

Can the problem of nitrate tolerance be solved?

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Introduction

The question if there is any nitrate tolerance, "yes or no", must be answered by "yes", because it is well known that nitrates develop tolerance to headaches and it is also generally accepted that nitrates develop tolerance to the decrease in blood pressure and to the increase in heart rate. However, the discussion which arose in recent years was especially focussed on the problem of tolerance development to the anti-ischemic (anti-anginal) effects. It was assumed that there may be tolerance to the arterial but no tolerance to the venous system, which represents the most important mechanism for nitrates' action.

Analyzing all the controversial studies concerning tolerance to the anti-ischemic effects, the different findings in all these studies cannot be explained by the use of different substances, because tolerance is described for isosorbide dinitrate as well as for isosorbide-5-mononitrate. Neither can different formulations of isosorbide dinitrate account for the controversies since there were results for and against tolerance with and without the use of sustained-release forms of isosorbide dinitrate. Different study-protocols, i.e. the methods of exercise, the time interval between ingestion and recordings as well as the duration of the long-term treatment phase do not solve the problems either. Even a placebo-controlled, randomized double-blind and cross-over study-design is not the key for the explanation of the controversial results since there are randomized double-blind and cross-over studies which did not observe the disappearance of the anti-ischemic effects, whereas there are open trials which could demonstrate the development of tolerance.

A partial role for the explanation of the different results may be a different individual extent of the development of tolerance: if you consider the relatively small number of patients investigated in most of the studies, it is conceivable why this factor

should exert such a great influence on the calculated mean values. However, the most important explanation may be the different amount of the patients' compliance ingesting each tablet. Compliance seems to be the key answer, since nitrate tolerance develops rapidly and disappears rapidly. The rapid development and rapid disappearance of nitrate tolerance explains why the ingestion of each single tablet, i.e. the dosage interval, is the critical point.

Method

At the time we began our studies three years ago, no clinical studies were available using longer dosage-intervals. At this time in all studies the tablet intake was prescribed at least three times daily. Our first study (randomized and with respect to the dosage interval double-blind) investigated the possible development of tolerance within two weeks of treatment with 80 mg tablets of isosorbide dinitrate (ISDN) in sustained-release form: patients ingested the tablets twice daily (i.e. in the morning and in the evening, resulting in dosage intervals of 12 hours) and other patients received the tablets only once daily (i.e. every morning, dosage intervals = 24 hours). Recordings were performed after a 4 day in-hospital period with placebo treatment. Only short acting sublingual nitrates were allowed to be administered in the presence of angina. During the whole washout-period there was no ingestion of other anti-ischemic drugs, especially no β -blockers and no calcium antagonists. The parameters of exercise induced ischemia were exercise induced ST-segment depression and the simultaneously recorded left ventricular ejection fraction during exercise as determined by radionuclide ventriculography before, as well as 2 hours, 6 hours and 12 hours after the ingestion of isosorbide dinitrate.

As initially pointed out, patients' compliance plays the major role. Therefore we decided to control the ingestion of each single tablet by the riboflavin fluorescence urine method. The criteria for patients' inclusion were quite strict: beside the angiographically proven coronary artery disease, left ventricular ejection fraction at rest had to be within the normal range. Patients with signs of prior myocardial infarction were excluded. Further prerequisites were chronic stable angina, exercise-inducible reproducible ST-segment depression of at least 0.15 mV as determined 80 ms after the J-point, responding to nitrates, and sinus rhythm without the presence of complex arrhythmias. A history of minimal nitrate headache and other assumptions for a high likelihood of a good compliance were necessary. It is important to emphasize that the ECGs were analyzed completely blindly, that is without knowledge whether they were recorded on the first day or on the 15th day of the study.

Results

Let us first have a look at the compliance. If even the equivocal fluorescence of the urine were

set to negative, the compliance in this study was 95%, meaning the 95% of all tablets prescribed were actually ingested.

The following Figures (1–4) show in the upper panel the results from the ECG and in the lower panel the radionuclide ejection fraction. First the control values for the first day and the 15th day, then the corresponding values after the ingestion of isosorbide dinitrate. In the group of patients taking the 80 mg tablets once daily for two weeks, there was no attenuation of the anti-ischemic effects on the ST-segment depression or on the left ventricular ejection fraction during exercise (Fig. 1).

