Noninvasive Assessment of Portal–Systemic Shunting: Evaluation of a Method to Investigate Systemic Availability of Oral Glyceryl Trinitrate by Digital Plethysmography

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The systemic availability of oral glyceryl trinitrate may be a measure of the fraction of portal blood bypassing the hepatocytes through portal–systemic shunts. In order to test this hypothesis without the need for blood sampling, measurements of drug concentrations in plasma were replaced by assessments of pharmacologic effects by using digital plethysmography. Dose-response curves resulting from graded intravenous infusions of glyceryl trinitrate (8 and 25 μg/min) were used as standard of comparison for the pharmacologic response resulting from an oral dose of 800 μg. In 9 normal volunteers, systemic availability of oral glyceryl trinitrate was 2 ± 4% SD. In 7 patients with end-to-side portacaval shunts it was 94 ± 18%, in 3 patients with distal splenorenal shunts 57 ± 11%, and in 10 patients with cirrhosis of the liver it varied between 15% and 85%. Systemic availability of glyceryl trinitrate was negatively correlated with the initial plasma disappearance rate of sulfobromophthalein ($r = -0.72$, $p < 0.01$). No significant correlation was found with the galactose elimination capacity ($r = -0.12$, $n = 17$). The lack of systemic availability of glyceryl trinitrate in healthy volunteers together with an availability close to 100% after end-to-side shunts is compatible with a very high hepatic extraction of the test compound by the normal liver, and with the idea that the systemic availability of oral glyceryl trinitrate comes close to representing portal–systemic shunting. The procedure is rapid, essentially noninvasive, and well tolerated by patients.

Portal–systemic shunting is an important consequence of all diseases that lead to portal hypertension. Major complications of such shunts are esophageal variceal hemorrhages and portal–systemic encephalopathy. The more subtle sequellae of portal–systemic shunting, however, such as hormonal (1), immunologic (2–5), nutritional (6–8), and pharmacologic (9–16) changes have received relatively little attention. This may be because up to now it has not been practical to measure the fraction of portal blood that bypasses the hepatocytes to reach the systemic circulation. The available methods are either highly invasive (17,18) or time consuming (19), and their applications have been limited to few studies. The purpose of this paper is to describe a feasibility study of a new, noninvasive procedure that approaches a quantitative assessment of portal–systemic shunting.

The principle of the method consists in a comparison of the systemic availability of an oral and an intravenous dose of glyceryl trinitrate. This compound is eliminated almost completely in a single passage through the normal liver (20–22). Absorption from the gut is likely to be rapid and complete because the drug penetrates through mucus membranes and even through intact skin (23). Plasma concentrations can be easily manipulated, because this test substance has a half-life of only about 2 min

Received March 12, 1981. Accepted December 4, 1981.

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This work was supported by the Swiss National Science Foundation, and by the Cilag-Chemie Foundation for Therapeutic Research.

The authors are grateful to Professor Dr. M. Sahli and to Mr. M. Oesch for analysis of glyceryl trinitrate in oral and intravenous dose preparations, and to Professor E. Koller for stimulating discussions. The cooperation of the referring physicians is greatly appreciated, in particular that of Professor Dr. Aeberhard, Professor A. Akovbiantz, Professor R. Berchtold, Professor Dr. F. Harder, Dr. P. Jeanneret, Dr. R. Schroeder, and Professor Dr. P. Tondelli.

The authors also thank Miss M. Kappeler for technical assistance, and Miss R. De Paoli for secretarial help.

0016-5085/82/040629-09$02.50

(24). Finally it appears that blood sampling is unnecessary because the pharmacologic effects of glyceryl trinitrate can be measured by plethysmography, as already shown by Murrell in 1879 (25). An attempt was made, therefore, to evaluate a simple and noninvasive approach to the measurement of systemic availability of glyceryl trinitrate when given orally. The data have been sufficiently promising to justify efforts for a further development of the test.

Materials and Methods

Subjects

Nine volunteers without liver disease participated in this investigation. All of them were studied exclusively for the purpose of establishing normal data. The 5 men and 4 women had a mean age of 28.1 ± 4.7 (SD) yr and a mean body weight of 61.4 ± 10.9 kg. All were healthy clinically and had normal values of total bilirubin, aspartate and alanine aminotransferases, γ-glutamyl transpeptidase, alkaline phosphatase, hemoglobin, total leucocytes, and thrombocyte count.

