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Use of Indocyanine Green (ICG) in Hepatology

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Abstract

The organic anion indocyanine green (ICG) is eliminated solely via hepatobiliary excretion. Consequently, ICG is used to measure the hepatic blood flow by a constant intravenous infusion of ICG, with measurements of ICG blood concentrations in an artery and a hepatic vein, and calculation by Fick's principle according to simple mass conservation. Secondly, ICG is used to estimate various hepatic clearances, using constant intravenous infusion or bolus injection of ICG and measurements of concentrations of ICG in peripheral blood. These clearance values reflect hepatic blood flow and hepatobiliary excretory function depending on hepatic removal kinetics and systemic blood circulation at the (patho)-physiological condition studied. Third, during recent years, a simple ICG 15-minute retention test (ICG-r15) is developed, using intravenous bolus injection of ICG, measurements of ICG concentration in peripheral blood after 15 minutes, and calculation of percentage ICG of the dose injected which is retained in the body. The ICG-r15 test, which is primarily used to assess the hepatobiliary excretory function but also a wide range of other conditions, is however based on dubious physiological assumptions. In this review, we go through these various applications of ICG measures in hepatology, focusing on physiological background of the tests and their use in studies of liver hemodynamics during normal conditions and liver diseases.

Keywords: Hepatic blood flow; Hepatic clearance; Hepatic excretory function; Liver diseases; Liver removal kinetics

Introduction

Indocyanine green (ICG) is a synthetic organic anion that is bound to lipoproteins in plasma [1] and as such, ICG is transported efficiently from the sinusoidal blood within the liver into the hepatocytes [2,3]. From the hepatocytes, it undergoes active transport into the biliary canaliculi [3]. Hepatobiliary excretion comprises 100% of un-changed ICG elimination from the body. These observations constitute the background for the use of ICG for measurements of the hepatic blood flow rate as well as the intrinsic hepatic clearance, the latter as a measure of the hepatobiliary excretory capacity. These classical procedures require measurements of ICG concentration in blood samples from an artery and a liver vein. Simplified measures with the need for only peripheral venous blood samples have been developed, which methods, however, are not based on sound physiological principles. Consequently, their clinical applications are dubious. We here take the opportunity to go rigorously through the various methodologies and clinical applications of ICG in hepatology.

Methodologies and Clinical Applications

Hepatic Blood Flow – Constant ICG Infusion – Fick's Principle

ICG distributes in the extended plasma volume [4] and during a constant intravenous ICG infusion rate of about 0.13 μmol/min to a human subject, 95% or more approximation to steady state blood concentrations is achieved after 90 minutes [5]; at higher infusion rates, the time to reach steady state is longer. All infused ICG is eliminated by the liver and at steady state-concentrations, we have

$$F = \text{Infusion rate} / (A - V) \quad (1)$$

where F is the hepatic blood flow (L blood/min) and A and V are mean blood concentrations of ICG in a peripheral artery and a hepatic vein, respectively (μmol/L blood). In practice, we use a 15-60 min measurement period with four to five pairs of plasma

samples. ICG concentration is determined in plasma either by spectrophotometry [6] or HPLC [4] and corrected for measured arterial hematocrit values to achieve blood concentrations.

This flow measurement depends on mass conservation and achievement of good approximation to steady state blood concentrations of ICG. It is independent of the hepatic elimination kinetics of ICG. We calculate the deviation from steady state as the linear slope of the time course of the arterial blood concentration of ICG multiplied with 5% of the body weight under the assumption of this volume equals the volume of distribution of ICG during the measurement period (μmol/min). If necessary, measured infusion rate may be corrected accordingly [5]; in our hands, the correction for non-steady state amounts to less than 1% of the infusion rate. The method shows good agreement with electromagnetic technique in dogs [7] and anesthetized pigs (S. Keiding, unpublished data, 2020). Figure 1 shows an example of the ICG plasma concentration measurements for estimation of the hepatic blood flow in a human subject.

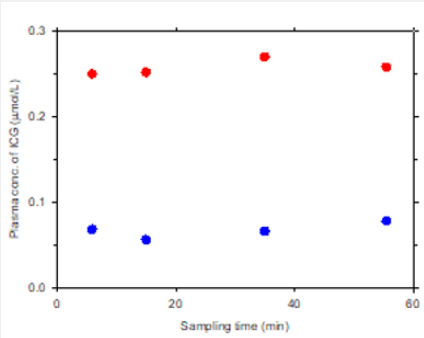

Figure 1. Example of how the hepatic blood flow can be measured by constant intravenous infusion of ICG and calculation according to Fick's principle of mass conservation. Time course of plasma concentrations of ICG in a radial artery (•) and a hepatic vein (•) during constant intravenous infusion of ICG of 0.13 μmol/min, initiated 90 min before start of sampling in a 67 year patient with primary biliary cholangitis.

