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EFFECT OF INHIBITORS OF PROSTAGLANDIN SYNTHESIS ON HEPATIC DRUG CLEARANCE

JOHN FEELY* & ALASTAIR J.J. WOOD

Departments of Pharmacology and Medicine, Vanderbilt University, Nashville, Tennessee 37232, U.S.A.

The effect of inhibition of prostaglandin synthesis on the systemic clearance of indocyanine green and antipyrine was studied in seven subjects. Antipyrine clearance was not altered by indomethacin suggesting that oxidative metabolism was not affected. Both aspirin and indomethacin decreased the clearance of indocyanine green presumably by reducing liver blood flow. These results suggest that an effect of inhibitors of prostaglandin synthesis on hepatic drug clearance is likely to be confined to high clearance drugs when given systemically.

Introduction

Non-steroid anti-inflammatory drugs such as aspirin and indomethacin inhibit the synthesis of prostaglandins and thromboxane by blocking fatty acid cyclo-oxygenase. In animals the intestinal vasculature may be affected by such blockade. Aspirin and indomethacin decrease basal blood flow in the stomach and small intestines (Gerkens *et al.*, 1977; Gerber & Nies, 1979) and we (Feely & Wood, 1982) have recently shown that indomethacin reduces apparent liver blood flow in man. It has also been recognised that *in vitro* prostaglandins inhibit the hepatic metabolism of a wide variety of drugs including aminopyrine (Weiner, 1980), benzpyrene and hexobarbitone (Kupfer, 1980).

The hepatic clearance of drugs depends largely on the extent to which they are extracted by the liver (Wilkinson & Shand, 1975). For poorly extracted drugs such as antipyrine, aminopyrine and hexobaribitone the activity of drug metabolising enzymes determines clearance while for drugs, such as indocyanine green (ICG) and lignocaine, that are highly extracted by the liver it is the rate of delivery–liver blood flow that primarily determines clearance. We examined the effects of indomethacin and aspirin on the clearance of antipyrine and of indocyanine green.

Methods

Seven healthy male volunteers (aged 20–43 years) with normal renal and hepatic function participated in this study which was approved by the Institutional Review Board. All were non-smokers taking no other drugs and four drank 1–1.5 l of beer each week. After an overnight fast and resting in the supine position for 1 h six subjects were given a rapid (10 s) intravenous injection of ICG (0.5 mg/kg). Blood samples were drawn (through an indwelling cannula kept patent with normal saline) from the contralateral antecubital vein at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15 and 20 min to determine the plasma concentration of ICG by the spectroscopic method of Caesar *et al.* (1961). Thirty minutes later subjects were given an intravenous injection of antipyrine (18 mg/kg) over 3 min. Samples were again drawn through the cannula at 5 min, 30 min and 1, 2, 4, 6, 8, 24 and 26 h following the mid time point of injection for estimation of plasma antipyrine concentration by high performance liquid chromatography (Wood *et al.*, 1979). The above studies were performed in random order and at least 1 week apart both as control and following pre-treatment with indomethacin 50 mg three times eight hourly for 24 h and a fourth dose 1 h before the studies. Five subjects also had the ICG study performed as described above, in random order and at least 1 week apart both as control and following pretreatment with aspirin (325 mg) six hourly for 24 h with a fifth dose 1 h before the injection of ICG. In all cases the subject's blank plasma was used to construct the calibration curve and samples containing indomethacin or aspirin did not interefere with the assays.

The plasma concentration of ICG and of antipyrine (from 30 min onwards) declined monoexponentially. Plasma clearance (CL) was estimated from the rate constant (k) of the logarithm of the plasma concentration–time curve and the extrapolated zero-time level (C_{p0}) according to the equation

$$CL = \frac{k \cdot \text{Dose}}{C_{p0}}$$

*Present address: Department of Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY

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The volume of distribution was determined by dividing the dose by C_{p0}. The blood clearance of ICG, considered equivalent to liver blood flow (Caesar *et al.*, 1961) was obtained by correcting the plasma value for the measured haematocrit. Statistical analysis was performed with a paired Student's *t*-test.

Results

Both indomethacin and aspirin significantly reduced the systemic clearance of ICG (Table 1) and estimated liver blood flow from control 1264 ± 48 to 1066 ± 56 and from 1121 ± 101 to 864 ± 56 ml/min (mean ± s.e. mean) respectively. Indomethacin did not alter the rate of elimination of antipyrine (Table 1). However, during treatment with indomethacin the mean peak antipyrine concentrations (67.4 *v* 47.8 μg/ml, measured 5 min post-injection) was ($P < 0.05$) 45 ± 12% higher (Figure 1).