Seventeen patients with liver diseases were also studied (Table 1). They had been referred to our department by other hospital services or by practicing physicians. All but 2 had their diagnoses supported by liver biopsy (26). The other 2 (A.M. and W.S.) had both a history of ethanol intake in excess of 100 g/day, enlarged and firm livers, and esophageal varices as criteria for a diagnosis of alcoholic cirrhosis. All but patient L.H. had elevated fasting bile acid concentrations and clinical evidence for abnormal portal blood flow, such as endoscopically diagnosed esophageal varices or a history of surgery of the portal venous system. Only 3 patients had platelet counts above 120,000 mm^{-3}. Apart from treatment of ascites and edema with spironolactone, no drugs were given that belong to the important enzyme inducers in humans (27).

Standard laboratory tests were used for serum bilirubin (28), aspartate aminotransferase (29), and serum bile acids (30). The initial plasma disappearance of sulfobromophthalein was determined according to the method of Hacki et al. (31) and the galactose elimination capacity as previously published (32).

Table 1. Investigation in Patients with Liver Diseases

Patient	Diagnosis[a]	Total bilirubin (μmol/L)	Aspartate transaminase (IU)	BSP–k_i[b] (%/min)	GEC[c] (mg/min · kg)	Serum bile acids[d] Fasting (μmol/L)	Serum bile acids[d] 2 h Postprandial (μmol/L)	Thrombocyte counts (1000/mm^3)
Patients with liver diseases (n = 10)								
L.I.	CAH, EV	17	91	4.5	4.7	34		78
L.H.	CAH	15	14	7.3	4.7	2	7	195
M.W.	ACL, EV	31	63	7.7	5.6	22	50	70
V.M.	CFL, EV	16	45	6.2	5.8	22	29	67
G.E.	PBC, EV	27	61		4.3	39	51	92
Mu.A.	ACL, EV	22	35	4.4	4.6	8		85
S.W.	ACL, EV	27	24		3.3	105	143	75
G.M.	ACL, EV	19	12		3.6	21	30	210
M.A.	ACL, EV	27	13	5.0	6.6	14		80
vA.H.	ACL, EV	26	12	4.1	3.3	37	84	38
$\bar{x}$		23	37	5.6	4.7	30	56	99
SD		6	27	1.5	1.1	29	45	57
Patients with end-to-side portacaval shunts (n = 7)								
G.M.	ACL	15	27					183
T.O.	CAH	30	21		4.2	25	74	80
D'A.A.	ACL	56	21	3.1	3.9	90	340	92
F.H.	ACL, CAH	21	56		4.0	96	144	105
W.H.	PBC	57	34			102		101
B.L.	NTL	50	66	2.7	4.2	50		50
vS.R.	ACL, SSS	34	29	1.0	5.6	108		189
$\bar{x}$		38	36		4.4	79		114
SD		17	18		0.7	33		52
Patients with distal splenorenal shunts (n = 3)								
B.R.	ACL	23	41					75
V.M.	CFL	29	48	5.1	5.2	90		92
M.W.	ACL	21	34	7.7	6.9	11	25	99

[a] ACL = Alcoholic cirrhosis of the liver; CAH = Chronic aggressive hepatitis; PBC = Primary biliary cirrhosis; CFL = Congenital fibrosis of the liver; NTL = Nodular transformation of the liver; EV = Esophageal varices; SSS = Side-to-side portacaval shunt. [b] Initial plasma disappearance rate constant of BSP, normal range: 12.6 ± 1.6%/min SD (31). [c] Galactose elimination capacity, normal range: 7.5 ± 0.9 mg/min·kg SD (52). [d] Normal range: 3.5 ± 2.2 SD μmol/L (30).

The procedure was explained in detail and informed consent was obtained from all subjects.

Glyceryl Trinitrate Test

All studies were carried out in the morning in a quiet room. The fasting subjects were made comfortable in a supine position with the head slightly raised and the left arm and hand supported horizontally at the level of the right atrium. They were asked to stay awake, but to move as little as possible. A pneumoplethysmographic cuff was placed at the tip of the left middle finger and inflated to a level of 10 mmHg below the diastolic blood pressure.

