Physiol. Res. 51: 413-416, 2002

Noninvasive Evaluation of Portal-Systemic Shunting by Glyceryl Trinitrate

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Received April 15, 2001
Accepted November 22, 2001

Summary

Portal-systemic shunting is an important circulatory abnormality in patients with liver cirrhosis. Glyceryl trinitrate (GTN) that is normally subject to first pass elimination, may exhibit higher bioavailability in these patients. This study compares the pharmacodynamic effects of GTN after peroral and sublingual administration for noninvasive assessment of shunting. Six control subjects and 15 patients with cirrhosis were studied after oral and sublingual application of 0.5 mg of GTN. Liver cirrhosis was complicated by portal hypertension in 7 of the patients and 4 patients had surgically implanted portocaval anastomosis. Digital plethysmography, which is highly sensitive and is essentially noninvasive in nature, was used to assess and compare the pharmacodynamic effects of GTN. The following values of the ratio of areas under the pharmacodynamic effects/time curve were obtained: 0.08±0.06 in healthy subjects, 0.52±0.21 in patients with uncomplicated cirrhosis, 0.99±0.34 in patients with portal hypertension and 1.24±0.43 in patients with portal-systemic shunts. We conclude that increased bioavailability of GTN reflects portal-systemic shunting and might be used providing that the pharmacodynamic data reflect both pharmacokinetic variability and the pharmacokinetic-pharmacodynamic interrelations.

Key words

Plethysmography • Portal-systemic shunting • Cirrhosis • Glyceryl trinitrate • Bioavailability

Introduction

Portal-systemic shunting is an important circulatory abnormality, which develops in patients with liver cirrhosis. Serious clinical manifestations that accompany these changes include hemorrhage from esophageal varices, hepatic encephalopathy and ascites.

Several pharmacokinetic noninvasive methods using high extraction compounds have been developed to measure this phenomenon (Preisig 1985, Cavanna *et al.* 1987, Molino *et al.* 1998). The principle of the methods consists in the comparison of the systemic availability of an intravenous and a peroral dose of the compound.

Glyceryl trinitrate (GTN), which is also normally subject to high first pass elimination, may exhibit higher bioavailability in patients with portal-systemic shunting. The advantage of GTN is that its pharmacodynamic effect can be measured by digital plethysmography. The systemic availability of an oral dose compared to intravenous infusion of GTN was used

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to measure the shunting (Porchet and Bircher 1982). The aim of our study was to compare the ratio of areas under the pharmacodynamic effects/time curve after peroral and sublingual administration in patients with liver cirrhosis with different degrees of blood shunting.

Methods

Subjects

Six volunteers (4 men, 2 women, mean age 38 years, range 26-53) without any clinical or laboratory signs of liver disease participated in our study as a control group and 15 patients (5 men, 10 women, mean age 60.5 years, range 37-78) with histologically confirmed liver cirrhosis, with various degrees of liver blood flow impairment. The etiology of cirrhosis was alcoholic in 8 patients, postviral in 6 patients and in one patient of unknown origin. Four patients with clinically compensated cirrhosis had Child-Pugh classification A, in 7 of the patients (with Child-Pugh classification B or C) the cirrhosis was complicated with significant portal hypertension and 4 of the patients (Child-Pugh classification B or C) underwent surgically performed either spleno-renal or side-to-side porto-caval anastomosis. Portal hypertension was diagnosed by the presence of splenomegaly and collateral blood flow (oesophageal varices and other collaterals). This diagnosis was confirmed by ultrasound measurements of portal vein enlargement.

The patency of porto-caval anastomosis was evaluated clinically and sonographically. None of the subjects enrolled in the study used any vasoactive drugs and all other medication was discontinued two days prior to the investigation.

All subjects gave their informed consent prior to the study.

