Airway and Cardio Vascular Responses to Nebulized Glyceryl Trinitrate in Normal Subjects

Abdelmonem M. Sharara *[1]

Abstract

Background: Glyceryl Trinitrate (GTN) is a potent smooth muscle relaxant and vasodilator. There are conflicting reports regarding its efficacy as a bronchodilator. The aim of this study was to examine the effect of nebulized GTN on airway calibare and cardio vascular system in normal subjects.

Methods: We studied 24 normal subjects (6 female) on two occasions, administering either nebulized GTN 6 mg or placebo in a double-blind, randomized, crossover fashion. Bronchial response was assessed by measurement of FEV_1.

Results: A systemic effect of this dose of GTN was demonstrated by a supine to erect increase in heart rate of 36.0 (8.6) % mean (95% CI) after GTN compared with 16.2 (6.1) % after placebo. Systolic Blood Pressure (BP) decreased by 8.0 (3.8) % after GTN compared with 1.4 (2.8) % after placebo. Diastolic BP did not change. Baseline FEV_1 did not differ on the two study days. There was no acute bronchodilator effect.

Conclusions: Nebulized GTN has cardio vascular effects but does not have any bronchodilator effect in normal subjects. Further investigation in airways disease is justified.

Keywords: Glyceryl trinitrate, bronchodilator, inhalation.

(J Med J 2010; Vol. 44 (1):50- 54)

Received	***Accepted***
November 2, 2008	*April 23, 2009*

Introduction

Glyceryl Trinitrate (GTN) and other nitrates which are widely used in the treatment of ischaemic heart disease are potent smooth muscle relaxants and vasodilators. It has been known for many years that nitrates induce bronchial relaxation. [1] However, there are conflicting reports regarding their efficacy in airways obstruction when administered sublingually [2-4] or intravenously. [3, 5] We have found only 2 reports examining the bronchial effects of inhaled nitrates in humans and another 2 reports examining both mean pulmonary artery pressure and pulmonary vascular resistance in patients with mitral valve diseases and in children with congenital heart disease, respectively. [6, 7]

The aim of this study was to examine the effect of inhaled GTN on airway calibre and cardio vascular system in normal humans.

Methods

We studied 24 normal subjects (6 female, mean age 35 (range 25-46) years) for about one hour on two occasions, separated by at least three days.

1. Consultant & Head of Chest Diseases Division at King Hussein Medical Centre, Amman, Jordan.
**** Correspondence should be addressed to:***
Abdelmonem M. Sharara
P. O. Box: 180, Amman, 11118, Jordan
E-mail: abedsharara@yahoo.com

All subjects gave written informed consent to the study, which was approved by the Research Ethics Committee of the Royal Medical Services at King Hussein Hospital.

Bronchial response was assessed by measurement of FEV_1 using a dry wedge spirometer (Vitalograph, Bucks, UK). At each visit subjects received either nebulized GTN 6 mg or placebo (ethanol 30% v/v) allocated in a double-blind, randomized, crossover fashion. The nebulizer (Intertech/Inspiron, Ilinois, USA) was driven by air at a pressure of 400 kPa and a flow rate of 8 liters per minute for 4- 6 minutes.

Heart rate and Blood Pressure (BP) were measured at baseline, 1, 5 and 10 minutes after nebulization by manual recording in the supine posture and after standing for 30 seconds. FEV_1 were measured at baseline and 6 minutes after nebulization.

Statistics

A Wilcoxon signed rank test was used to compare between placebo and GTN treatment days. A value of $p<0.05$ was considered statistically significant.

Results

Details of the study subjects are shown in table (1). Twenty of the 24 normal subjects developed mild-to-moderate headache and two experienced dizziness after nebulization of GTN. Four subjects had mild headache after placebo. Baseline heart rate, blood pressure and FEV_1 did not differ on the two study days. The different increase in heart rate (95% CI) between GTN and placebo after standing for 1 minute was 15.3 (6.2) (fig. 1A, $p<0.005$). This postural change in heart rate remained significantly greater after GTN compared with placebo at 5 minutes. After placebo there was a small but significant increase ($p<0.05$) in heart rate with change in posture presumably related to nebulizer use. A statistically significantly greater effect ($p<0.005$) was found after GTN.

The different reduction in systolic BP on standing at 1 minute between GTN and placebo was 6.8 (4.3) ($p<0.02$). This reduction remained significantly greater after GTN than placebo at 5 minutes (fig 1B). Diastolic BP did not change significantly at any time. There was no acute bronchodilator effect (fig 2).

Table 1. Details of subjects.