Plethysmographic recordings were obtained through a Philips (type 133–4) air differential transducer, a Philips pulse amplifier, and an eight-track writer (Cardiopan, F. Liechti AG, Berne, Switzerland). Two electrocardiographic electrodes were fixed on the chest to record electrocardiogram and respiration.

Glyceryl trinitrate (Nitroglycerin Ampullen, Pohl–Boskamp, Holstein, Federal Republic of Germany) in physiologic saline (20 μg/ml) was infused by a Guldener variable Perpex II infusion pump. The exact infusion rates were calculated by weighing the infusion bottles on an analytical scale before and after the infusions and by calibrating the pump after each study.

To study the dose-response relationships, six plethysmographic recordings were obtained at 1-min intervals before drug infusion. Thereafter glyceryl trinitrate was infused for 20 min at a dose of approximately 8 μg/min, followed by infusions of approximately 13, 19, and 25 μg/min for 10 min each. Plethysmographic recordings were obtained at 1-min intervals during the final 6 min of each period of infusion, and thereafter continued until a baseline had been reached again. Immediately afterwards the systemic availability of the oral dose was assessed starting with six baseline recordings at intervals of 1 min. Thereafter 0.8 mg of glyceryl trinitrate—diluted in a mixture of physiologic saline (75 ml) and isotonic bicarbonate (25 ml)—was administered orally and plethysmographic recordings were taken at 2-min intervals for 30 min or until the waves again showed baseline characteristics. Pilot studies had shown that glyceryl trinitrate is stable in 0.1 N HCl for at least 1 h. The slightly alkaline, isotonic solution of the test dose was used to achieve rapid gastric emptying.

Investigations of in vivo glyceryl trinitrate recoveries were performed by infusions of increasing followed by decreasing rates of glyceryl trinitrate, thereby simulating intestinal absorption, but assuring a systemic availability of 100%. In practice infusion rates of approximately 8, 13, 17, 21, 25, 21, 17, 13, and 8 μg/min were given for 2 min each, and plethysmographic recordings were obtained before and during the infusion period at 1-min intervals. This procedure was carried out as soon as baseline conditions were reestablished after the calibrating intravenous infusion or the oral dose.

Analysis of Plethysmographic Recordings

Each plethysmographic recording was long enough for an evaluation of eight consecutive cardiac cycles corresponding to about two respiratory cycles.

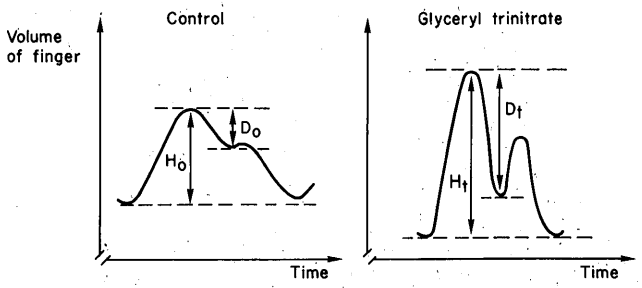

Figure 1. Diagrammatic representation of plethysmographic waves during a control period and during infusion of glyceryl trinitrate. The values D and H were measured at each cycle and the estimated pharmacologic effect (E) was calculated from appropriate average values as $E = \ln(\overline{D}_t/\overline{H}_t - \overline{D}_o/\overline{H}_o)$.

The effect of glyceryl trinitrate on the plethysmographic wave is shown diagrammatically in Figure 1. The vertical distance between the systolic peak and the diastolic notch (D) of each cycle was measured and divided by the total height of the systolic peak (H). For each plethysmographic measurement the results of eight consecutive cardiac cycles were averaged. To get the baseline value, the six averaged measurements taken at 1-min intervals before the administration of glyceryl trinitrate were also averaged.

To estimate the pharmacologic effect of glyceryl trinitrate at time t, the average baseline ratio $\overline{D}_o/\overline{H}_o$ was subtracted from each subsequent determination of the average ratio $\overline{D}_t/\overline{H}_t$. In order to achieve straight dose-response curves, the natural logarithm (ln) of this value was defined as estimated pharmacologic effect (E). Thus:

$$E = \ln\left(\frac{\overline{D}_t}{\overline{H}_t} - \frac{\overline{D}_o}{\overline{H}_o}\right).$$

For the construction of dose-response curves the six values for E corresponding to the final 6 min of each glyceryl trinitrate infusion rate were averaged.

