Br. J. clin. Pharmac. (1990), **30**, 634–637

Hepatic drug clearance: the effect of age using indocyanine green as a model compound

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The hepatic extraction ratio and clearance of indocyanine green (ICG) were determined and used to derive apparent liver blood flow in nine subjects between the ages of 22 and 83 years. There was no correlation between the hepatic extraction ratio of ICG and age ($r_s = -0.435$, NS). There was a significant negative correlation between both ICG clearance and age ($r_s = -0.710$, $P < 0.05$) and apparent liver blood flow and age ($r_s = -0.750$, $P < 0.05$). These results validate the comparison of liver blood flow values derived from ICG clearance in humans over a wide age range and confirm that liver blood flow does fall with age.

Keywords age indocyanine green liver blood flow drug extraction

Introduction

Liver blood flow is an important determinant of drug metabolism, particularly of drugs with a high hepatic extraction ratio. Because of its dual blood supply, direct measurement of liver blood flow in humans is difficult and an indirect value is most commonly derived from the clearance of a flow limited substance such as indocyanine green (ICG). ICG clearance has been used as an indicator of liver blood flow in ageing man (Wood *et al.*, 1979; Wynne *et al.*, 1989). These extrapolations assume that there is no change in the extraction of ICG by the liver with ageing. Thus, any decline in the removal of ICG by the liver would exaggerate the fall in apparent liver blood flow. We have investigated the effect of ageing upon the hepatic extraction ratio of ICG in humans.

Methods

Subjects

Nine patients (five females), between the ages of 22 and 83 years, undergoing cardiac catheterisation for the investigation of aortic stenosis (3), mitral stenosis (1), Ebstein's anomaly (1), possible ischaemic heart disease (2) and possible cardiomyopathy (2), were recruited. No subject was suffering from hepatic, renal or respiratory disorders as assessed by full clinical history and examination. In addition, all subjects had normal blood count, serum bilirubin, alkaline phosphatase, aminotransferase and plasma proteins, creatinine and electrolytes. All had right atrial pressures which were in the normal range. Only two subjects were taking any medication (one frusemide and one digoxin and cyclopenthiazide with potassium). All gave informed, written consent and the study had the approval of the Newcastle Health Authority Ethics Committee.

Procedure

An 8 French sheath was inserted percutaneously into the femoral artery and a 7 French Gensini catheter (Cordis Europe, NV, The Netherlands) was positioned in the aorta with its tip at the level of the second lumbar vertebra. A 6 French

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Goodale-Liebin catheter (Cordis, The Netherlands) was inserted via the femoral vein through a 7 French sheath and positioned in the hepatic vein using fluoroscopic control. An initial blood sample was taken from the arterial catheter. Indocyanine green (Myson, Westcott & Dunning, Baltimore, MD), 0.5 mg kg^{-1} was injected via the sheath of the venous catheter over 20 s. After discarding 5 ml of blood contained in the aortic catheter 'dead space', heparinised blood (5 ml) was withdrawn at 3 min simultaneously from the hepatic vein and from the arterial catheter, and from the arterial catheter at 2 min intervals for a further 10 min.

Blood was centrifuged at 3,000 *g* for 20 min, and the plasma removed. ICG concentrations were measured by absorption spectrophotometry (Pye Unicam PU 8800) at a wavelength of 800 nm (Caesar *et al.*, 1961). The hepatic extraction ratio (E_H) was calculated as:

$$E_H = \frac{\text{arterial concentration ICG} - \text{hepatic vein concentration ICG}}{\text{arterial concentration ICG}}$$

Clearance of ICG (CL_{ICG}) was calculated by dividing the dose by the area under the plasma concentration time curve (AUC) determined by the trapezoidal rule extrapolated to infinity;

$$CL_{ICG} = \frac{\text{Dose}}{\text{AUC}}$$

Liver blood flow was estimated as:

$$\text{Liver blood flow} = \frac{CL_{ICG}}{E_H(1-\text{HCT})}$$

Where HCT is the haematocrit, determined by Coulter Counter (erythrocyte count × mean corpuscular volume) and E_H is the hepatic extraction ratio. The correlations between age and ICG clearance, apparent liver blood flow and hepatic extraction ratio were examined by calculating Spearman's rank correlation coefficient, r_s.

Results

Plasma ICG concentration *vs* time data were well described by a single exponential function. There were significant negative correlations between ICG clearance and age ($r_s = -0.710$, $P < 0.05$) and apparent liver blood flow and age ($r_s = -0.750$, $P < 0.05$) (Figure 1). Values for liver blood flow calculated from linear regression analysis gave a value of 2189 ml min^{-1} at the age of 22 years and 1123 ml min^{-1} at the age of 83 years. The mean value for the hepatic extraction ratio of ICG was 0.78 (range 0.63–0.85). There was no correlation between the hepatic extraction ratio of ICG and age ($r_s = -0.435$, NS) (Figure 2). Thus the significant age related fall in ICG clearance confirmed here is not the result of an impairment of ICG extraction by the liver with ageing.

