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Review Article

Indocyanine green plasma disappearance rate as dynamic liver function test in critically ill patients

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Background: Indocyanine green (ICG) is a water-soluble fluorescent dye that is bound to plasma protein when administered intravenously. Removal of ICG from the blood depends on hepatic blood flow, function of the parenchymal cells and biliary excretion. ICG elimination is described as a useful dynamic liver function test.
Methods: In this review, we looked at the most recent literature to clarify why ICG is useful in critically ill patients, the validity of the ICG plasma disappearance rate (ICG-PDR) measured transcutaneously and whether ICG-PDR has any prognostic value.
Conclusion: In conclusion, measuring ICG-PDR is a valuable method for dynamic assessment of liver function, and is found to be a valuable prognostic tool in predicting survival for septic patients, patients presenting with acute liver failure and critically ill patients.

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Liver function tests – static and dynamic

Liver function tests can be divided in to two groups – static/passive and dynamic.

The static tests include bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, albumin and coagulation factors V and VII. They cannot be used as a quick tracker of changes in liver function. They can be used to determine the type of jaundice, the extent of cholestasis or hepatocellular necrosis.[1]

Static tests are used, often as part of scoring systems, e.g. Model for End-stage Liver Disease (MELD) or Child-Pugh score, to monitor chronically impaired liver function like cirrhosis.[2]

Assessing liver function in critically ill patients require a more dynamic approach to detect changes in liver function, which is not possible with the static tests.

The dynamic tests assess the liver function by determining the livers ability to eliminate or metabolise defined substances in time. This gives us an instant idea of the function at the moment of measurement, and it can be repeated shortly after.[1,3] The result is a more 'global' measurement of liver function, and the tests are able to detect the rapid changes in liver function associated with critical illness.[2]

The dynamic tests include indocyanine green (ICG) clearance, caffeine test, bromosulfophthalein clearance, amino acid clearance, galactose elimination capacity, monoethylglycinexylidide test and aminopyrine test.[1]

Why ICG?

ICG is a water-soluble fluorescent dye, with a spectral absorption at 800 nm in blood plasma. When administered intravenously, it is bound to plasma protein (albumin and lipoproteins), selectively taken up by hepatocytes, and it is eliminated into the bile unchanged. Its distribution volume approximates the plasma volume; ICG does not undergo enterohepatic recirculation. Removal of ICG from the blood depends on hepatic blood flow, function of the parenchymal cells and biliary excretion.[1,4,5] Overdosage has not been described. ICG should be used with caution in people with known iodide allergy or thyrotoxicosis*.

**http://www.drugs.com/drp/indocyanine-green.html (accessed 7 December 2013)*

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How?

Due to these features, ICG elimination is considered to correlate with hepatic function and thereby useful as a dynamic liver function test. Its elimination can be expressed as half-life time, clearance, retention or plasma disappearance rate (ICG-PDR).[1]

Blood clearance requires absolute ICG blood concentration and distribution volume; in contrast, ICG-PDR is based on relative concentration changes. The accuracy of ICG-PDR is found to reflect blood clearance, and is clinically more attractive as it can be measured transcutaneously.[6]

ICG retention ratio after 15 min (ICG R15) and ICG-PDR, are the most widely used parameters to express the elimination, and thereby hepatic function. ICG R15 is expressed in percent and is calculated by $C_{ICG(15)}/C_{ICG(0)} \times 100$; normal values are under 10%.[7]

ICG-PDR is expressed as percentage change over time, and the initial concentration at time 0 is 100%. Normal values for ICG-PDR is above 18%/min.[1]

In this review, we use ICG-PDR, as done by the studies and articles on critically ill patients we have reviewed.