Table 1 The influence of inhibition of prostaglandin synthesis on the disposition of indocyanine green and antipyrine (mean ± s.e. mean, $n = 6$).

	Elimination half-life (ICG min; antipyrine h)	*Volume of distribution (l)*	*Clearance (ml/min)*
ICG			
Control ($n = 6$)	3.1 ± 0.3	3.3 ± 0.3	735 ± 26
Indomethacin	3.7 ± 0.3*	3.3 ± 0.3	623 ± 24*
Control ($n = 5$)	3.9 ± 0.2	3.7 ± 0.2	670 ± 52
Aspirin	4.4 ± 0.4	3.2 ± 0.2	516 ± 25*
Antipyrine			
Control ($n = 6$)	13.0 ± 0.8	50.7 ± 2.6	38.7 ± 3.3
Indomethacin	13.7 ± 1.0	50.7 ± 3.3	35.0 ± 2.9

* $P < 0.05$ significantly different from control

Discussion

The model drugs used in this study represent the two extremes of behaviour in which hepatic clearance is essentially rate limited, by either metabolic capacity in the case of antipyrine, or blood flow to the liver in the case of ICG. Our results show that *in vivo* indomethacin does not affect the clearance of antipyrine. While it has been shown *in vitro* that the addition of certain prostaglandins competitively inhibit aminopyrine *N*-demethylation (Weiner, 1980) other prostaglandins may have the opposite effect on oxidative metabolism (Kupfer, 1980). Furthermore, there is an organ and species difference in the response to the addition of prostaglandins (Kupfer, 1980). Extrapolation of such data to the *in vivo* situation must therefore be viewed with caution. The finding that peak antipyrine concentrations were 45% higher when the subjects received indomethacin is of interest. Whereas the volume of distribution of antipyrine (body water) was not altered indomethacin may reduce the initial volume of distribution. Further studies are required to determine the mechanism of this finding.

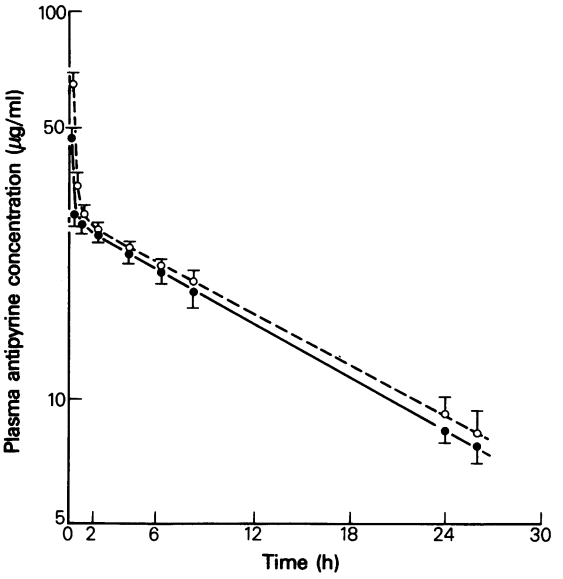

Figure 1 Plasma concentration time profile of intravenous antipyrine (18 mg/kg) in six volunteers both as control and following pre-treatment with indomethacin. ● control, O indomethacin.

Although the effect of these drugs on the hepatic extraction and biliary excretion of ICG is unknown the reduction in the systemic clearance of ICG by both aspirin and indomethacin is most likely as a consequence of inhibition of prostaglandin synthesis. In addition to a possible effect on the hepatic artery (Gerber & Nies, 1979) it is probable that by decreasing gastric and mesenteric flow these drugs may also reduce portal flow. While estimated liver blood flow was significantly reduced to the same extent as in our previous study (Feely & Wood, 1982) the effect of inhibitors of prostaglandin synthesis on blood flow measured directly also requires to be studied.

These results suggest that the systemic clearance of highly extracted, but not poorly extracted drugs, may be reduced by inhibition of prostaglandin synthesis leading to a rise in steady state concentrations. Therefore when non-steroidal anti-inflammatory agents are used in patients who are receiving a concomitant continuous systemic infusion of drugs such as propranolol or lignocaine the effects of the latter agents should be monitored carefully.

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