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Equal anti-ischemic properties of isosorbide dinitrate plus verapamil and isosorbide dinitrate plus propranolol
A randomized, double-blind and crossover study

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Zusammenfassung: Obwohl Nitrate die Basistherapie der ischämischen Herzerkrankung darstellen und zahlreiche Kombinationen mit Betablockern und/oder Kalziumantagonisten klinisch untersucht wurden, ist keine Studie bekannt, die intraindividuell die Kombinationen Nitrat plus Betablocker mit Nitrat plus herzfrequenzsenkendem Kalziumantagonist verglichen hat. Aus diesem Grunde prüften wir in einer randomisiert, doppelblind und crossover durchgeführten Studie die Wirksamkeit von 80 mg retardiertem Isosorbid dinitrat (ISDN, 1 × täglich) plus 120mg Verapamil (3 × täglich) im Vergleich zu 80 mg ISDN plus 80 mg Propranolol (2 × täglich). Im Anschluß an diese jeweils 3wöchigen Phasen erhielten die Patienten einfachblind die Kombination aller drei Substanzen in unveränderter Dosierung. Neben den üblichen Standard-Einschlußkriterien wurde zusätzlich ein nach ISDN immer noch pathologisches Belastungs-EKG sowie eine linksventrikuläre Auswurffraktion (EF) von ≥ 35% vorausgesetzt. Insgesamt konnnte dieses Protokoll bei 26 der 30 eingeschleusten Patienten abgeschlossen werden. Die Kombination ISDN plus Verapamil zeigte die gleiche antiischämische Wirkung wie die Kombination ISDN plus Propranolol. Die Dreierkombination führte zu einer weiteren Steigerung des antiischämischen Effektes ohne Verschlechterung der EF in Ruhe oder während Belastung. Wenn auch erst mit dieser Dreierkombination bei rund einem Drittel der Patienten eine optimale antiischämische Einstellung zu erzielen war, so sollte sie doch vorsichtig eingeleitet werden, da in Einzelfällen mit dem Auftreten symptomatischer Bradykardien zu rechnen ist.

Summary: Although nitrates are the basic treatment for patients with ischemic heart disease and numerous clinical studies have compared the anti-ischemic effects of different combinations with beta-blockers and/or calcium antagonists, no study is known on a controlled intraindividual comparison of the combination nitrate plus beta-blocker with the combination nitrate plus a heart rate-decreasing calcium-antagonist. Therefore we performed a randomized, double-blind and crossover study to compare the effects of 80 mg isosorbide dinitrate in slow-release form (ISDN, once-daily) plus 120 mg verapamil (t.i.d.) with those of 80 mg ISDN plus 80 mg propranolol (b.i.d.). After these two phases of 3 weeks' duration respectively, patients received the combination of all three drugs with the same dosages in a single-blind manner. In addition to the standard inclusion criteria, a pathological exercise-ECG even after ISDN was required as well as a left ventricular ejection fraction (EF) of ≥ 35%. This protocol could be completed in 26 of the 30 enrolled patients. The combination ISDN plus verapamil proved to exert the same anti-ischemic effects as the combination ISDN plus propranolol. The triple therapy showed a further improvement of exercise-induced ischemia without deterioration of the EF at rest or during exercise. Even though only this triple therapy led to an optimal anti-ischemic result in about one third of the patients, it should be initiated cautiously, since symptomatic bradycardia may occur.

Nitrates are the basic treatment in the long-term prophylaxis of myocardial ischemia in patients with coronary artery disease. Numerous clinical studies compared the anti-ischemic effects of nitrates with those of beta-blockers and calcium-antagonists as well as several combinations (1-6, 9, 11, 12, 14-23, 25, 26, 28, 30, 31, 34, 40-42, 45-47). However, there is no literature reporting a controlled intraindividual comparison of the combination nitrate plus beta-

blocker with the combination nitrate plus a heart rate-decreasing calcium-antagonist. Since these two dual combinations are frequently used in practice, we compared the anti-ischemic properties of isosorbide dinitrate (as the traditionally accepted oral nitrate) plus verapamil (as the standard heart rate-decreasing calcium-antagonist) with those of isosorbide dinitrate plus propranolol (the standard beta-blocker) according to a randomized, double-blind and crossover protocol.

