Intensive Care Med (2000) 26: 1557–1560
DOI 10.1007/s001340000662

BRIEF REPORT

Christian Lehmann
Kasra Taymoorian
Helmar Wauer
Dietmar Krausch
Jürgen Birnbaum
Wolfgang J. Kox

Effects of the stable prostacyclin analogue iloprost on the plasma disappearance rate of indocyanine green in human septic shock

Received: 13 April 2000
Final revision received: 28 July 2000
Accepted: 3 August 2000
Published online: 9 September 2000

C. Lehmann (✉) · K. Taymoorian · H. Wauer · D. Krausch · J. Birnbaum · W. J. Kox
Klinik für Anästhesiologie und operative Intensivmedizin, Universitätsklinikum Charité, Campus Charité Mitte, Schumannstrasse 20/21, 10117 Berlin, Germany
E-mail: christian.lehmann@charite.de
Fax: +49-30-28022096

Abstract *Objectives:* To evaluate the effect of the stable prostacyclin analogue iloprost on the plasma disappearance rate of indocyanine green (PDR) in patients with septic shock.
Design and setting: A prospective clinical study in a university hospital intensive care unit.
Patients and interventions: 20 patients in septic shock. Patients received iloprost infusion (1 ng/kg per minute) for 24 h.
Measurements and results: PDR was determined by a femoral arterial fiberoptic catheter before, 1, 6, and 24 h after start and 1 h after end of iloprost infusion. PDR increased significantly 24 h after start of iloprost infusion (baseline: 13.9 ± 1.7 % vs. 18.6 ± 2.2 %/min) and decreased 1 h after end of infusion (13.7 ± 1.7 %/min; $p < 0.002$). There was no change in pH_i, cardiac index, mean arterial pressure, heart rate, central venous pressure, or intrathoracic blood volume index.
Conclusion: Administration of the stable prostacyclin analogue iloprost significantly increases PDR, indicating improvement in liver function.

Key words Iloprost · Indocyanine green · Sepsis · Septic shock · Liver

Introduction

Deterioration in hepatosplanchnic perfusion is a common finding in critical ill patients [1]. Various causes have been proposed, such as vasoconstriction because of autoregulating mechanisms, release of mediators, disseminated intravascular coagulation, swelling of endothelial cells, and adherence of leukocytes [1,2]. This hypoperfusion may lead to a disturbance of gut barrier function, resulting in bacterial translocation, endotoxemia, and multiple organ dysfunction and failure, and may have an impact on liver function [3].

Monitoring of hepatosplanchnic blood flow is either inaccurate and controversial, for example, using pH_i [4], or invasive and difficult to perform, for example, using a liver vein catheter [5]. In our study we used the COLD system as a bedside monitoring device for splanchnic perfusion and liver function. The COLD system is a minimally invasive monitoring system for determining cardiac output, arterial oxygen saturation, extravascular lung water, and other derived values [6]. The system can be used to monitor liver function by measuring the plasma disappearance rate (PDR) of indocyanine green (ICG).

During septic shock the mismatch between endogenous thromboxane A_2 and prostaglandin I_2 (prostacyclin, PGI_2) balance is well known. Levels of both substances are increased, but the amount of the vasoconstricting thromboxane A_2 is disproportionally higher [7]. Administration of PGI_2 may reestablish the eicosanoid balance. PGI_2 is a cytoprotective agent synthesized by endothelial cells. One of the PGI_2 activities is vasodilation. PGI_2 has also been shown to inhibit leukocyte activation by inhibiting tumor necrosis factor-α production by monocytes, neutrophil activation, and neutrophil adhesion to endothelial cells. Because activated leukocytes release a variety of inflammatory mediators, including cytokines, neutrophil proteases, and reactive

oxygen species, all of which can damage adjacent endothelial cells, they have been thought to play a role in tissue injury. Therefore the administration of PGI_2 may improve hepatosplanchnic perfusion and liver function during septic shock.

This study evaluated the effects of continuous infusion of the stable PGI_2 analogue iloprost on the PDR of ICG measured by the COLD system.

Materials and methods

Patients

The study was approved by the local hospital ethics committee and was conducted according to the principles established in Helsinki. Twenty patients in septic shock [8] were included in the study (4 women, 16 men; median age 62 years, range 20–71). The median score on the Acute Physiology and Chronic Health Evaluation II was 24 points (range 14–38). The distribution of underlying diseases was as follows: 10 pneumonia, 4 urosepsis, 2 pancreatitis, 2 spondylodiscitis, 1 peritonitis, and 1 mediastinitis. At the time the investigation started the patients already were in intensive care unit (ICU) for an average of 3 days.

All patients were ventilated and received norepinephrine for maintenance of mean arterial pressure at 60 mmHg or higher. A fiberoptic catheter (COLD system, Pulsion, Munich, Germany) was inserted into a femoral artery. A nasogastric tube with a silicone balloon on its tip (Trip TGS catheter, Tonometrics, Worcester, Mass., USA) was inserted to measure intramucosal pH of the stomach wall (pH_i). All patients received 50 mg ranitidine repeated after 8 h [9]. We infused iloprost (Ilomedin, Schering, Germany) for 24 h at a dose of 1 ng/kg per minute. Measurements were performed at baseline (time 0), 1, 6, and 24 h after beginning iloprost infusion and 1 h after ending iloprost infusion (time 25).

