ELSEVIER

Plasma Disappearance Rate of Indocyanine Green in Liver Dysfunction

P. Faybik and H. Hetz

ABSTRACT

The presence of hepatic dysfunction significantly affects the length of hospital stay and the outcome in critically ill patients. Considering the important partial hepatic functions of metabolism, synthesis, detoxification, and excretion, the worse clinical course of patients suffering from hepatic dysfunction is not surprising. The most often used indicator of hepatic dysfunction is bilirubin. However, bilirubin and other commonly used static laboratory tests provide only indirect measures of hepatic function. In contrast to these static tests, dynamic liver tests, such as indocyanine green (ICG) disappearance rate should provide better direct measures of the actual functional state of the liver at the time of assessment. The ICG is a water-soluble inert compound that is injected intravenously. It mainly binds to albumin in the plasma. ICG is then selectively taken up by hepatocytes, independent of adenosine triphosphate (ATP), and later excreted unchanged into the bile via an ATP-dependent transport system. The ICG is not metabolized; it does not undergo enterohepatic recirculation. Thus, ICG excretion rate in bile reflects the hepatic excretory function and hepatic energy status. Because of these features, ICG has been found to be useful to assess liver function in liver donors and transplant recipients, in patients with chronic liver failure, and as a prognostic factor in critically ill patients. Further trials concerning liver dysfunction have applied the noninvasive bedside assessment of ICG among other clinical variables to monitor the progress and/or the reversal of liver dysfunction.

HEPATIC dysfunction is characterized by disturbances of partial hepatic functions. It can appear as a sole organ dysfunction, in combination with other organ dysfunctions, or as a part of a multiple organ dysfunction syndrome (MODS). Although numerous publications address hepatic dysfunction, there is no unique definition of this clinical syndrome.

INDICATORS OF HEPATIC DYSFUNCTION

The most often used indicator of hepatic dysfunction is bilirubin with a threshold value greater than 2 mg/dL.[1,2] However, bilirubin and other commonly used static laboratory tests, such as aminotransferase activity, albumin, clotting factors, and lactate, provide only indirect measures of hepatic function. Therefore they have limited prognostic value. In contrast to these static tests, dynamic liver tests, such as clearance (indocyanine green, caffeine), elimination capacity (galactose), and metabolite formation test (CO_2 exhalation: ^{14}[C] aminopyrine-,^{13}[C] methacetin-breath test) provide direct measures of the actual functional state of the liver at the time of the assessment. Among these, we chose to examine indocyanine green.

INDOCYANINE GREEN

Indocyanine green (ICG), a water-soluble, inert anionic compound, is injected intravenously. It mainly binds albumin and β-lipoproteins in the plasma. Independent of adenosine triphosphate (ATP), ICG is then selectively taken up by hepatocytes, and later excreted unchanged into the bile via an ATP-dependent transport system. Thus, ICG excretion rate in bile reflects the hepatic ATP level and energy status. The ICG is not metabolized; it does not undergo enterohepatic recirculation.[3] Owing to these features, ICG has been proposed to assess liver function in donors and recipients, in patients with chronic liver failure, and in criti-

From the medical university of Vienna, Vienna, Austria.

Address reprint requests to Peter Faybik, Department of Anesthesiology and General Intensive Care, Medical University of Vienna, Vienna, Austria. E-mail: peter.faybik@meduniwien.ac.at

© 2006 by Elsevier Inc. All rights reserved.
360 Park Avenue South, New York, NY 10010-1710

0041-1345/06/$–see front matter
doi:10.1016/j.transproceed.2006.01.049

cally ill patients as a prognostic factor.[4–6] Plasma disappearance rate of ICG (PDR_{ICG}) is the most commonly used ICG-derived parameter for clinical and experimental assessment of liver function; the normal range is 18% to 25%/min. However, it must be emphasized that PDR_{ICG} does not represent the liver blood flow but the ICG uptake by hepatocytes, its excretion into the bile, blood flow-dependent liver metabolism, and energy status.

There are various techniques to assess PDR_{ICG} in vivo. The gold standard relies on serial blood sampling after ICG injection with spectrophotometric analysis of concentrations.[4,5] However, it is both expensive and rather time-consuming. Another method uses a fiberoptic aortic catheter inserted via a femoral artery sheath.[7,8] This method correlates with the serial blood sampling method.[9] Although this is a bed-side technique, its use remains restricted mostly to experimental settings. Furthermore, a noninvasive pulse-densitometric method uses a transcutaneous system adapted from pulse oximetry and a peripheral or central venous access for ICG injection. This method correlates well with the invasive method in hemodynamically stable and mechanically ventilated critically ill patients as well as hemodynamic unstable patients undergoing liver transplantation.[7,10] According to Gottlieb et al,[11] PDR_{ICG} is a good indicator of hepatic dysfunction following injury. In the seven patients studied, PDR_{ICG} preceded an increase in serum bilirubin levels and was more sensitive.