ICG-PDR can be assessed using various techniques. The gold standard is serial blood sampling after injection of ICG and spectrophotometric analysis to obtain the concentrations.[4]

The ICG-PDR is determined by transforming the ICG concentration curve to a 'point zero' (100%) and then describing the decay as percentage change per time (%/min) in a logarithmic graph, which is seen as a negative slope.[7–9]

This can be done bedside using a fiberoptic catheter inserted in e.g. a femoral artery that is rather time consuming and not without risk for the patient. Instead, a non-invasive technique has been developed, using transcutaneous pulse spectrophotometry (LiMON, PULSION Medical Systems, Munich, Germany).[4,10] This measures the arterial concentration based on the difference in absorbance between oxyhaemoglobin and ICG. This is similar to the principles of pulse oximetry, where the arterial oxygen saturation represents the difference in absorbance between oxyhaemoglobin and reduced haemoglobin.[8,9]

The dosage has been evaluated by Sakka et al. They used standard dosage of ICG 0.5 mg/kg and a reduced dosage 0.25 mg/kg. They compared the results of ICG-PDR obtained by the two dosages, and found that the reduced dosage was sufficiently accurate.[11]

The correlation between the invasive and the transcutaneous method to assess ICG-PDR has been analysed in critically ill patients with stable hemodynamics, in patients with hepatocellular carcinoma assessed for hepatic resection, and in patients undergoing liver transplantation. The invasive and non-invasive methods were found to be highly correlated, and the LiMON was an acceptable alternative to serial blood sampling methods.[5,9,12]

Other uses

ICG-PDR is widely used to assess liver function before and after hepatic resection. Transcutaneous measuring of ICG-PDR has been validated in various studies in this field. de Liguori et al. concludes that ICG-PDR measured with LiMON is a useful tool for the prediction and detection of post-hepatectomy liver dysfunction.[13] Perioperative changes in liver function, morbidity during hepatectomy and postoperative outcomes have been assessed by Okochi et al., Greco et al., Derpapas et al. and Vos et al.[14–17]

Faybik et al. concludes that the noninvasive transcutaneous method for assessing ICG-PDR can be used instead of the invasive aortic fiber-optic method in both haemodynamically stable and unstable patients undergoing liver transplantation.[5]

ICG is also widely used as a fluorescence during surgery. Recently, Lim et al. published a study on ICG fluorescence imaging as a promising technique in liver surgery.[18]

Limitations

Factors that compromise hepatic haemodynamics, ie. intrahepatic shunting or thrombosis, will result in changes in hepatic blood flow and influence the clearance rate of indocyanine green. The result is a 'global' view on liver function and does not explain local changes. The role of different liver perfusion rates on ICG R15 ratio has been assessed by Janssen et al. They used pig livers and found that ICG R15 was lower in the high flow group, no difference in hepatocellular damage or excretional function were found. They conclude that ICG R15 ratio in hyperdynamic states may conceal the true excretory graft function.[19] In patients with steatosis and hepatitis (global hepatocellular dysfunction), some of the transport polypeptides can be downregulated, thus affecting the uptake of indocyanine green, making all of the measurements lower.[3,17]

Hyperbilirubinaemia (> 51 μmol/l) can reduce ICG-PDR probably because ICG and bilirubin use

the same transport carrier and a competitive inhibition of the two is seen in patients with obstructive jaundice. This is described by Vos et al., Nanashima et al. and D'Onofrio et al.[17,20,21]

As mentioned, the test reflects the global liver function and does not measure local variations; this applies to all liver function tests that do not include an imaging component.[3]

Validity

Traditionally ICG-PDR has been determined by series of blood tests. This is a time-consuming and invasive procedure. The analysis of the tests is also relatively slow.

In recent years, a transcutaneous method for measuring ICG retention has been developed; one of the most described is LiMON, which uses a pulse detection device to determine the ICG-PDR. The peak of plasma ICG is in decay 6 min after injection, the difference in concentration in plasma is translated to a decay constant and the ICG retention after 15 min can be determined by an early projection.

