J W.; Muller, J.; Kastor, A. J. - Nifedipine in the treatment of Prinzmetal's variant angina. Am. J. Cardiol. 44: 804, 1979.
46. Moses, J.; Feldman, J. S.; Helfant, H. - Efficacy of nifedipine In the intermediate syndrome refractory to propranolol and nitrate therapy Am. J. Cardiol. 45: 390, 1980.
47. Antman, E.; Muller, J.; Gondberg, S.; Mae Alpin, R.; Rubinfire, M.; Tabekznik, B.; Liang, C.; Heupler, F.; Achoff, S.; Reichek N.; Geltman, E.; Kerin, N.; Neff, R.; Braunwand E. - Nifedipine therapy for coronary artery spasm. N. Engl. J. Med. 302: 1269, 1980.
48. Bertrand, M. E.; Lablanche, J. M.; Tilmant, P. - The treatment of coronary arterial spasm with nifedipine. Eur. Congr. Cardiol. Paris, 1980. P. 91.
49. Serruys P. W. et al - Effect of nifedipine on regional ventricular shortening during pacing after coronary artery bypass grafting. In Lichtlen et al. - Adalat Panel Discussion, Tokio. Excerpts Medica Amsterdam, Oxford, n979. p. 3n
50. Rousseau, M. F.; Pouleurs, H.; Detry, J. M. R.; Brasseur,A. L. - Increased sentitivity of left ventricular relaxation to inotropic interventions in patients with coronary artery disease: Comparison with normal subjects, mitral stenosis and asymetric septal hypertrophy- Eur. Heart 3- 1 (suppl B): 37, 1980.
51. Kaltenbach, M.; Schulz, W.; Kober, G. - Effects of nifedipine after intravenous and intracoronary administration. Am. Cardiol. 4: 832, 1979.
52. Aoki, K et al - Antihypertensive effect of cardiovascular Ca++ antagonist in hypertensive patients in the absence and presence of 8-adrenergic blockade. Am. Heart J. 96: 218, 1978.
53. Aoki, K. - Uber die Wirkung eines Calcium-Antagonisten (Nifedipin) bei Normo - und Hypertension Schwerpunkt-Medizin (SM.) 4: 72, 1979.
54. Nicita-Mauro, V; Barbera, N.; Savica, V; Frasini, N.; Ceruso, D - Influenza di un chalcio-antagonista, la nifedipina, sula pressione arteriosa. Considerazioni. Bonl. Soc. Ital. Cardiol. 23: 389, 1978.
55. Lederballe, P. O.; Mikkelsen, E.; Christensen, N. J.; Komerup, H. J.; Pedersen, E. B. - Effect of nifedipine on plasma renin, aldosterone and catecholamines in arterial hypertension. Eur. J. Clin. Pharmacol. 15: 235, 1979.
56. Olivari M. T.; Bartorelli, C.; Polese, A-; Fiorentini, C.; Moruzzi, P.; Guazzi, M. - Treatment of hypertension with nifedipine, acalcium antagonistic agent. Circulation, 59: 1056 1979.
57. Aoki, X.; Yoshida, T.; Kato, S.; Tazumi, K.; Sato, I.; Takikawa, K.; Honta, X. - Hypotensive action and increased plasma renin activity by Ca++-antagonist (nifedipine) in hypertensive patients. Jap. Heart J- 17: 479, 1976.
58. Varrichio, M.; Cacciaprioti, F.; Russo, R.; Giunta, R.; Verza, M.; Grandiollo, F. - Valutazioni dei parametri emodinamici dopo somministrazione di nifedipina nei soggetti ipertesi Min. Cardioang. 27: 1, 1979.
59. Capro, L.; Saviano, R.; Violini, R.; Luciano, R.; Bellotti, P.; Cuomo, S.; Spinelli, L.; Rengo, F. - La nifedipina nella cardiopatia ipertensiva; effetti delela somministrazione sublinguale sulla funzine ventriculare sinistra. Progres. Med. 35: 1, 1979.
60. Lederballe, O. P.; Mikkelsen, E. - Acute and chronic effects of nifedipine in arterial hypertension. Eur. J. Clin. Pharmac. 14: 375, 1978.
61. Tschirkov, A.; Just, H.; Dragoitscher, Tsch. - Pharmacological cardioplegia and myocardial protection in hypothermia with nifedipine. Comparison with procain-magnesium cardioplegia. In Druck.
62. Christlien, I - Cardioprotective effects of Ca++-antagonists-Int. Sympos on "New Aspects of Unstable Angina", Hannover, 1980.
63. Clark R. E.; Fereguson, T. B.; West, Ph, N.; Shuchleib, R C.; Henry, Ph. D - Pharmacological preservation of the ischemic heart. Ann. Thorac. Surg. 24: 307, 1977.