To assess the systemic availability of glyceryl trinitrate, the effect corresponding to each 2-min period of observation was considered to be the arithmetic average of the two adjacent measurements. Assuming that this effect resulted from a "hypothetical infusion rate," such infusion rates corresponding to each period were derived from the dose-response curve of the investigated subject. By numerical integration of these hypothetical infusion rates the systemically available or effective fraction of the dose was obtained. The effects observed after the rapidly increasing and decreasing intravenous infusions were evaluated analogously.

Statistics

Linear regression analysis and Student's t-tests were performed taking $p < 0.05$ as level of statistical significance (33). The coefficient of variation (cv) after duplicate determinations was calculated as

$$cv = \frac{100}{\bar{x}}\sqrt{\frac{\Sigma d^2}{2n}},$$

where $\bar{x}$ represents the average of all determinations, d the difference between two determinations, and n the number of pairs.

Results

The chosen rates of intravenous glyceryl trinitrate infusion were generally well tolerated. Only in some normal volunteers were the two highest doses associated with a mild sensation of pressure in the head, which never necessitated interruption of the experiment. The same infusions, however, did not produce any discomfort in patients. No other inconveniences were noted by the participants.

The pharmacologic effects, measured by digital plethysmography increased with every increase in intravenous infusion rate. A representative dose-response curve is shown in Figure 2. Most of these curves were linear. In all but 3 instances r was > 0.96, the lowest value being 0.91. Interestingly, the slopes and intercepts of the dose-response curves varied widely among different individuals. In patients with liver diseases the slopes were significantly steeper than in healthy volunteers ($p < 0.005$), and the effects corresponding to an infusion of 10 μg/min were significantly smaller ($p < 0.02$; Table 2).

A study showing the pharmacologic response after an oral dose of glyceryl trinitrate is given in Figure 3. When an effect was observed, it usually started within 2–4 min after the oral dose and lasted for 10–40 min. Among the 9 healthy volunteers a measurable change in the plethysmographic wave occurred only in 2 subjects. In these the response was small, corresponding to a systemic availability of 5% and 13%, respectively. In patients with cirrhosis of the liver, the systemic availability of glyceryl trinitrate varied between 15% and 85% (Table 2). In those with end-to-side or side-to-side portacaval shunts, systemic availability of glyceryl trinitrate was 94 ± 18% SD. It was lower when a distal splenorenal shunt had been carried out (57 ± 11% SD).

In 5 patients the examination was carried out twice. Although the dose-response curves were not superimposable in the two experiments, the calculated systemic availabilities of oral glyceryl trinitrate agreed relatively well, the first measurements being 37%, 47%, 47%, 66%, and 113%, and the second being 43%, 37%, 60%, 59%, and 114%, respectively. The coefficient of variation calculated from these figures is ±9.9%.

Further studies were conducted to validate whether or not the general procedure could be used to assess systemic availability of glyceryl trinitrate. For this purpose rapidly increasing and decreasing intravenous infusions of glyceryl trinitrate were given in the expectation that the systemic availability should be 100%. An example of such an experiment is shown in Figure 4. When applied to 9 healthy volunteers it was found that the plethysmographic method detected a systemic availability of glyceryl trinitrate of 91 ± 12% SD.

The systemic availability of glyceryl trinitrate was compared with the other investigations defining severity of the liver disease in the examined patients. A statistically significant negative correlation was found between the availability of glyceryl trinitrate and the initial plasma disappearance rate constant of sulfobromophthalein (BSP) (k_i; Figure 5). Positive correlations were found with the fasting and particularly with the 2-h postprandial bile acids (Figure 6). By contrast, the systemic availability of glyceryl trinitrate appeared to be unrelated to the galactose elimination capacity ($r = -0.12$, $n = 17$). The slopes and the intercepts of the dose-response curves were not correlated with any of the above liver function tests.