Cheung et al. conducted a study of 70 patients with liver tumors and Child-Pugh A cirrhosis. In this study, they compared the LiMON results of ICG retention with results obtained by the gold standard with serial blood samples. They found that the plasma ICG obtained with LiMON was very close to the plasma concentration found with the traditional method. LiMON constantly underestimated the ICG retention rate at 15 min by 4.36%. As this was constant, they concluded that the LiMON results are usable, and as long as the results are corrected, they can be compared with invasive measurements.[22]

Sakka et al. made a similar study, analysing the correlation between ICG-PDR obtained by the invasive and the transcutaneous method in critically ill patients. They found that the results obtained transcutaneously were highly correlated with those derived from the invasive technique. They conclude that the transcutaneous method for determining ICG-PDR can be recommended in evaluation of critically ill patients.[9]

A prognostic factor in an ICU setting?

The evidence of using ICG-PDR as a prognostic factor in critically ill patients is starting to emerge. Traditionally IGG-PDR has been used to assess liver function in patients undergoing hepatectomy or liver transplantation or as a supplement to other tests evaluating the need for transplantation or degree of liver damage. An example is the study by Greco et al., where they conclude that addition of ICG measurements to traditional biochemical assessment of hepatic function, such as MELD, may improve the pre-operative evaluation of risk in a patient population with chronic liver disease.[15]

Kortgen et al. prospectively investigated the development of liver dysfunction in patients with severe sepsis who were admitted to the ICU. They calculated APACHE II (Acute Physiology and Chronic Health Evaluation) score, MOD (Multiple Organ Dysfunction) score and SOFA (Sepsis-related Organ Failure Assessment) score daily. ICG-PDR was measured via a catheter in arteria femoralis and they followed routine laboratory tests for liver function. Mortality rate was 38%. The non-survivors were older and had higher scores in APACHE II, SOFA and MOD at inclusion. No difference was found regarding SEPSIS criteria, haemodynamics, oxygenation or vasopressor/inotropic support at time of inclusion. Lactate, urea and creatinine were higher in non-survivors at baseline. ICG-PDR was significantly higher in survivors at days 1 and 3, whereas the conventional markers for liver damage did not predict any difference in the two groups. ICG-PDR less than 8%/min predicted death with a sensitivity of 81% and a specificity of 70%. They conclude that ICG-PDR is superior to serum bilirubin levels and that impaired ICG-PDR is correlated with poor prognosis.[23]

Sakka et al. also analysed the prognostic value of ICG-PDR in critically ill patients. The patients were admitted to the ICU all under the diagnosis sepsis/septic shock and all scored according to SAPS II (Simplified Acute Physiology Score) and APACHE II. Patients were later divided into three diagnostic groups: sepsis, acute respiratory distress syndrome and others. All patients were intubated and sedated, and ICG-PDR was measured via a catheter in arteria femoralis twice a day. They used the lowest value of ICG-PDR in each patient and found that ICG-PDR was significantly lower in non-survivors independent of diagnosis and in patients with sepsis. The mortality was 80% in patients with ICG-PDR < 8%/min and survival was 80% in patients with ICG-PDR > 16%/min.

In 53% of the patients, ICG-PDR was measured within the first 24 h of admission. These values were compared with the APACHE II and SAPS II scores, and they found that ICG-PDR on ICU admission as one single variable was as accurate as the more complex scores (SAPS II and APACHE II) regarding outcome prediction.

They conclude that ICG-PDR is a reliable prognostic marker of survival in critically ill patients.[24]

ICG-PDR has been evaluated by Merle et al. as a tool to predict outcome in patients presenting with acute liver failure.[8] In their study, the physicians were blinded to the ICG-PDR measurements. ICG-PDR was measured using the non-invasive transcutaneous LiMON. Directly after inclusion, the first ICG-PDR was determined, and repeated daily until death, liver transplantation or discharge from ICU. Standard laboratory tests for liver injury were also followed. They found that the ICG-PDR measured at day 1 was significantly lower in patients not recovering spontaneously. An ICG-PDR < 6.3%/min on day 1 predicted death or transplantation with a sensitivity of 85.7% and a specificity of 88.9%. Measurements of the lowest ICG-PDR in each individual at any time point showed that ICG-PDR < 5.3%/min predicted death or transplantation with a sensitivity of 85.7% and specificity of 66.7%. They conclude that ICG-PDR is a valuable dynamic liver function tool to predict outcome in patients suffering from acute liver failure early during its course.

