Comparison of the Efficacy of Isosorbide Dinitrate Spray and Nitroglycerin Spray in the Regression of Symptoms of Exercise-Induced Moderate Angina Pectoris

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Summary

This single-centre, controlled, randomised, double-blind, crossover trial was carried out to evaluate the time to recovery from angina pectoris after application of an isosorbide dinitrate (ISDN) spray formulation, which was developed a few years ago (Isoket® spray, Schwarz Pharma, Monheim, Germany), in comparison with that with nitroglycerin (NG) spray in patients with chronic stable angina with documented coronary artery disease. A secondary objective of this trial was to evaluate the safety and tolerability of ISDN spray. 65 patients were randomised to this study; 62 patients were evaluated for efficacy in the intent-to-treat analysis and 28 patients could be evaluated for the per-protocol analysis. Considering the pooled data of the intent-to-treat analysis, patients receiving ISDN spray (2 squirts of 1.25mg ISDN each) recovered after 67.16 seconds, compared with patients administered NG spray treatment (2 squirts of 0.4mg NG each) who recovered after 74.11 seconds (mean difference 6.95 seconds). The Moses 90% confidence interval clearly indicated that the two treatments were equivalent with regard to the clinically relevant difference of 30 seconds as defined in the protocol. In the per-protocol analysis, the pooled data demonstrated that the mean time to recovery from angina pectoris was 63.86 seconds in the ISDN spray-treated patients compared with 71.14 seconds in the NG spray-treated patients. This analysis also indicated that the treatments were equivalent with regard to the clinically relevant difference of 30 seconds as defined in the protocol (Moses 90% confidence interval). In the intent-to-treat analysis the global evaluation of efficacy showed that the investigator rated ISDN spray to be ‘very good’ or ‘good’ in 55 cases and NG spray to be ‘very good’ or ‘good’ in 54 cases. In 56 cases in the ISDN spray group and in 55 cases in the NG spray group treatment was classified as ‘very good’ or ‘good’ by the patients. Comparable results were obtained in the per-protocol analysis. Four adverse events were reported: 2 cases of orthostatic hypotension occurred during the nitrate response test, and 2 patients developed ventricular arrhythmia. In all cases the investigators denied any relationship to the study medication.

In conclusion, this study shows that the two nitro sprays had similar effects on the recovery from angina pectoris when administered immediately after cessation of exercise and that they were equally well tolerated.
The treatment of angina pectoris consists of prophylactic treatment and rapid relief from anginal attacks. Organic nitrates such as nitroglycerin (NG) and isosorbide dinitrate (ISDN) are the drugs of choice for the prevention and treatment of angina pectoris. In the last 25 years new formulations of NG and ISDN have been developed. Both NG and ISDN are currently used as sublingual tablets or spray for rapid relief from attacks. NG and ISDN sprays may offer advantages over sublingual tablets because of their rapid onset of action.\(^{[1-3]}\)

The higher lipophilicity of NG theoretically enables this substance to be absorbed more rapidly by the mucosa, thus inducing a more rapid effect. Besides the lipophilic properties of the drug, the onset of action also depends on the galenic preparation. Pharmacokinetic investigations have shown that the new galenic preparation of ISDN spray (Isoket\(^{®}\) spray, Schwarz Pharma, Monheim, Germany) rapidly attains therapeutic plasma concentrations.\(^{[4,5]}\) It has also been shown in several studies that ISDN spray is effective in patients with angina pectoris.\(^{[6,7]}\)

The aim of the present study was to compare the onset of action of ISDN spray with NG spray and to show that ISDN spray can be equated with the standard NG spray with regard to its onset of action.

**Patients and Methods**

**Patients**

Male and female patients aged between 30 and 70 years, who had classic exertional angina (class I and II according to the Canadian Cardiovascular Society) with documented coronary artery disease, were enrolled in this study.

In patients receiving long-acting nitrate preparations, this medication was discontinued at least 2 days before onset of the investigation and for the duration of the study. Patients could continue to take sublingual NG to treat episodes of angina pectoris. Prophylactic nitrate medication was not permitted. Ingestion of alcohol and/or beverages containing caffeine was prohibited 1 hour prior to the exercise test.

**Study Design**

The study was a single-centre, controlled, double-blind, 2-period, crossover trial preceded by a washout phase and a nitrate response test. Ethical approval was obtained from the Ethical Committee for Experimental Clinical Studies of the Medical Academy ‘Nicolaus Copernicus’ in Cracow, Poland.

On the first visit, an initial ergometric test (baseline determination) was performed on the first day after a 2-day washout phase (5 half-lives in cases of prior \(\beta\)-blocker treatment). The next day (day 2) patients were randomly assigned to the 2 sequences of treatment before their first exercise test under medication. Group 1 was given ISDN spray (2 squirts of 1.25mg ISDN each) on the first day of the treatment phase and NG spray (2 squirts of 0.4mg NG each) on the next day, and group 2 received the medication in the reverse order.

The total duration of the study was 7 days (including the screening phase) for all patients. The patients were examined 4 times during this period.

ISDN and NG sprays were identical with regard to appearance and taste and were put into bottles of identical shape. These bottles were assigned and labelled at random for each subject number on the subsequent two visits during the treatment phase using a predetermined random list containing 25 randomly permuted blocks of 4 patients each. Decoding was performed after the study had finished and the database had closed. Decoding an individual patient’s medication was permitted in urgent cases and had to be documented.

All patients who entered the study were assigned a preliminary run-in number. Those patients who had successfully terminated the screening phase were then assigned to the final subject numbers of the blinded study medication in chronological order when they entered the treatment phase. Randomisation and assignment was done with respect to the crossover design in such a way.