Patients and methods

The criteria for enrolment were based on angiographically proven coronary artery disease ($\geq 75\%$ stenosis of at least one of the three major coronary arteries), left ventricular ejection fraction $\geq 35\%$ in the contrast biplane ventriculogram, a history of stable, exercise-dependent angina pectoris and a reproducible exercise-induced ST-segment depression of ≥ 0.1 mV (≥ 1 mm) 2 hours after the ingestion of an 80 mg tablet of isosorbide dinitrate (ISDN). Patients with inconclusive exercise ECGs (e.g. resting ST-abnormalities, bundle-branch block, digitalis etc.) and those with complex and/or frequent arrhythmias, AV-blocks or a heart rate < 50 bpm during the washout phase were excluded.

The following dosages were administered: ISDN in 80 mg tablets slow release form[1] once-daily at 8 a.m. (36), verapamil in non-sustained release form[2] 3×120 mg/d (2, 3, 22, 33) and propranolol in non-sustained release form[3] 2×80 mg/d (8 a.m. and 8 p.m.). After a washout-period of 4 days (i.e. discontinuation of all anti-ischemic medication with only sublingual nitroglycerin allowed) the 2 dual combinations were compared according to a randomized, double-blind and crossover protocol (Fig. 1) in a double-dummy technique. Then the triple combination was assessed in a single-blind manner (Fig. 1). After a treatment period of 3 weeks each respectively, the effects of the different drug combinations were tested 2 hours after the ingestion (Fig. 1). The triple combination was initialized in-hospital in order to survey possibly induced conduction disturbances. Patients' compliance was assessed by actual tablet counts as well as by diaries.

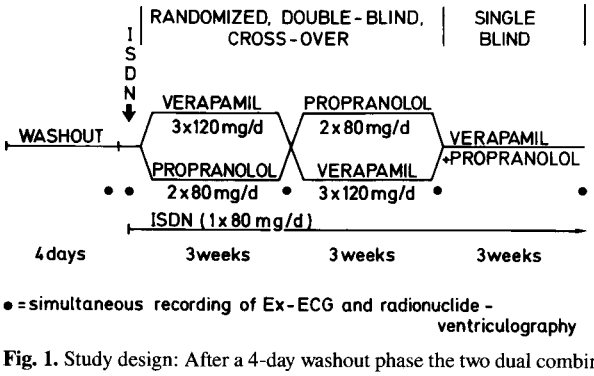

Fig. 1. Study design: After a 4-day washout phase the two dual combinations were administered according to a randomized, double-blind and crossover protocol. The triple therapy was assessed single-blindly. The duration of each phase was 3 weeks. Exercise-ECG and radionuclide ventriculography were recorded simultaneously.

[1] Isoket retard 80, Schwarz
[2] Isoptin 120, Knoll
[3] Dociton 80, ICI

Exercise tests were performed on a bicycle in semi-supine position with the legs below heart level. Depending on the individual exercise capacity (as derived from previous stress tests), exercise was started with 50 or 80 watts and, if possible, increased by 30 watts every 3 minutes. The end-point of the control exercise test, i.e. following the washout period, was defined as angina pectoris associated with ST-segment depression of ≥ 1.5 mm. The subsequent exercise tests were performed until this individual work load had been reached. The 12-lead ECG was documented with a chart speed of 50 mm/sec at 1 1/2 and 2 1/2 minutes of each work load. ST-segment depression was measured 80 ms after the J-point in the precordial lead with maximal ST-depression during the control exercise test. Blood pressures were measured automatically by an oscillometric method.

Radionuclide ventriculography was performed at rest and simultaneously with the ECG during exercise. After standard stannous in vivo labeling of the red blood cells with approximately 25 mCi (925 MBq) technetium-99m, the data were acquired with a low-energy, all purpose collimator and an Anger gamma camera in a modified LAO position. The dedicated online computer was a MDS/A^2 system. Using the equilibrium multiple gated technique (MUGA), 21 frames per cardiac cycle were generated, rejecting each premature beat as well as the 2 postextrasystolic contractions. Ventriculograms were acquired for 6 minutes at rest and for the last 2 minutes of each exercise step. Left ventricular ejection fraction was calculated by the count-rate method applying a semi-automatic, clinically validated algorithm which defines the left ventricular edges frame by frame according to a second derivative method.

Initially 30 patients were enrolled. One patient dropped out because he refused to take drugs any longer. Three patients discontinued because of serious side-effects: 1 developed pulmonary edema while on isosorbide dinitrate plus propranolol (left ventricular ejection fraction and filling pressure were normal during previous cardiac catheterization) and 2 patients suffered from symptomatic sinus bradycardia within the first week on triple therapy. Thus the final results are based on 26 completed cases.