However, in the group of patients taking the tablet every morning and evening (dosage interval = 12 hours) there was a significant attenuation of the anti-ischemic effects as demonstrated by an increase of the ST-segment depression on the 15th day compared to the first day, and a decrease of left ventricular ejection fraction during exercise (Fig. 2). I would like to point out that the exercise tests on the 1st and 15th days were performed at the same hour of the day, so the problems of circadian changes need not be considered in this context.

1st day = BEFORE, 15th day = AFTER
TWO WEEKS OF DAILY TREATMENT WITH
1 x 80 mg ISDN-s.r., EVERY MORNING -
(INTERVALS: 24 hrs)

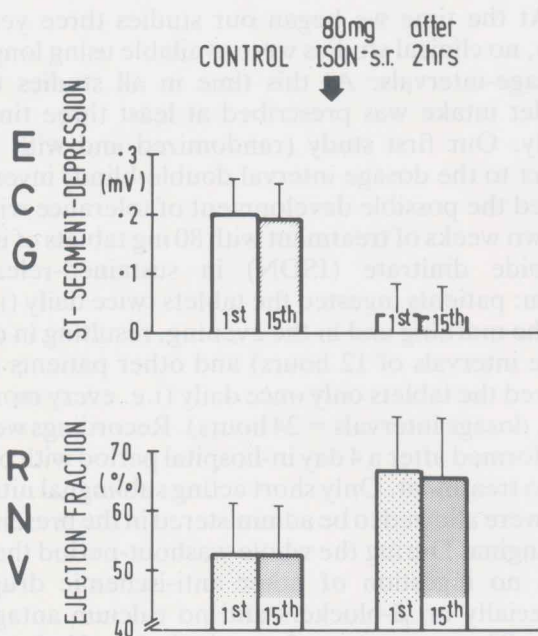


Fig. 1. Effects of a single 80 mg tablet of isosorbide dinitrate (ISDN) in sustained-release form before (first day) and after (15th day) the intake of 1 x 80 mg per day each morning (dosage intervals: 24 hours) on the exercise-induced ST-segment depression and the left ventricular ejection fraction during exercise measured by radionuclide ventriculography (RNV).

1st day = BEFORE, 15th day = AFTER
TWO WEEKS OF DAILY TREATMENT WITH
2 x 80mg ISDN-s.r., MORNING + EVENING
(INTERVALS: 12 hrs)

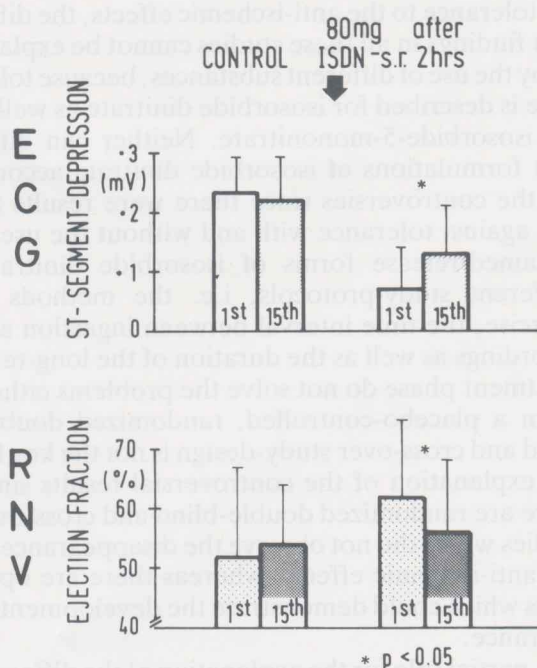


Fig. 2. Effects of a single 80 mg tablet of isosorbide dinitrate (ISDN) in sustained-release form before (first day) and after (15th day) the intake of 2 x 80 mg per day taken each morning and evening (dosage intervals: 12 hours) (see also Fig. 1).