Discussion

The results of the present study suggest that in patients with various liver diseases noninvasive assessment of portal–systemic shunting may now be feasible. The test was found to be well accepted by patients, and the inconvenience appeared to be min-

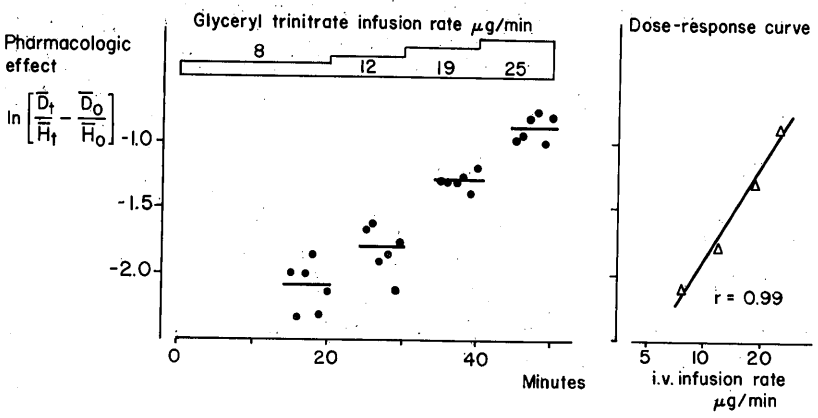

Figure 2. Pharmacologic effects observed by plethysmography in patient M.W. during graded intravenous infusions of glyceryl trinitrate. The *points* represent averages of eight cardiac cycles and the *horizontal lines* averages of the six measurements corresponding to each infusion rate. The right-hand side shows the corresponding dose-response curve. It was obtained by plotting the average effects against the simultaneously administered infusion rates. In view of the short half-life (approximately 2 min, 21) of glyceryl trinitrate, it was possible to achieve steady states within 10 min.

Table 2. Results of Glyceryl Trinitrate Tests

Patient	Dose-response curve: Slope[a]	Dose-response curve: Effect at infusion of 10 μg/min[b]	Systemic availability of oral dose (%)
Patients with liver diseases (*n* = 10)			
L.I.	1.74	−3.12	15
L.H.	1.17	−2.91	18
M.W.	1.29	−1.92	37
V.M.	1.39	−2.18	47
G.E.	1.23	−3.17	47
Mu.A.	1.87	−2.71	57
S.W.	0.97	−2.90	60
G.M.	1.09	−1.94	62
M.A.	2.12	−3.95	75
vA.H.	1.66	−2.85	85
x̄	1.45	−2.77	50
SD	0.38	0.62	23
Patients with end-to-side portacaval shunts (*n* = 7)			
G.M.	1.42	−1.80	66
T.O.	1.21	−1.70	79
D'A.A.	1.38	−2.70	88
F.H.	1.85	−2.61	95
W.H.	1.66	−2.92	102
B.L.	3.04	−3.90	113
vS.R.	1.21	−2.31	114
x̄	1.68	−2.56	94
SD	0.64	0.74	18
Patients with distal splenorenal shunts (*n* = 3)			
B.R.	0.80	−2.51	46
V.M.	1.29	−2.59	57
M.W.	1.08	−1.93	68
x̄	1.06	−2.34	57
SD	0.24	0.36	11
Healthy volunteers (*n* = 9)			
x̄	0.88[c]	−2.05[d]	2
SD	0.40	0.41	4

[a] ln $(D_t/H_t - D_o/H_o)$/(ln infusion rate) (in micrograms per minute). [b] ln $(D_t/H_t - D_o/H_o)$. [c] Significantly different from the 20 investigations in patients ($p < 0.005$). [d] Significantly different from the 20 investigations in patients ($p < 0.02$).

imal. Furthermore, the subjects investigated had to remain within the laboratory for only about 2 h. An appreciation of the validity and the limitations of the method, however, requires a detailed appraisal of all aspects of the procedure.

Effect measurements by digital plethysmography instead of measurements of plasma concentrations introduces two special problems: the pharmacologic effect of glyceryl trinitrate must be adequately measurable, and a reproducible relationship between effect of glyceryl trinitrate and its concentrations in the biophase needs to be postulated.