All exercise parameters were compared at maximal intra-individually identical work loads. Statistical analysis was performed by the 2-tailed Wilcoxon's test for matched pairs. Probabilities (p) were considered significant at the $p < 0.05$ level (*=$p < 0.05$; **=$p < 0.01$; ***=$p < 0.001$). The p-values were corrected using Bonferroni's adjustment. All data are expressed as mean $\pm$ one standard deviation.

Results

The compliance with respect to the ingestion of each individual tablet was 97%. There was no carry-over efffect for any parameter concerning the two double-blind phases.

Heart rate and blood pressure

At rest:

The heart rate at rest significantly increased after ISDN from 71 ± 11 bpm to 86 ± 14 bpm but did not differ from the control values when ISDN was combined with verapamil

(67 ± 10 bpm). The resting heart rate during the combination ISDN+ propranolol was significantly lower than the control values (56 ± 6 bpm). The triple combination did not further diminish the resting heart rate (53 ± 6 bpm).

The systolic blood pressure at rest was 138 ± 11 mm Hg during control conditions and significantly decreased after ISDN alone to 127 ± 12 mm Hg. Compared to the control values, both dual combinations significantly lowered the systolic blood pressure with 126 ± 9 mm Hg after ISDN+ verapamil and 124 ± 12 mm Hg after ISDN+propranolol. There was a slight further reduction of the systolic resting blood pressure to 118 ± 12 mm Hg during triple therapy. Diastolic blood pressures are listed in the same sequence: 85 ± 7, 85 ± 9, 79 ± 7, 77 ± 6 and 75 ± 7 mm Hg, showing statistical significance for all combinations.

The pressure-rate product (systolic blood pressure × heart rate, mm Hg/min) after ISDN was significantly increased (10 907 ± 1896) compared to its control values (9796 ± 1882), whereas ISDN plus verapamil significantly decreased this parameter to 8513 ± 1480. A further decrease was demonstrable during ISDN plus propranolol (6874 ± 716) as well as during triple therapy (6314 ± 974).

During exercise:

ISDN significantly increased the heart rate during exercise from 128 ± 20 bpm to 137 ± 19 bpm, whereas the 2 dual combinations led to significantly lower heart rates of 117 ± 16 bpm for ISDN+verapamil and 96 ± 12 bpm for ISDN+propranolol. The triple therapy did not additionally diminish the exercise heart rate (91 ± 13 bpm).

ISDN alone significantly decreased the systolic blood pressure during exercise from 175 ± 17 mm Hg to 166 ± 17 mm Hg. The corresponding values for the 2 dual combinations were 165 ± 16 mm Hg (ISDN+verapamil) and 159 ± 17 mm Hg (ISDN+propranolol). The mean systolic blood pressure during exercise on triple therapy was 147 ± 19 mm Hg. The diastolic blood pressures decreased from 105 ± 16 mm Hg to 95 ± 11 mm Hg (ISDN alone, signif.), 94 ± 13 mm Hg (ISDN+verapamil, signif.), 100 ± 14 mm Hg (ISDN+propranolol, not signif.) and 87 ± 13 mm Hg (triple therapy, signif.).

The initial pressure-rate product (mm Hg/min) of 22 406 ± 4678 remained unchanged after ISDN alone (22 756 ± 4237). In contrast, ISDN plus verapamil significantly reduced the product to 19 337 ± 3866, ISDN plus propranolol to 15 277 ± 2438 and the triple therapy to 13 432 ± 2811.

Left ventricular ejection fraction

At rest:

During resting control conditions left ventricular ejection fraction (EF) was 56 ± 10%. ISDN alone slightly but consistently induced a significant increase to 60 ± 9%. The additon of neither verapamil nor propranolol altered the EF (60 ± 12% vs. 59 ± 10% respectively). Even during triple therapy EF remained unchanged (57 ± 8%).

During exercise:

The initial EF of 53 ± 11% significantly increased after ISDN alone to 59 ± 14% (Fig. 2). The two dual combinations showed identical EFs with 59 ± 10% for ISDN+verapamil and 60 ± 10% for ISDN+propranolol. Neither did triple therapy lead to any deterioration of the EF (56 ± 10%, Fig. 2).