Measurements using the COLD system

For assessment of PDR a cold (< 10 °C) ICG bolus of 0.3 mg ICG/kg body weight at a concentration of 2.5 mg ICG/ml was injected into a central vein. After dye injection the COLD system determines the time of intermixture in subject to primary circulation time. PDR results from the decrease in ICG concentration from the time of intermixture to the end of measurement after 240 s. PDR indicates the percentage of injected dye disappearing from circulating blood per minute. We measured the cardiac index and intrathoracic blood volume index by the COLD system using the double indicator method.

Statistics

All values are given as mean ± SD. We performed the analysis of variance test for repeated measurements with Bonferroni's correction for multiple testing. Statistical significance was defined at $p < 0.05$.

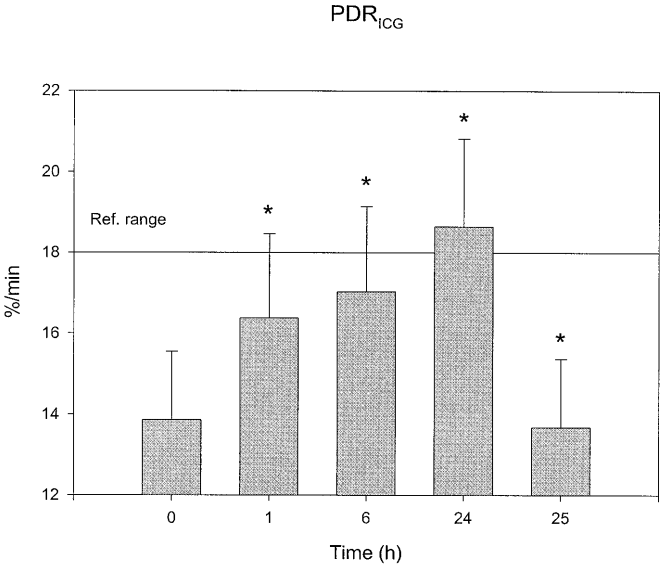

Fig. 1 Plasma disappearance rate of ICG (%/min; $n = 20$, mean ± standard deviation); measurements at baseline (time 0), 1, 6, and 24 h after the beginning of iloprost infusion and 1 h after the end of iloprost infusion (time 25)

Results

Figure 1 presents the PDR values. At baseline the mean PDR was 13.9 ± 1.7 %/min (reference range: 18–25 %/min). One hour after beginning iloprost infusion PDR was significantly increased, to 16.4 ± 2.1 %/min ($p < 0.05$); 24 h after the beginning the PDR was 18.6 ± 2.2 %/min ($p < 0.05$). The overall increase was 34.5 %. After the end of infusion values decreased significantly again to baseline level (13.7 ± 1.7 %/min; $p < 0.05$). All hemodynamic parameters were stable (see Table 1). Baseline pH_i values were in the reference range. There was no significant change in norepinephrine dose during the observation period.

Discussion

In the present study iloprost administration reversibly improved the plasma disappearance rate of ICG in human septic shock. The observed effects on PDR are obviously not a result of volume supply or change in cardiac index because volume state was kept constant. There was no change in central venous pressure or intrathoracic blood volume. Beside standard therapy, patients received no additional infusions. The norepinephrine dose was unchanged during the observation period.

The increase in PDR may be due to a redistribution of blood flow in favor of the hepatosplanchnic circulation or at least to hepatosplanchnic vasodilation. As a result of the increased blood flow to the liver a higher

Table 1 Clinical data

	Baseline	After 1 h	After 6 h	After 24 h	1 h after end of infusion
Cardiac index (l/min/m^2)	3.6 ± 1.1	3.7 ± 1.2	3.8 ± 1.5	4.0 ± 1.3	3.5 ± 0.9
Heart rate (1/min)	99 ± 22	105 ± 20	103 ± 18	104 ± 20	107 ± 20
Mean arterial pressure (mmHg)	80 ± 26	82 ± 9	85 ± 8	81 ± 9	79 ± 7
Central venous pressure (mmHg)	9 ± 6	8 ± 5	7 ± 4	8 ± 5	10 ± 4
intrathoracic blood volume index (ml/m^2)	969 ± 346	1044 ± 523	1012 ± 345	1076 ± 293	984 ± 169
Intramucosal pH	7.34 ± 0.12	7.30 ± 0.11	7.32 ± 0.15	7.31 ± 0.13	7.25 ± 0.05
Norepinephrine (μg/kg per minute)	0.11 ± 0.07	0.12 ± 0.07	0.15 ± 0.11	0.13 ± 0.12	0.12 ± 0.13

amount of ICG is extracted by the liver into the bile, and PDR is increased. Other investigators have also shown that iloprost increases blood flow in the hepatosplanchnic region because it acts as a vasodilator [10].