Testing

The tests were carried out in fasting subjects after 30 min of rest in the supine position. The last 5 min of this period were used for baseline plethysmographic measurements. All subjects were randomly given a single dose of 0.5 mg of GTN either sublingually or perorally. Both applications were separated by a 48 h washout period. Plethysmographic recordings were performed with a digital plethysmograph with a Hewlet-Packard (USA) probe and computer data analysis (Aubrecht *et al.* 1990). The measurements were evaluated in one minute intervals for 20 min after GTN application. The value in each minute represents the mean of four cardiac cycles taken at 15-second intervals. The D/H ratio was obtained from each plethysmographic wave as shown in Figure 1. The effect (ΔD/H) of GTN was calculated as:

$$\Delta D/H = D_t/H_t - D_0/H_0$$

where D_t and D_0 is the distance between the systolic wave peak and diastolic notch at time t and basal value, H_t and H_0 is the amplitude of the systolic peak at time t and basal value. One minute average values of ΔD/H were recorded and the ratio of the areas under the effect/time curves after peroral and sublingual applications were used to assess the portal-systemic shunting.

Statistical analysis

Means and standard deviations were calculated. The statistical significance of differences among groups was analyzed by Kruskal-Wallis test at p=0.005.

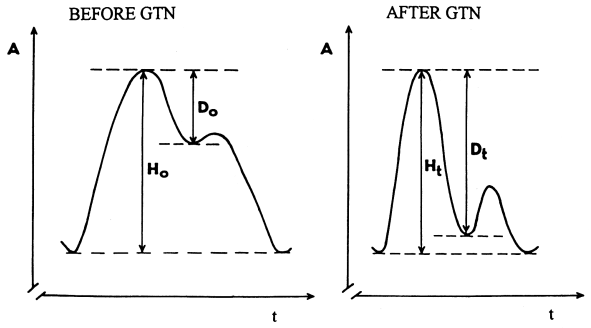

Fig. 1. *Pulse wave before and after GTN administration and measurement of the depth (D) of the dicrotic notch in respect to the total height (H) of the systolic wave.*

Results

The effect of GTN on the plethysmographic wave is shown in Figure 1. The height of the systolic peak and distance of the systolic wave peak and diastolic notch was substantially increased after GTN administration.

Representative effect/time curves in a patient and a control individual after sublingual and peroral application of GTN are shown in Figure 2. While in the healthy subject almost no effect of GTN after peroral application was noted, the effect in the patient with porto-caval anastomosis was similar to that after sublingual administration.

The ratio (mean±SD) of the area under the effect/time curve after peroral and sublingual dose of GTN was 0.08±0.06 in the control group, 0.52±0.21 in patients with cirrhosis without portal hypertension,

0.99±0.34 in patients with portal hypertension and 1.24±0.43 in patients with portal-systemic shunts. There was a significant difference between the control individuals and patients. A more detailed analysis showed that the difference was caused mainly by the control group.

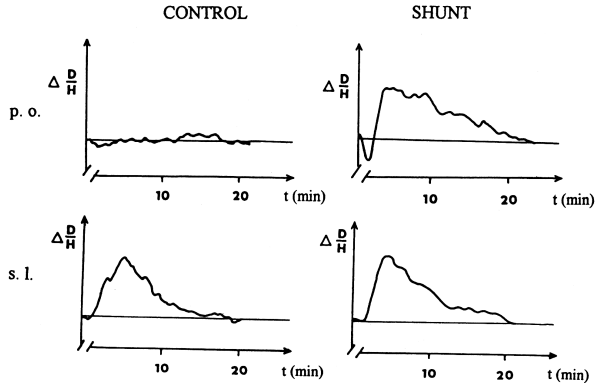

Fig. 2. *Representative recording of D/H ratios after peroral and sublingual administration of GTN in control subjects and patients with porto-caval shunt. The curve is composed of one-minute average values.*

Discussion

Digital plethysmography, which is essentially noninvasive, detects rhythmic changes of digital tissue volume during the cardiac cycle under physiological conditions. These volume changes depend on the amount of blood in the digital tissue and are detected as a pulse wave. Peripheral blood supply defects and pharmacodynamic effects of some drugs can be diagnosed by digital plethysmography (Klemsdal *et al.* 1996, Stengele *et al.* 1996, Tan and da Silva 1999). This method was recommended as a useful tool for evaluating and comparing the biological response to nitrates (Lund 1986).