Our method to define the pharmacologic effect is arbitrary and cannot be directly related to any physiologic parameter describing the hemodynamic changes produced by glyceryl trinitrate (34). We have tested several published methods of curve analysis (35–38) and found that the two measurements *D* and *H* could be obtained more reproducibly and in more patients than the other methods. Nevertheless, the shape of the plethysmographic curve or cardiac arrhythmias prevented proper curve-analysis in 4 patients. Also the definition of the effect and the construction of dose-response curves are purely empirical. Their justification lies in the fact that straight dose-response curves could be obtained reproducibly, although they varied markedly from subject to subject and from day to day in a single subject (Table 2). Thus an adequate basis for the intravenous doses could be established.

One problem related to digital plethysmography was the variability of the plethysmographic curve from cycle to cycle and from minute to minute (39). It was, therefore, necessary to obtain a large number of measurements and to take averages. An entire study involved 400–450 cardiac cycles, and hand analysis proved to be cumbersome and time consuming. For this reason the measurement and averaging process have now been computerized in collabora-

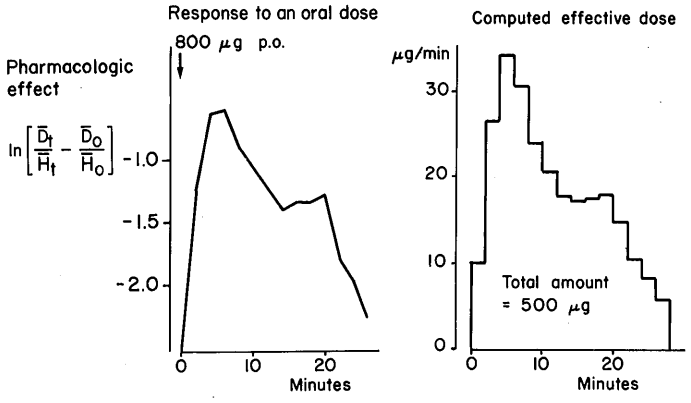

Figure 3. Pharmacologic response after an oral dose of 800 μg glyceryl trinitrate in patient M.W. By use of the dose-response curve shown in Figure 2 the pharmacologic effects were transformed into computed effective doses and plotted in the graph on the right-hand side. The total area corresponds to an available dose of 500 μg of glyceryl trinitrate that represents 63% of the oral dose. For details of calculations see Methods.

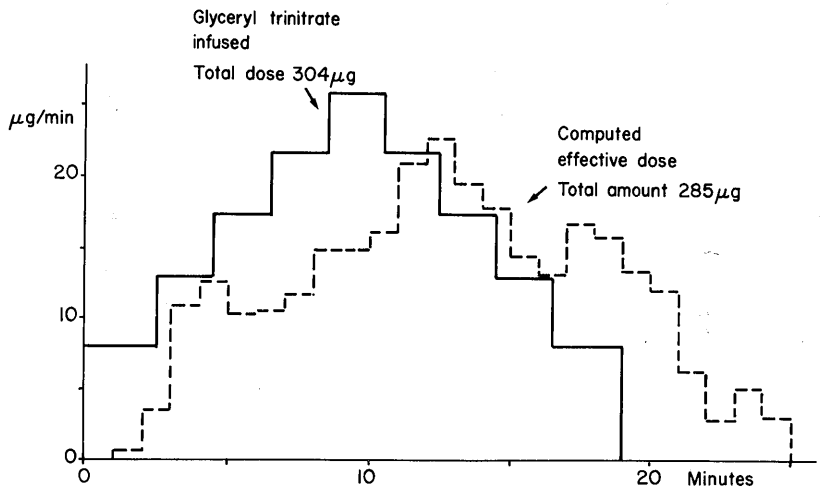

Figure 4. Intravenous glyceryl trinitrate infusion rates in a normal volunteer and corresponding computed effective doses. The latter were obtained as in Figure 3. Effect measurements revealed that 94% of the infused dose had been pharmacologically active. The rapidly changing infusion rates resulted in some delay in the pharmacologic effects.

tion with the Department of Electronics of the Swiss Federal Institute of Technology in Zürich (Prof. W. Guggenbühl). The inclusion of all cardiac cycles gives 8–10 times more data thereby improving the averaging process. The immediate display of the data allows verification of steady-state conditions when performing the dose-response part of the test. Stability of the baseline can also be evaluated immediately. Finally the integration process takes only a few minutes. These technical advances should not only facilitate data analysis, but are also expected to contribute significantly to the precision of the method.