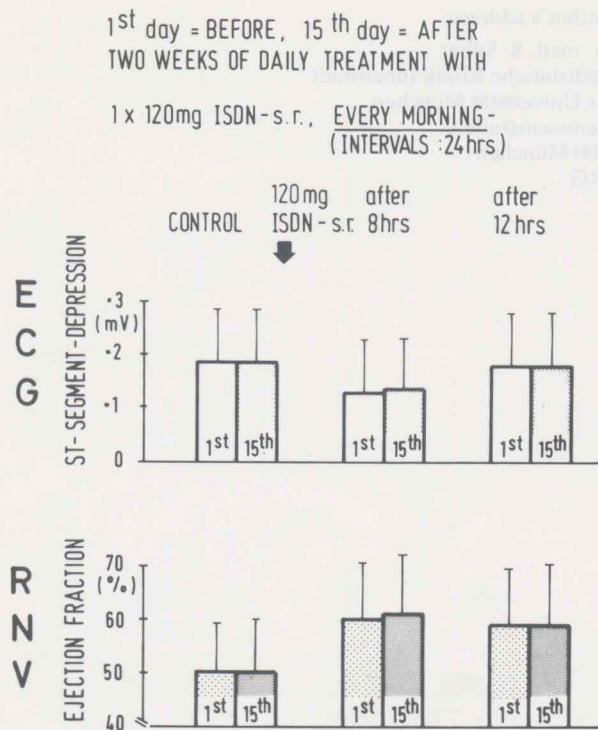


Fig. 3. Effects of a single 120 mg capsule of isosorbide dinitrate (ISDN) in sustained-release form before (first day) and after (15th day) intake of 1 x 120 mg per day each morning (dosage intervals: 24 hours) (see also Fig. 1).

So with respect to the development of tolerance a dosage interval of 12 hours cannot be regarded as sufficient to prevent the development of tolerance and the once daily intake might be favoured. But the problem of a once daily regimen with 80 mg tablets is that the effect on exercise-induced ischemia during the late afternoon and the evening is not satisfactory in some patients. To solve this problem basically two different ways may be examined: the use of a once daily higher single dosage or of twice daily regimen which includes a dosage interval of more than 12 hours, i.e. ingestions in the morning and in the early afternoon.

Let us first have a look at the first possibility using a higher single dosage of the 120-mg-capsule of ISDN in sustained-release form. This study (Fig. 3) was performed in 10 patients according to a similar protocol as mentioned above, but the measurements were obtained 2, 8 and 12 hours after the ingestions. As you can see, 8 hours after the ingestion there was no development of tolerance, but the extent of the anti-ischemic effects was rather limited. 12 hours after the ingestion we could not find any demonstrable effects on the ST-segment depression whereas the effects on the exercise-induced ejection fraction were still present.

The alternative way of solving this problem is shown Figure 4. Patients taking 80 mg tablets in the morning and in the early afternoon (8.00 a.m.

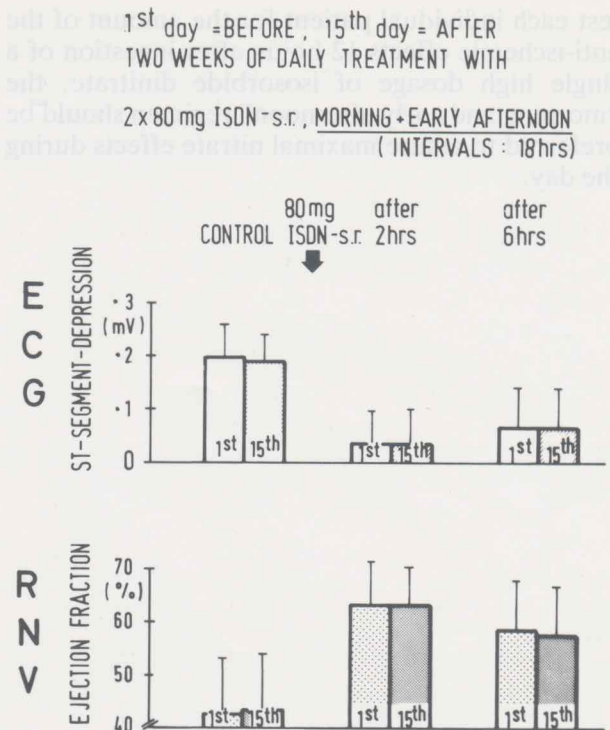


Fig. 4. Effects of a single 80 mg tablet of isosorbide dinitrate (ISDN) in sustained-release form before (first day) and after (15th day) intake of 2 x 80 mg per day taken each morning and early afternoon (maximal dosage intervals: 18 hours) (see also Fig. 1).

and at 2.00 p.m., i.e. a maximal daily dosage interval of 18 hours) 2 hours as well as 6 hours after the ingestion did not show any attenuation in the exercise radionuclide ventriculogram comparing the values of the 15th day with those of the first day. The duration of the maximal anti-ischemic action of a single 80 mg tablet can be considered to be in the range of about 6 hours.