The results of the present study have shown the increased effect of perorally administered GTN in patients with liver cirrhosis, which is in agreement with various clinical degrees of portal blood shunting.

There was a certain age difference between the patient and control group in our study. Nevertheless, it was shown that there is a reduction of hepatic blood flow with aging without any additional intrahepatic shunting (Zoli *et al.* 1999). Therefore, the ratio of the area under effect/time curve after peroral and sublingual dose of GTN should not be substantially affected by age.

The advantage of the proposed method is that it is a noninvasive approach, requiring simple and easily available equipment. The administration of GTN was well tolerated with the exception of three subjects, where cephalea was noted. However, our method to define the pharmacodynamic effect of GTN by digital plethysmography is not directly related to the fraction of portal blood bypassing hepatocytes. There are several factors that can modify the relationship between the time course of the GTN plasma concentration and its pharmacodynamic effect. One of the complicating factors could include the biotransformation and action of nitrates, which readily enter vascular smooth muscles where they are converted to nitric oxide which acts as a cellular messenger leading to the activation of cyclic guanosine monophosphate (cGMP) and vasodilation. Reduced sulfhydryl groups, probably supplied by cysteine, are a necessary co-factor; their intracellular depletion and possible changes in the endothelium-derived relaxing factor (endogenous NO) in liver diseases can modify this effect.

Nevertheless, our results suggest that digital plethysmography and a simplified GTN test after peroral and sublingual administration could be clinically useful for portal systemic shunting evaluation in patients with various liver diseases. This noninvasive and rapid procedure seems to provide valuable information of circulatory changes in portal hypertension, which were previously available only through highly invasive or time consuming investigations.

References

AUBRECHT J, SOCHOR L, PERLÍK F: Automatic recording and evaluation of reflex digital plethysmography (in Czech). *Lekar a technika* **21**: 134-137, 1990.

CAVANNA A, MOLINO G, BALLARE M, TORCHIO M, FRACCHIA M, AVAGNINA P, BIRCHER J: Non-invasive evaluation of portal-systemic shunting in man by D-sorbitol bioavailability. *J Hepatol* **5**: 154-161, 1987.

KLEMSDAL TO, MUNDAL HH, GJESDAL K: Effects of carvedilol and atenolol on arterial pulse curves (plethysmography) and finger temperature after hand cooling. *Eur J Clin Pharmacol* **50**: 483-489, 1996.

LUND F: Digital pulse plethysmography (DPG) in studies of the hemodynamic response to nitrates – a survey of recording methods and principles of analysis. *Acta Pharmacol Toxicol* **59** (Suppl 6): 79-96, 1986.

MOLINO G, AVAGNINA P, BELFORTE G, BIRCHER J: Assessment of the hepatic circulation in humans: new concepts based on evidence derived from a D-sorbitol clearance method. *J Lab Clin Med* **131**: 393-405, 1998.

PORCHET H, BIRCHER J: Noninvasive assessment of portal-systemic shunting: evaluation of a method to investigate systemic availability of oral glyceryl trinitrate by digital plethysmography. *Gastroenterology* **82**: 629-637, 1982.

PREISIG R: Foreign substances as indicators of liver function (In German). *Schweiz Med Wochenschr* Suppl 19: 36-42, 1985.

STENGELE E, WINKLER F, TRENK D, JAHNCHEN E, PETERSEN J, ROSKAMM H: Digital pulse plethysmography as a non-invasive method for predicting drug-induced changes in left ventricular preload. *Eur J Clin Pharmacol* **50**: 279-282, 1996.

TAN YK, DA SILVA AF: Digital photoplethysmography in the diagnosis of suspected lower limb DVT: is it useful? *Eur J Vasc Endovasc Surg* **18**: 71-79, 1999.

ZOLI M, MAGALOTTI D, BIANCHI G, GUELI C, ORLANDINI C, GRIMALDI M, MARCHESINI G: Total and functional hepatic blood flow decrease in parallel with ageing. *Age Ageing* **28**: 29-33, 1999.

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