Because the relationship between measured effects and glyceryl trinitrate concentrations in the biophase is unknown, it is not possible to calculate drug concentrations. However, if it is assumed that the concentration-effect relationship remains constant throughout the 2 h of the experiments, a comparison of the oral to the intravenous dose should be valid.

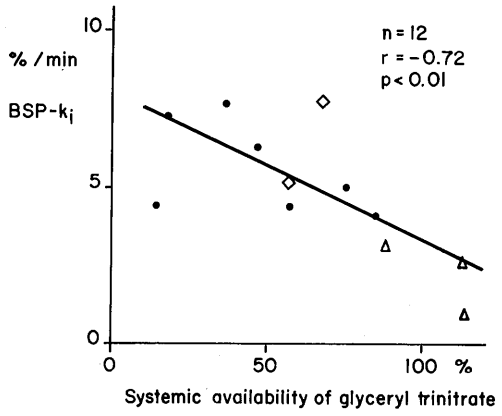

Figure 5. Correlation of systemic availability of glyceryl trinitrate with the initial plasma disappearance of BSP. The patients with cirrhosis are indicated by ●, with distal splenorenal shunt by ◇, and with end-to-side shunt by △.

Tolerance was not noted within this short period of time (40). The experimental design of a comparison between oral and intravenous doses to assess systemic availability of a test compound is classical. It requires the assumption of first-order kinetics, which has not been tested in our patients. Saturation of first-pass elimination after oral glyceryl trinitrate is now well recognized (41). We, therefore, have chosen to apply small oral doses of 800 μg and could observe a practically complete elimination in normal subjects (Table 2). Thus no evidence for saturation could be found. Evaluation of the non-steady-state kinetics after the oral dose with steady-state kinetics after the intravenous infusions appears, therefore, justifiable. Empirically this approach has been verified by the rapidly increasing and decreasing intravenous infusions that simulated the non-steady-state of an oral dose but assured 100% systemic availability (Figure 4). The result of 98 ± 18% availability confirms this general procedure.

Glyceryl trinitrate was given orally as an isotonic slightly alkaline solution. Thus, drug absorption through oral or esophageal mucosa may also bypass the liver and simulate portal–systemic shunting. It was assumed that of the total volume of 100 ml only few milliliters might be retained above the diaphragm for drug absorption. Correspondingly, the error should be small. Fluid retention in the mouth or esophagus may perhaps explain the slight systemic availability seen in 2 of the 9 normal subjects, and it may render the test invalid in subjects with esophageal diseases. The use of gelatine capsules, however, resulted in more erratic absorption and made the studies much more difficult.

The short half-life of glyceryl trinitrate of approximately 2 min (24) is an important advantage, because it allows establishment of a steady state within a few minutes. Other properties of the compound may, however, contribute to some inaccuracies. Glyceryl

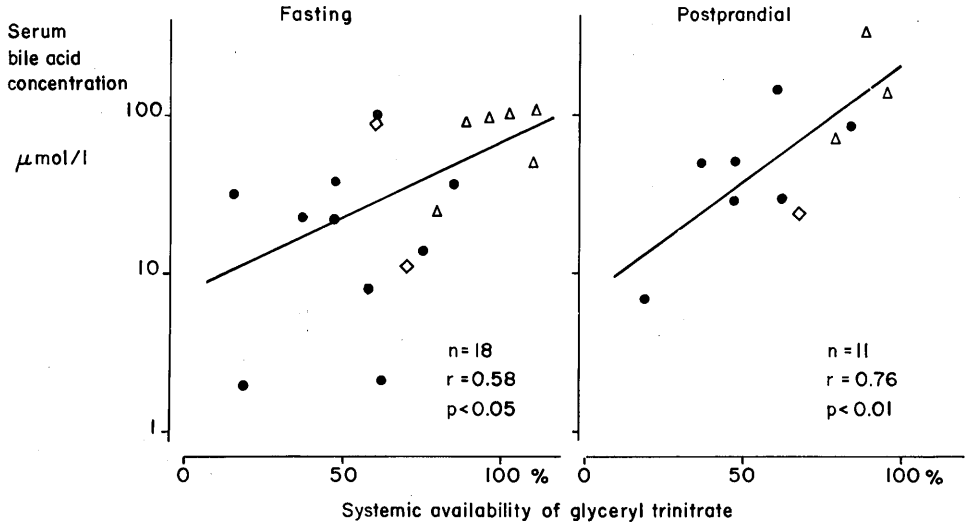

Figure 6. Correlation of the systemic availability of glyceryl trinitrate with the fasting and 2-h postprandial serum bile acid concentrations. The symbols are used as in Figure 5.