Conclusion

Based on analysis of the presently available studies a loss or attenuation of the anti-ischemic effects must be considered during oral long-term treatment with nitrates according to a t.i.d. regimen. A dosage interval of 12 hours is not sufficient to prevent the development of tolerance using 80 mg tablets. A once daily ingestion of high single dosages (80 or 120 mg ISDN) does not lead to the development of tolerance, the effects on exercise-induced ischemia during the late afternoon and the evening are not satisfactory in a special subset of patients. According to a regimen which includes a dosage interval of 18 hours, for example ingestion at 8.00 a.m. and 2.00 p.m., there is also no development of tolerance but increased evidence of a remarkable effect on exercise induced ischemia for about 12 hours. Since it is not feasible to

test each individual patient for the amount of the anti-ischemic effects 12 hours after ingestion of a single high dosage of isosorbide dinitrate, the "morning and early afternoon" regimen should be preferred to assure maximal nitrate effects during the day.

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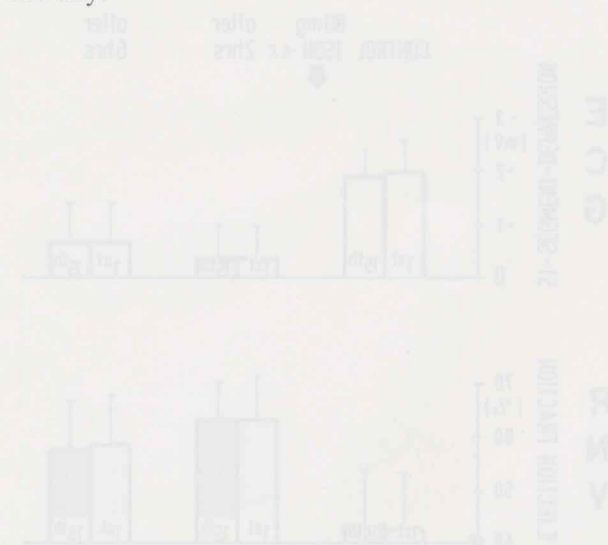


Fig. 4. Effects of a single 80 mg tablet of isosorbide dinitrate (ISDN) in sustained-release form before (first day) and after (12th day) ingestion of 2 x 80 mg per day taken each morning and early afternoon (sustained dosage interval: 18 hours) (see also Fig. 1).



Fig. 5. Effects of a single 120 mg capsule of isosorbide dinitrate (ISDN) in sustained-release form before (first day) and after (12th day) ingestion of 1 x 120 mg per day each morning (dosage interval: 24 hours) (see also Fig. 1).

and at 2.00 p.m., i.e. a maximal daily dosage interval of 18 hours) 2 hours as well as 6 hours after the ingestion did not show any attenuation in the exercise tolerance test. The results of the exercise tolerance test of the 12th day with those of the first day. The duration of the maximal anti-ischemic action of a single 80 mg tablet can be considered to be in the range of about 6 hours.

Conclusion

Based on analysis of the presently available data, a loss or attenuation of the anti-ischemic effect must be considered during oral long-term treatment with nitrates according to a 12-hour regimen. A dosage interval of 12 hours is not sufficient to prevent the development of tolerance during 80 mg tablets. A once daily ingestion of high single dosages (80 or 120 mg ISDN) does not lead to the development of tolerance, the effects on exercise-induced ischemia during the late afternoon and the evening are not satisfactory in a special aspect of patients. According to a regimen which includes a dosage interval of 18 hours, for example ingestion at 8.00 a.m. and 2.00 p.m., there is also no development of tolerance but increased evidence of a reproducible effect on exercise-induced ischemia for about 12 hours. Since it is not feasible to

so with respect to the development of tolerance a dosage interval of 12 hours cannot be regarded as sufficient to prevent the development of tolerance and the once daily intake might be favored. But the problem of a once daily regimen with 80 mg tablets is that the effect on exercise-induced ischemia during the late afternoon and the evening is not satisfactory in some patients. To solve this problem basically two different ways may be examined: the use of a once daily higher single dosage (2 or twice daily regimen which includes a dosage interval of more than 12 hours, i.e. ingestion in the morning and in the early afternoon).

Let us first have a look at the first possibility using a higher single dosage of the 120-mg capsule of ISDN in sustained-release form. This study (Fig. 1) was performed in 10 patients according to a similar protocol as mentioned above, but the measurements were obtained 2, 8 and 12 hours after the ingestion. As you can see, 8 hours after the ingestion there was no development of tolerance, but the extent of the anti-ischemic effects was rather limited. 12 hours after the ingestion we could not find any demonstrable effects on the exercise tolerance test whereas the effects on the exercise-induced ischemia fraction were still present. The alternative way of solving this problem is shown in Figure 4. Patients taking 80 mg tablets in the morning and in the early afternoon (8.00 a.m.