Discussion

Original assertions that liver blood flow declines with age were based upon measurement of BSP clearance. However when it became clear that not only does BSP have a significant enterohepatic circulation but that there is also an age related fall in metabolism of BSP—independent of blood flow, the size of this apparent age related decline became uncertain (Thompson & Williams, 1965). Liver blood flow is now more commonly calculated from ICG clearance, in preference, as ICG is eliminated solely by the liver. Although no alteration in the hepatic extraction of ICG occurs from adulthood to senescence in the rat (Kitani *et al.*, 1978), the effect of age on the hepatic extraction of ICG in man has not previously been studied.

Because of the clinical circumstances of this investigation, we were unable to measure the hepatic extraction ratio of ICG by the constant

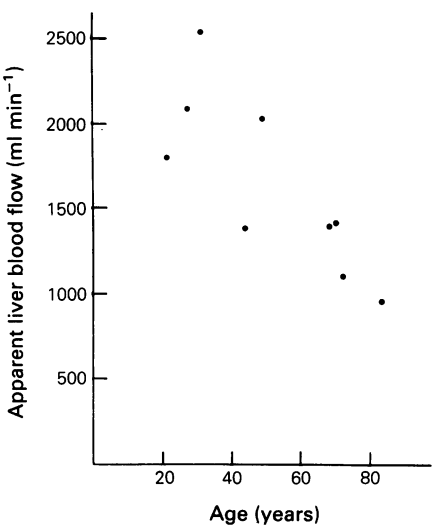

Figure 1 Relationship ($P < 0.05$) between age and apparent liver blood flow (ml min^{-1}) in the subjects studied.

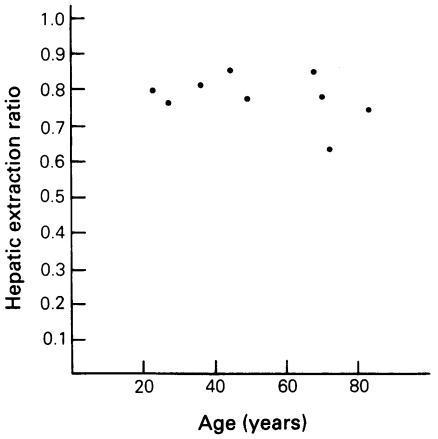

Figure 2 Relationship (NS) between age and the hepatic extraction ratio of indocyanine green in the subjects studied.

but prolonged infusion method first described by Bradley *et al.* in 1945. The value for the hepatic extraction ratio of ICG obtained here therefore relies on a single point estimation which, in the presence of a falling plasma concentration of ICG, is subject to error. However, the observations that hepatic venous concentrations of ICG after a bolus dose are lower but parallel to arterial concentrations (Caesar *et al.*, 1961) and that there is a significant correlation between the estimated hepatic extraction ratio of ICG after a bolus injection or after a constant infusion (Caesar *et al.*, 1961; Villeneuve *et al.*, 1982), support the validity of our measurements. Several studies have measured the hepatic extraction ratio of ICG directly in healthy volunteers and have found it to average 74% (range 53%–90%) (Grainger *et al.*, 1983; Leevy *et al.*, 1962; Weigand *et al.*, 1960). The present results not only support this estimate but also show no change in drug extraction with ageing. Although, ideally, the derivation of liver blood flow from drug clearance would always involve a direct measurement of the extraction of the drug across the liver, this is practically and ethically impossible. The present study validates the comparison of liver blood flow values derived from ICG clearance in humans over a wide age range.

Plasma concentrations of ICG fitted well to a mono-exponential disappearance pattern in these subjects, measured up to 13 min after injection. It is now recognised that, if sampling is continued, a second compartment of plasma ICG decay emerges, due to hepatic storage, impurities or degradation products (Meijer *et al.*, 1988). The measurement of complete disappearance curves of ICG might be important in some investigations, for example of biliary excretion. Clearance values derived from the major part of the ICG elimination curve, as employed here, should remain valuable in comparative studies.

Values for liver blood flow calculated from linear regression analysis show a 49% fall between the ages of 22 and 83 years in this small study. This is very similar to the 53% fall in apparent liver blood flow derived from ICG clearance in 66 healthy subjects between the ages of 24 and 91 years, whom we have previously studied, and in which the assumption of no change in hepatic extraction with age was made (Wynne *et al.*, 1989). This significant fall in liver blood flow must be an important contributor to the reduced systemic elimination of drugs by the elderly. This will be of greatest importance for high and intermediate clearance drugs such as chlormethiazole (Nation *et al.*, 1977), labetalol (Kelly *et al.*, 1982), verapamil (Storstein *et al.*, 1984), propranolol (Castleden & George, 1979) and morphine (Baillie *et al.*, 1989), for all of which a significant age related fall in metabolism has been reported.

The pharmacokinetic consequences of the fall in liver blood flow with age should be considered, particularly during the development of high clearance drugs with a low therapeutic index, in order to achieve the aim of maximising clinical benefit whilst minimising dose dependent adverse drug reactions from which the elderly are at risk.

We wish to thank the staff of the Cardiac Catheter Laboratory, Freeman Hospital for their help with this study.

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(Received 23 January 1990, accepted 25 May 1990)