A further study demonstrating the superiority of ICG over bilirubin was performed by Pollack et al[12] in a population of patients with trauma or shock. Bilirubin, but not ICG, failed to discriminate survivors from nonsurvivors. This observation could be due to the high intrahepatic concentration of inflammatory cytokines during hepatic dysfunction. These factors inhibit the expression of hepatobiliary transport systems for organic anions (OATP2), such as ICG at the mRNA level.[13] Second, ICG excretion is an ATP-dependent process, and thus a decrease in ATP content during hepatic dysfunction may affect these results.[3] The lower sensitivity of bilirubin compared with ICG probably results from the later increase in bilirubin during the course of hepatic injury and further due to the formation of delta-bilirubin, which has a longer half-time.

There is evidence that the presence of hepatic dysfunction significantly affects the hospital length of stay and outcome among critically ill patients with acute respiratory distress syndrome or after trauma.[1,14,15] Considering some of the important partial hepatic functions, such as metabolism, synthesis, detoxification, and excretion of the end-products of metabolism and toxins, the worsening clinical course in patients suffering from hepatic dysfunction is not surprising. Correspondingly, the sensitivity and specificity of PDR_{ICG} values upon ICU admission with respect to survival were comparable to those of APACHE II and SAPS.[7]

In conclusion, PDR_{ICG} is a valuable dynamic liver function tool to assess critical ill patients suffering from liver dysfunction. Because of the possibility of its user-friendly noninvasive bedside assessment, further studies concerning liver dysfunction should use PDR_{ICG} together with other clinical variables to monitor the progress or reversal of liver failure.

REFERENCES

1. Hebert PC, Drummond AJ, Singer J, et al: A simple multiple system organ failure scoring system predicts mortality of patients who have sepsis syndrome. Chest 104:230, 1993
2. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 23:1638, 1995
3. Bernal W, Donaldson N, Wyncoll D, et al: Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 359:558, 2002
4. Wesslau C, Krueger R, May G: Clinical investigations using indocyanine green clearance for evaluation of liver function in organ donors. Transplantology 5:1, 1994
5. Tsubono T, Todo S, Jabbour N, et al: Indocyanine green elimination test in orthotopic liver recipients. Hepatology 24:1165, 1996
6. Plevris JN, Jalan R, Bzeizi KI, et al: Indocyanine green clearance reflects reperfusion injury following liver transplantation and is early predictor of graft function. J Hepatol 30:142, 1999
7. Sakka SG, Reinhart K, Meier-Hellmann A: Comparison of invasive and noninvasive measurements of indocyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable hemodynamics. Intensive Care Med 26:1553, 2000
8. Sakka SG, Reinhart K, Meier-Hellmann A: Prognostic value of the indocyanine green plasma disappearance rate in critically ill patients. Chest 122:1715, 2002
9. Kisch H, Leucht S, Lichtwarck-Aschoff M, et al: Accuracy and reproducibility of the measurement of actively circulating blood volume with an integrated fiberoptic monitoring system. Crit Care Med 23:885, 1995
10. Faybik P, Krenn CG, Baker A, et al: Comparison of invasive and noninvasive measurement of plasma disappearance rate of indocyanine green in patients undergoing liver transplantation: a prospective investigator-blinded study. Liver Transpl 10:1060, 2004
11. Gottlieb ME, Stratton HH, Newell JC, et al: Indocyanine green. Its use as an early indicator of hepatic dysfunction following injury in man. Arch Surg 119:264, 1984
12. Pollack DS, Sufian S, Matsumoto T: Indocyanine green clearance in critically ill patients. Surg Gynecol Obstet 149:852, 1979
13. Lund M, Tygstrup N, Ott P: Endotoxin pretreatment affects hepatic sinusoidal ICG uptake by reduction of mRNA for organic anion transporting(oatp). J Hepatology 26 (suppl 1):71A, 1997
14. Schwartz DB, Bone RC, Balk RA, et al: Hepatic dysfunction in the adult respiratory distress syndrome. Chest 95:871, 1989
15. Harbrecht BG, Zenati MS, Doyle HR, et al: Hepatic dysfunction increases length of stay and risk of death after injury. J Trauma 53:517, 2002