Subjects Age / Sex	***FEV_1* (% predicted)***
46/M	*4.32*
38/F	*3.60*
38/M	*3.85*
30/M	*4.55*
39/M	*4.85*
25/M	*5.00*
40/M	*3.87*
28/F	*4.42*
27/M	*5.03*
32/M	*4.59*
37/M	*4.80*
33/M	*3.98*
31/M	*3.90*
31/F	*3.58*
41/M	*3.14*
33/M	*3.77*
34/M	*3.90*
39/M	*3.12*
40/F	*3.63*
32/M	*3.87*
30/F	*4.47*
44/M	*4.28*
35/M	*3.79*
33/F	*3.61*
Mean	*4.08 (107%)*
± 95% CI	*0.31*

Note: Male (M), Female (F), * measurements made at the first visit

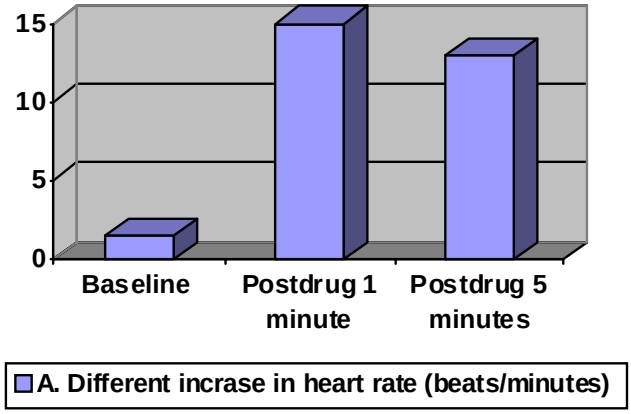
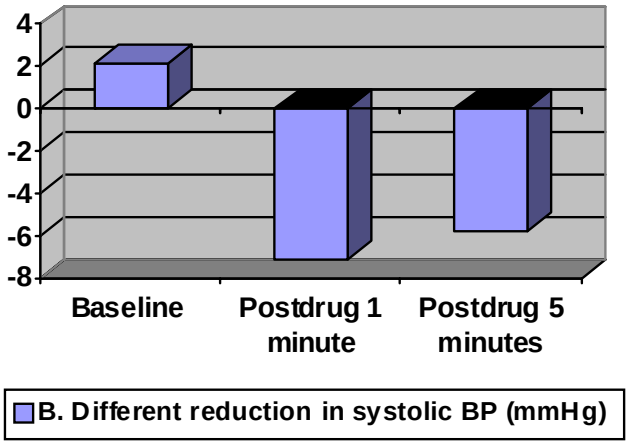


Fig.(1): The changes in difference between the GTN and placebo in heart rate (A) and systolic (B) blood pressure from supine to erect posture, before, 1 minute and 5 minutes after administration of placebo and GTN (different, n=24).



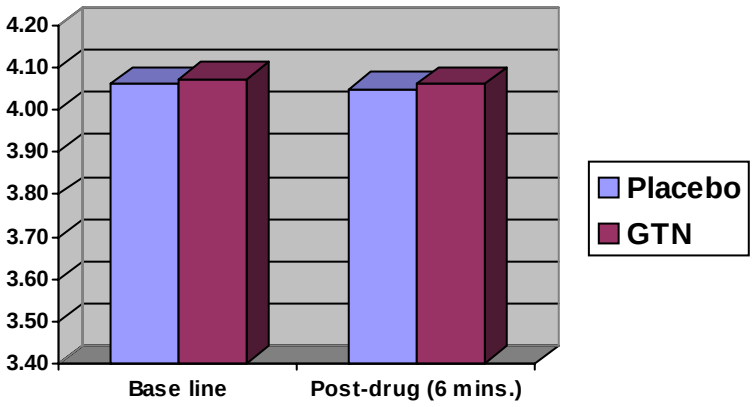


Fig. (2): FEV_1 before and 6 minutes post-drug after inhalation for the two study days (placebo and GTN). Mean, n=24.

Discussion

We have shown no effect of inhaled GTN 6 mg on baseline FEV_1 in 24 normal volunteers in this placebo-controlled double-blind study. Intravenous GTN at 20-fold lower doses reduced intratracheal pressure in 12 patients undergoing coronary artery surgery. [5] This response was independent of the pulmonary circulation. It may have been direct or indirect: mediated by vagal pathways as a reflex response to systemic vasodilatation or due to secondary catecholamine release. These considerations also apply in our study as we demonstrated systemic vasodilatation even though GTN was inhaled.

Nitrates have long been considered clinically useful in the treatment of bronchial asthma [1] but in 10 patients with acute asthma sublingual GTN 1.2 mg had no effect. [2] In a placebo controlled double-blind, randomized study in 10 stable asthmatics sublingual GTN 0.4 mg had no effect. [4] Nebulized ISDN protected slightly against EIA in one study [8] but not in another. Therefore, conflicting reports exist regarding the efficacy of nitrates in asthmatics.

Inhaled nitroglycerin produces a significant reduction in both mean pulmonary artery pressure and pulmonary vascular resistance in patients after mitral valve operations without reducing mean arterial pressure and systemic vascular resistance. [6] In another study, nebulized nitroglycerine used in the treatment of severe pulmonary hypertension in children with congenital heart disease, especially in areas where other treatments such as extracorporeal membrane oxygenation or inhaled nitric oxide are inaccessible. [7]

There have been relatively few studies of the *in vitro* effects of nitrates on airway smooth muscle. On bovine airway preparations the relaxant effects of GTN, ISDN and sodium nitroprusside (SNP) were comparable to that of isoprenaline. [9] Inhaled nitrates induced bronchodilatation in dogs and guinea-pigs *in vivo.* [10]

It is unknown how nitrovasodilators relax smooth muscle but they are thought to act as NO donors leading to elevation of cyclic GMP. [11] It is unclear why high dose inhaled GTN produces systemic vasodilatation without bronchial effects. Exogenous NO had no demonstrable bronchodilator effect in normal subjects but minor bronchial effects were found in asthmatics. [12] Further study of nitrovasodilators is justified in airways disease using the inhaled route for administration, even though systemic vascular effects predominated in the present study in normal subjects.