Secondly, an improvement in liver function may explain the PDR increase. One of the most important factors impairing hepatic function in septic shock is the release of tumor necrosis factor-α. Wang et al. [11] reported that tumor necrosis factor-α depresses hepatocellular function measured by indocyanine clearance. It has been shown that iloprost inhibits tumor necrosis factor-α synthesis via cAMP activation, transcriptional, and posttranscriptional effects [12]. Thus liver function may be improved during iloprost therapy.

These two effects together can cause increased PDR. Considering the unchanged normal pHi – regarding it as a parameter for hepatosplanchnic perfusion – improvement in liver function seems to be the dominant effect. The delayed effect after the beginning of iloprost infusion is also more likely a result of improved liver function as a perfusion effect. However, pHi does not always reflect changes in hepatosplanchnic blood flow [4]. Moreover, PDR decreased immediately after the end of iloprost infusion. This effect is related to the short half-life time of iloprost. The fast change suggests a perfusion effect.

Distinguishing between the effects on liver function and hepatic perfusion requires separate examinations of liver function, for example, using tests such as the ICG extraction fraction test and the monoethylglycinexylidide test, and measurement of liver blood flow, for example, using a liver vein catheter. The extraction fraction of ICG is the fractional amount of ICG which is extracted by the liver into the bile during a defined period of time. Therefore it is independent of liver blood flow. The higher the liver blood flow, the greater is the absolute amount of ICG taken into the bile. Without change in liver function, however, there is no change in extraction fraction.

Iloprost has also a reversible anticoagulatory effect by inhibiting platelet function. The effect is dose-related. Platelet aggregability returns to baseline levels within the 1st h after the end of the infusion [13]. In patients who are at risk of developing bleeding complications iloprost should be used with caution. In our study there was no case of bleeding.

Septic shock is still related to a high mortality in critically ill patients. Standard therapy consists of volume replacement and the use of vasopressors. Because of disturbance of organ microcirculation septic shock may result in multiple organ failure. Iloprost therapy may be useful for preventing deterioration in microcirculation. The administration of iloprost improves PDR, as shown in our study. As PDR seems to be related to outcome in critical ill patients [14], the use of iloprost may be justified although further details of its effects on the hepatosplanchnic blood flow and on liver function were not clarified in this study.

References

1. Mythen MG, Webb AR (1994) The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. Intensive Care Med 20: 203–209
2. Fiddian Green RG (1990) Gut mucosal ischemia during cardiac surgery. Semin Thorac Cardiovasc Surg 2: 389–399
3. Lautt WW (1985) Mechanism and role of intrinsic regulation of hepatic arterial blood flow: hepatic arterial buffer response. Am J Physiol 249:G549–G556
4. Uusaro A, Ruokonen E, Takala J (1995) Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. Br J Anaesth 74: 149–154
5. Ruokonen E, Takala J, Kari A (1993) Regional blood flow and oxygen transport in patients with the low cardiac output syndrome after cardiac surgery. Crit Care Med 21: 1304–1311
6. Pfeiffer UJ, Backus G, Blümel G, Eckart P, Müller P, Winkler P, Zeravik J, Zimmermann GJ (1990) A fiberoptics-based system for integrated monitoring of cardiac output, intrathoracic blood volume, extravascular lung water, O_2 saturation, and a-v differences. In: Lewis FR, Pfeiffer UJ (eds) Practical applications of fiberoptics in critical care monitoring. Springer, Berlin Heidelberg New York, pp 114–126

7. Bihari DJ, Tinker J (1988) The therapeutic value of vasodilator prostaglandins in multiple organ failure associated with sepsis. Intensive Care Med 15: 2–7
8. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101: 1644–1655
9. Heard SO, Helsmoortel CM, Kent JC, Shahnarian A, Fink MP (1991) Gastric tonometry in healthy volunteers: effect of ranitidine on calculated intramural pH. Crit Care Med 19: 271–274
10. Manasia A, Kang H, Hannon E, Lu Y, Oropello J, Leibowitz A, Stein J, Benjamin E (1997) Effects of the stable prostacyclin analogue iloprost on mesenteric blood flow in porcine endotoxic shock. Crit Care Med 25: 1222–1227
11. Wang P, Ayala A, Ba ZF, Zhou M, Perrin MM, Chaudry IH (1993) Tumor necrosis factor-alpha produces hepatocellular dysfunction despite normal cardiac output and hepatic microcirculation. Am J Physiol 265:G126–G132
12. Jörres A, Dinter H, Topley N, Gahl GM, Frei U, Scholz P (1997) Inhibition of tumour necrosis factor production in endotoxin-stimulated human mononuclear leukocytes by the prostacyclin analogue iloprost: cellular mechanisms. Cytokine 9: 119–125
13. Grant SM, Goa KL (1992) Iloprost. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischaemia and extracorporeal circulation procedures. Drugs 43: 889–924
14. Kholoussy AM, Pollack D, Matsumoto T (1984) Prognostic significance of indocyanine green clearance in critically ill surgical patients. Crit Care Med 12: 115–116