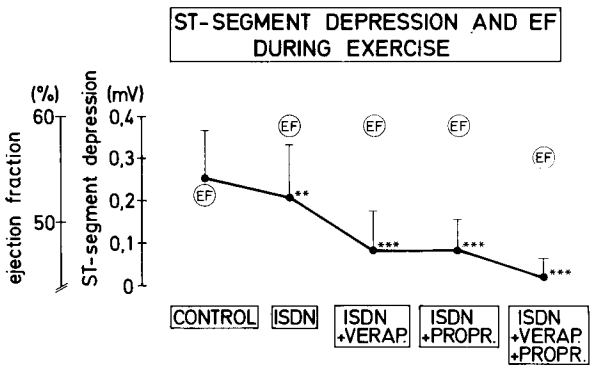

Fig. 2. Exercise-induced ST-segment depression (solid line) and mean left ventricular ejection fraction (EF) during exercise at individually identical work loads at control conditions, after isosorbide dinitrate alone (ISDN), ISDN plus verapamil (VERAP), ISDN plus propranolol (PROPR) and their triple combination. (For statistical significance see text).

ST-segment depression

With an initial exercise-induced ST-segment depression of 2.6 ± 1.1 mm, ISDN alone caused a mere reduction of ST-segment depression to 2.1 ± 1.2 mm (Fig. 2), keeping in mind that only patients with an abnormal exercise-ECG on ISDN were included. The two dual combinations (Fig. 2) equally caused a highly significant further reduction to 0.9 ± 0.9 mm (ISDN+verapamil) and 0.9 ± 0.7 mm (ISDN+propranolol). The triple therapy led to an additional anti-ischemic effect (0.2 ± 0.4).

Discussion

Nitrates are the anti-ischemic drugs with the longest history: they have been used sublingually for more than 100 years to curtail anginal attacks and orally for over 25 years as effective prophylactic agents. Nitrates offer several striking advantages: in contrast to beta-blockers and calcium-antagonists they reduce preload by venodilatation, which represents their major anti-ischemic mechanism in patients with exercise-inducible ischemia. Nitrates can be prescribed without reference to myocardial contractility, because they also improve hemodynamics in patients with congestive heart failure. The adverse reactions such as headache, nausea and hypotension are usually confined to the initial phase of therapy. Long-term treatment with nitrates has not been shown to cause any organic damage. Thus, nitrates seem to be the "ideal" anti-ischemic agents.

During the past few years, however, increasing evidence has been found that their anti-ischemic effects may become attenuated or even lost altogether during long-term therapy.

As we first showed in 1983, this problem can be circumvented by the once-daily administration of a relatively high single dosage (36). This new regimen was then proved by other groups (5, 27). Furthermore we could observe that even after a relatively high dosage (80 mg or 120 mg) of ISDN, several patients do still suffer from exercise-inducible ischemia, thus being inadequately treated with a nitrate monotherapy. These two reasons, i.e. no 24 hour protection with nitrates alone (36) and the possibility of a suboptimal nitrate response (18) make a combination therapy mandatory (if no contraindications exist) in order to assure an optimal anti-ischemic medication. Otherwise it would be necessary to check each patient with coronary artery disease for his individual degree of nitrate-response and possible spontaneous ischemic episodes by exercise- and Holter-ECGs (1, 2, 14, 23, 38).

Numerous clinical studies demonstrated that the anti-ischemic effects (walking time to angina) of verapamil alone (320 mg/d-480 mg/d) are comparable to those of propranolol alone (160-320 mg/d) (14, 16, 22, 34) or even superior to propranolol (1, 11, 21, 28). The combination verapamil plus propranolol usually was better than either drug alone (1, 21, 25, 28, 46). In our study it was necessary to select patients with insufficient nitrate response in order to be able to demonstrate differences between ISDN alone and the combinations. As the results show, the two combinations 80 mg ISDN plus 120 mg verapamil and 80 mg ISDN plus 80 mg propranolol reveal identical anti-ischemic properties. The triple therapy led to further anti-ischemic effects without deterioration of left ventricular ejection fraction (EF) at rest or during exercise in these patients with a control EF $\geq$ 35%. In the light of the above-mentioned studies one might comment that our results were as expected. However, previous studies assessing several anti-ischemic drugs revealed that the anti-anginal effects of the combinations were not necessarily better (4) or even worse (42) than those of their components.