References

1. Salter HH. Asthma: Its Pathology and Treatment. Philadelphia, Blanchard & Lea 1864; 144-150.
2. Kennedy T, Summer WR, Sylvester J, Robertson D. Airway response to sublingual nitroglycerin in acute asthma. JAMA. 1981; 246: 145-147.
3. Radenbach D, Oltmanns D, Hell G. Nitroglycerin also as a broncholytic. Med Klin. 1981; 76: 685-688.
4. Miller WC, Shultz TF. Failure of Nitroglycerin as a Bronchodilator. Am Rev Resp Dis . 1979; 120: 471.
5. Byrick RJ, Hobbs EG, Martineau R, Noble WH. Nitroglycerin relaxes large airways. Anesth Analg. 1983; 62: 421-425.
6. Yurtseven N, Karaca P, Kaplan M, Ozkul V, Tuygun AK, Aksoy T, Canik S, Kopman E. Effect of nitroglycerin inhalation on patients with pulmonary hypertension undergoing mitral valve replacement surgery. Anesthesiology. 2003; 99(4):855-858.
7. Omar HA, Gong F, Sun MY, Einzig S. Nebulized nitroglycerin in children with pulmonary hypertension secondary to congenital heart disease. W V Med J. 1999; 95(2):74-75.
8. Tullett WM, Patel KR. Isosorbide dinitrate and isoxsuprine in exercise induced asthma. Br Med J Clin Res Ed. 1983; 286: 1934-1935.
9. Gruetter CA, Childers CE, Bosserman MK, Lemke SM, Ball JG, Valentovic MA. Comparison of relaxation induced by glyceryl trinitrate, isosorbide dinitrate, and sodium nitroprusside in bovine airways. Am Rev Respir Dis. 1989; 139: 1192-1197.

10. Kreye VA, Marquard E. Comparison of sodium nitroprusside and isoprenaline aerosols in histamine-induced bronchial asthma of the guinea pig. Naunyn Schmiedebergs Arch Pharmacol. 1979; 306: 203-207.
11. Barnes P. Nitric oxide and airways. Eur Respir J. 1993; 6: 163-165.
12. Hogman M, Frostell CG, Hedenstrom H, Hedenstierna G. Inhalation of nitric oxide modulates adult human bronchial tone. Am Rev Respir Dis. 1993; 148: 1474-1478.

تأثير علاج جريسرل ثلاثي النيترات عن طريق التبخيرة على القصبات الهوائية والأوعية القلبية للإنسان العادي

عبد المنعم محمد شرارة

قسم الأمراض الباطنية، وحدة الأمراض الصدرية، مدينة الحسين الطبية، الخدمات الطبية الملكية، عمان، الأردن

الملخص

جريسرل ثلاثي النيترات هو علاج قوي يؤدي إلى ارتخاء العضلات والأوعية الدموية. وهناك تقارير متضاربة حول كفاءتها باعتبارها موسعا للقصبات الهوائية. وكان الهدف من هذه الدراسة هو دراسة تأثير علاج جريسرل ثلاثي النيترات عن طريق التبخيرة على القصبات الهوائية والأوعية القلبية للإنسان العادي.

أجريت الدراسة على 24 شخصاً (6 إناث)، وأعطي كل شخص 6 ملغم جريسرل ثلاثي النيترات أو محلول ملحي. وقد تم قياس وتقييم تأثير العلاج عن طريق قياس السعة الحيوية للرئتين في الثانية الأولى لعملية الزفير خلال التنفس.

كان التأثير الكلي للأشخاص الذين أعطوا علاج جريسرل ثلاثي النيترات عن طريق التبخيرة واضحا مقارنة بالأشخاص الذين أعطوا المحلول الملحي، حيث كان هناك ازدياد بعدد نبضات القلب للأشخاص الذين أعطوا العلاج (36%) مقارنة مع المحلول الملحي (16.2%). انخفض ضغط الدم الانقباضي بمقدار 8% بعد علاج جريسرل ثلاثي النيترات مقارنة بـ 1.4% بعد المحلول الملحي. ولم يكن هناك تأثير على قياس السعة الحيوية للرئتين في الثانية الأولى.

الخلاصة: علاج جريسرل ثلاثي النيترات عن طريق التبخيرة له تأثيرات على الأوعية القلبية للإنسان العادي ولكن ليس له أي تأثير على القصبات الهوائية. هناك حاجة إلى مزيد من الأبحاث عن هذا العلاج على مرضى الربو القصبي.

الكلمات الدالة: جريسرل ثلاثي النيترات، استنشاق، توسع القصبات.