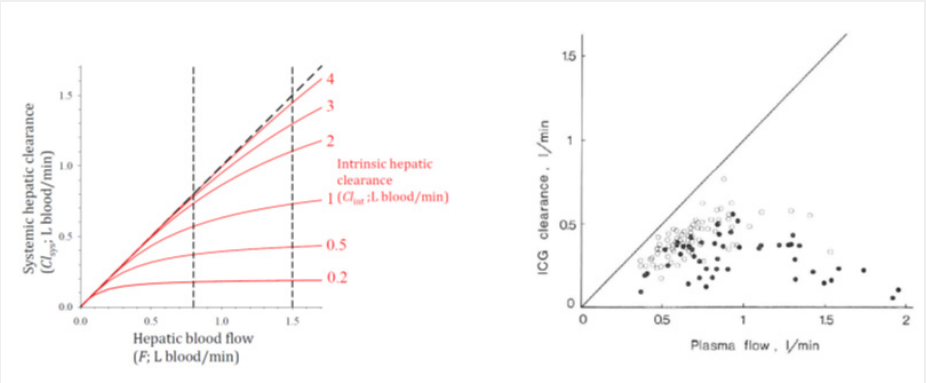

Figure 2: Left panel: Relationship between Cl_{sys} and F for various values of Cl_{int} according to Eq. 3b.
Right panel: Relationship between systemic hepatic plasma clearance of ICG (Cl_{sys}) and plasma flow (F) in subjects without liver disease (○) and patients with liver disease (•) (from ref 5).

Here we give two examples of clinical application of the method: In patients examined for abdominal pain, the estimated F discriminated well between patients with functional important stenosis of abdominal arteries or no stenosis [8]. Recently, we showed that the PET-determined unidirectional clearance of the conjugated bile acid tracer [N-methyl-11C]cholylsarcosine (11C-CSar) was determined by the hepatic blood flow - and not the hepatocyte plasma membrane transport capacity for 11C-CSar - in patients with primary biliary cholangitis [9].

Hepatic Clearances Measured by Constant ICG Infusion

Two first-order hepatic clearance concepts are defined according to the sinusoidal perfusion model of uptake of substrates from blood flowing through the intact liver [10-14]: First, the flow-independent intrinsic hepatic clearance Cl_{int} of ICG (L blood/min) is a measure of the maximal hepatobiliary excretory function (corresponding to Vmax/Km for enzymatic reactions; 10,11):

$$Cl_{int} = \text{Infusion}/((A - V)/\ln(A/V)) = -F \ln(1 - E) \quad (2)$$

where E = (A – V)/A is the hepatic extraction fraction.

Second, the flow-dependent systemic hepatic clearance, Cl_{sys} of ICG (L blood/min), measured with respect to the systemic blood concentration of ICG (here A) [10-12]:

$$Cl_{sys} = \text{Infusion}/A = F\,(A - V)/A = F\,E \quad (3a)$$

$$Cl_{sys} = F\,(1 - e^{-Clint}/F). \quad (3b)$$

Figure 2 shows the relationship between Cl_{sys} and F for various values of Cl_{int} according to Eq. 3b and the corresponding data points for 86 persons with no liver disease and 52 patients with cirrhosis [5]. For Cl_{int} >> F, the liver remove nearly all substrate

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supplied by the blood stream, and Cl_{sys} approximates F (Cl_{sys} is flow-determined); for Cl_{int} << F, the hepatic removal is determined by the hepatic removal capacity and Cl_{sys} approximates Cl_{int} [11]. The figures show that in general, Cl_{int} is larger in healthy subjects than in patients with liver disease. However, although Cl_{sys} approximates F better for the healthy subjects than for the patients with liver disease, the variation is large, ranging from 30 – 90%. Consequently, the use of Cl_{sys} as an approximation to F is not justified, even not in the healthy subjects. Similarly, although Cl_{sys} approximates Cl_{int} better for patients with liver disease than for the healthy subjects, the variation is large, ranging from 60 – 90%, and the use of Cl_{sys} as an approximation to Cl_{int} is not justified, even not in patients with liver impairment.

In passing, we may notice that the clearance-requirement of hepatic first-order kinetics for the biliary excretion of ICG was fulfilled at the infusion doses used in the above-mentioned studies [15].

Hepatic Clearance Measured by Bolus Injection of ICG

In order to simplify assessment of the hepatobiliary excretory function, some authors use bolus intravenous injection of ICG and calculation of the systemic hepatic clearance (Cl_{sys}) from the time course of the decay of the plasma concentration of ICG in peripheral blood; no use of hepatic vein blood samples. However, not only does Cl_{sys} not approximate Cl_{int} adequately (as shown above), but also the use of bi-exponential curve-fitting of the decay of the plasma ICG concentration to estimate clearance will unavoidably be biased of varying early time-dependent distribution of ICG in the extracellular volumes [14]. Moreover, also effects of the hepatic blood flow are ignored. Consequently, clinical use of the ICG bolus procedure is not justified.

ICG-r15 test

During recent years, the ICG 15-minute retention test (ICG-r15) is increasingly used as a measure of hepatobiliary excretory function [16]. This method comprises intravenous bolus injection of ICG, measurements of ICG concentration in peripheral plasma after 15 minutes, and calculation of percentage ICG of the dose injected which is retained in the body. The lower the percentage retained, the better the hepatobiliary excretory function. The test is used for pre-operative prognostic measure of the remnant liver excretory function after liver resection [16-18] but also as a marker of portal hypertension [19-21] and a wide range of other applications. A recent study comparing Cl_{sys} from constant intravenous infusion with the ICG-r15 [21] finds good negative correlation between the two measures. However, this finding does not overrule the fundamental biases within the use of Cl_{sys}, being highly dependent on both the hepatobiliary excretory function and the hepatic blood flow as mentioned in the foregoing section.

Conclusion

ICG infusion-based estimates of the hepatic blood flow, using Fick's principle, and of the hepatobiliary excretory capacity, using the intrinsic hepatic clearance, are based on basic physiological principles, experimentally validated, and proven clinically and experimentally useful. In contrast, neither the systemic hepatic clearance from ICG infusion or bolus, nor the 15 min retention test, are justified for (patho)-physiological studies or clinical applications in hepatology.

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