Myocardial ischemia results from an imbalance between myocardial oxygen demand and blood supply. In the present study the pressure-rate product, as an index for the oxygen demand, was reduced by about 13% during exercise on ISDN plus verapamil as compared to the control values, whereas it was reduced by about 32% with ISDN plus propranolol. These results are consistent with the findings in other studies comparing verapamil and propranolol as monotherapy (11, 16, 21, 34). Actually, verapamil shows identical anti-ischemic potencies at higher pressure-rate products as compared to propranolol (1, 11, 15, 16, 21, 34). It is reasonable that other anti-ischemic mechanisms, like a decrease in heart rate and contractility, cannot explain this difference since they are less pronounced for verapamil. As a reduction of ventricular volumes can also be neglected, an additional anti-ischemic mechanism must be considered for verapamil: coronary vasodilatation with subsequent increase in myocardial blood flow. However, this is a matter of substantial controversy: Chew et al. (8) showed verapamil to cause a significant fall in stenosis flow resistance of 14% by an increase of the stenosed lumen cross-sectional area of 13%, suggesting stenosis dilatation as a contributing mechanism. On the other hand, experimental (43) and clinical (33) studies did not corroborate this mode of action, favouring the reduced oxygen demand as the principal mechanism for verapamil's beneficial effects (33). A recent investigation demonstrated that, although verapamil could not be classified as a direct epicardial coronary dilator, it acts by preventing the constriction of diseased coronary segments, induced by alpha-adrenergic and serotonergic receptor stimulation (7). This mechanism might explain some of the controversies and be considered in some forms of effort-induced ischemia (7) as well as for spontaneous changes of the coronary tone. These data indicate that the different mechanisms underlying the anti-ischemic potency of verapamil are not yet completely understood (39, 43).

In patients with coronary artery disease (CAD) and normal or moderately depressed left ventricular ejection fraction (EF), most studies showed verapamil not to influence EF after oral (14-16, 34, 41) or i.v. (39, 44) administration , whereas only a minority observed a slight decrease (6, 28). Ferlinz et al. even documented a significant increase of EF after i.v. application in CAD (10). During pacing- (13) and exercise-induced ischemia EF after verapamil was increased (16, 34, 41) or remained unchanged (6, 14, 15, 28). Thus the influence of verapamil on left ventricular ejection fraction is within the range observed after the administration of nifedipine (26, 31, 37) which also might cause a deterioration even in CAD patients with normal resting EF (26).

Beta-blockers usually do not alter EF at rest in patients with CAD without congestive heart failure (6, 14-17, 20, 28, 34, 40). During exercise, propranolol, timolol and metoprolol do not change or slightly ameliorate EF in patients with CAD (6, 14-17, 20, 28, 31, 34). The combination of verapamil and propranolol did not relevantly alter the EF as compared to monotherapy at rest and during exercise in CAD patients with initial ejection fractions between 50% and 60% (6, 15, 20, 28).

It may be concluded from these numerous studies that the negative inotropic effects of verapamil and propranolol usually are offset at rest by decreasing the systolic blood pressure. During exercise-induced ischemia the anti-ischemic mechanisms of verapamil, propranolol and their combination might counterbalance their inherent negative inotropy (29, 33) leading to an even slightly increased EF accompanied by a reduction in ST-segment depression (Fig. 2).

Practical implications:

Even despite the widespread use of coronary bypass surgery and balloon dilatation, the application of anti-ischemic drugs is of major importance, since revascularization is sometimes technically impossible or myocardial ischemia may still be present after incomplete revascularization. In patients with optimal nitrate response the additional medication may be only administered at night to maintain the anti-ischemic protection during the necessary nitrate-poor interval (36). Patients with suboptimal nitrate response should receive the additional medication even throughout the day. Since it is reasonable to counteract the nitrate-induced tachycardia, the dual combination with a calcium-

antagonist of the nifedipine-type should be avoided. The inherent heart rate-increasing effect of nifedipine may explain its inferiority as compared to verapamil (2, 46) or propranolol (23) with respect to the anti-ischemic properties. Furthermore, a certain percentage of patients non-responding to nifedipine must be taken into account (35). These restrictions, however, are not applicable to patients with variant angina: This special subset of patients, in contrast, may show identical anti-ischemic response to the combinations ISDN plus verapamil and ISDN plus nifedipine (47), indicating different underlying mechanisms of angina pectoris (24). In these patients the use of propranolol might be detrimental and verapamil has been proven to be superior (30, 32).

In order to optimize anti-ischemic therapy it is recommended to control the ischemic situation during one of the proposed dual combinations not only by the anginal frequency but also by exercise-ECG and, if possible, a Holter monitoring system with evaluation of the ST-segment (1, 2, 14, 23, 38). If it is necessary to intensify the therapy the triple combination tested in our study can be suggested, providing that no contraindications exist. Although reports and fears about the danger of combining verapamil with a beta-blocker seem to be justified, this combination, in experienced hands, has been proven to be safe (1, 21, 25, 28). Care must always be taken about the possible induction of heart block or symptomatic sinus bradycardia (15) which we have observed in two patients. Therefore, this therapy should be initiated in-hospital. It is recommendable to begin with verapamil, subsequently titrating the beta-blocker until the optimal necessary and tolerated dose is reached.

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