Inal et al. evaluated the prognostic value of ICG-PDR in patients admitted in the ICU with sepsis and compared this with the APACHE II scores. All patients were haemodynamically stable and without heart, renal or liver failure at inclusion. They found that ICG-PDR was significantly lower in non-survivors (*P* 0.004) and so was APACHE II score but not significantly (*P* 0.039). They conclude that measurement of ICG-PDR with LiMON is a good predictor of survival in septic patients and can be recommended for routine evaluation of septic patients in hospital settings.[10]

A study of paediatric acute liver failure compared non-invasively measured ICG-PDR to Kings College criteria and Clichy's criteria (prognostic scores). They found that ICG-PDR was significantly lower in patients with irreversible liver damage. None of the patients with ICG-PDR < 5%/min survived without liver transplantation, and all patients with ICG-PDR > 6%/min survived with only medical care, regardless of age and etiology of acute liver failure. The categorization of patients into either irreversible or reversible liver damage groups was faster with ICG-PDR than Kings College criteria and Clichy's criteria. The authors conclude that ICG-PDR can be

Table 1

Overview of the literature assessing ICG-PDR in critically ill patients.

	AIM	Scoring systems	Mortality	Specificity and sensitivity	Non-survivors	Survivors
Kortgen et al.[23]	Patients with severe sepsis in ICU	APACHE II MOD SOFA ICG-PDR	38%	ICG-PDR < 8%/min predicts death specificity 70% and sensitivity 81%	Older higher MOD APACHE II SOFA lactate, urea and creatinine at inclusion	ICG-PDR significantly higher day 1 and 3
Sakka et al.[24]	Sepsis, ARDS others in ICU	SAPS II APACHE II ICG-PDR	80% in patients with ICG-PDR < 8%/min		ICG-PDR significantly lower independent of diagnosis	80% of patients with ICG-PDR > 16%/min
Merle et al.[8]	Acute liver failure	ICG-PDR		ICG-PDR < 6.3%/min day 1 predicts death or transplantation specificity 88.9% and sensitivity 85.7%	ICG-PDR significantly lower day 1	
Inal et al.[10]	Patients with sepsis in ICU	APACHE II ICG-PDR			ICG-PDR significantly lower	
Quintero et al.[25]	Pediatric acute liver failure	ICG-PDR Kings College, Clichy's criteria			Transplantation or death: ICG-PDR < 5%/min	ICG-PDR > 6%/min survived with only medical care

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ICG-PDR, indocyanine green plasma disappearance rate; MOD, Multiple Organ Dysfunction; SOFA, Sepsis-related Organ Failure Assessment.

a useful tool in combination with other scores to improve categorization of patients with pediatric acute liver failure.[25]

Inal et al., Sakka and Malbrain et al. describe the relationship between intra-abdominal pressure (IAP) and ICG-PDR measured transcutaneously in critically ill patients. They all describe that an increase in IAP may compromise hepatosplanchnic perfusion and thereby liver function. Sakka describes an increase in ICG-PDR after decompression of the abdomen and sees ICG-PDR as an attractive bedside tool to assess short time changes in hepatic blood flow.[26–28]

Table 1 gives an overview of the above-mentioned literature.

Conclusion

In conclusion, measuring ICG-PDR a valuable method for dynamic assessment of liver function. Its removal depends on hepatic blood flow, biliary excretion and function of the parenchymal cells. The more recent developments of transcutaneous devices such as LiMON make the bedside measurement faster, with less risk and are regarded to evaluate the liver function in critically ill patients as reliably as the invasive blood sampling methods. ICG-PDR is found to be a valuable prognostic tool in predicting survival for septic patients, patients presenting with acute liver failure and critically ill patients.

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