trinitrate may be subject to intestinal first-pass elimination, since the enzyme glutathione-S-transferase is present in rat enterocytes (42). Thus it might be possible, that patients with end-to-side portacaval shunts show <100% systemic availability of an oral dose. Furthermore, if glyceryl trinitrate is infused intravenously, some of the drug may be lost in the tubing of the infusion set (43), thereby leading to a systematic error in the calculation of infusion rates and systemic availabilities. Pilot experiments suggest that 10%–20% of the dose may have been lost in our experiments. The calculated availabilities of the oral doses would be correspondingly smaller. Perhaps, the losses of glyceryl trinitrate by intestinal first-pass and by the infusion sets may have been compensated mutually, thereby leading to the almost 100% systemic availability of oral glyceryl trinitrate found in patients with end-to-side portacaval shunts.

Glyceryl trinitrate may also modify the splanchnic circulation and thereby potentially change the degree of shunting (44). Studies of portal–systemic shunting with other test compounds will be needed as standard of reference in order to evaluate this question. The fact that glyceryl trinitrate is extensively metabolized in extrahepatic tissues and even in erythrocytes (45,46) does not invalidate the calculations of systemic availability, because the main difference between oral and intravenous administration is the passage through the splanchnic organs, particularly the liver.

Whether or not the systemic availability of glyceryl trinitrate may be regarded as a measure of "portal–systemic shunting" is a matter of definition. Portal blood flow may be subject to streamlining (47–49). If duodenal and upper-jejunal blood, where glyceryl trinitrate presumably is absorbed, is shunted through extrahepatic portal–systemic connections, glyceryl trinitrate is likely to become effective systemically. If the same blood, however, passes through the liver, the vascular bed may be distorted in such a way that ordinary definitions of shunting are hard to apply (50). Furthermore, the effects of hepatocellular injury on the bioavailability of glyceryl trinitrate are as yet unknown. Nevertheless other gut-derived compounds such as hormones, nutrients, or drugs are likely to share their fate with glyceryl trinitrate. Thus, irrespective of the definition of shunting the test compound may be valuable for the assessment of pathophysiologically relevant circulatory changes in portal hypertension.

Despite the limitations of the method, the results obtained in patients with various liver diseases are compatible with expectations. The increased slope of the dose-response curve supports the idea that disposition of glyceryl trinitrate is slowed in liver patients. The many other variables also influencing the dose-response relationship (51) may be responsible for the fact that no correlation could be found between slopes of the dose-response curve and severity of the liver disease as revealed by galactose elimination capacity, BSP-elimination, and serum bile acid concentrations. The good correlation between postprandial bile acid concentrations and systemic availability of glyceryl trinitrate suggests a common denominator that could be portal–systemic shunting. If this is the case, it is not surprising to find that fasting serum bile acids are less closely related to glyceryl trinitrate availability, and galactose elimination capacities not at all. The initial plasma disappearance of BSP (k_i) is to a certain degree dependent on hepatic blood flow (31). A reduction in BSP–k_i, therefore, may occur together with increasing systemic availabilities of oral glyceryl trinitrate (Figure 5), although such a relationship must be regarded as indirect. Thus, the comparisons of different tests of

hepatic function with the glyceryl trinitrate test reveal that their results are compatible with each other. However, the glyceryl trinitrate test seems to provide information that hitherto has been available only through highly invasive (17,18) or time-consuming (19) investigations. As patient acceptance of the new procedure is excellent, it might potentially be useful for prediction of hepatic first-pass effects of other compounds such as nutrients, hormones, or drugs. It might also be valuable for surgical or medical clinical trials in patients with liver diseases.

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