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INFLUENCE OF MESO-CAVAL SHUNT SURGERY ON VERAPAMIL KINETICS, BIOAVAILABILITY AND RESPONSE

It is now well documented (George, 1979) that for drugs essentially metabolized and having a systemic blood clearance approaching liver blood flow in healthy subjects or patients, when given orally and assuming complete absorption, the bioavailability is low due to the so called 'first-pass' effect. This phenomenon is mainly attributed to metabolism by the liver, although gut-wall metabolism cannot be totally excluded. Thus it is predicted that when the venous return from the stomach, small intestine and colon is diverted past the liver to the vena cava (portacaval shunt), then the bioavailability of high 'first-pass' effect drugs will dramatically increase and may even be complete. However, documentation of this mechanism is incomplete and virtually non-existent in man. Gugler, Lain & Azarnoff (1975) demonstrated in dogs, that the bioavailability of lignocaine was almost complete after portacaval shunt surgery, whereas antipyrine bioavailability remained complete on both occasions. Salicylamide bioavailability more than doubled to 57% after shunt surgery, the remaining dose being accounted for by intestinal wall metabolism.

Since there may be significant changes in liver blood flow after construction of a shunt, to study this effect adequately would require that the drug be given intravenously and orally before and after shunt surgery, resulting in extensive blood sampling and thus ethical considerations preclude this study in patients. Hence to date no study of bioavailability after a shunt has been fully presented in humans. We report here for the first time in man a substantial increase in the bioavailability of a normally, highly cleared drug, verapamil, in a single patient before and after shunt surgery, employing a technique whereby the drug is given orally and intravenously at the same time using a stable labelled form of the drug, thus reducing by half the blood sampling volume.

This patient formed part of an extensive study on the disposition and response to verapamil in patients with liver cirrhosis (Eichelbaum *et al.*, unpublished data). The patient was a 44 year old male weighing 62 kg with severe liver cirrhosis as a result of infectious

hepatitis. At the time of the initial study he had oesophageal bleeding due to marked portal hypertension. One week after the initial study (before shunt) because of a deteriorating condition he underwent surgery for a mesocaval shunt. This involved shunting the venous return from the small intestine to the vena cava, thus leaving the venous return from the stomach and colon patent though undefined. As a result of this surgery approximately 70% of the total venous return was diverted past the liver. Twelve days after surgery the patient was re-investigated. Formal written consent was obtained on both occasions after the patient was informed of the nature and risks of the study.

Both before and after shunt, verapamil was administered simultaneously as an oral and intravenous dose using stable labelled techniques. The intravenous dose was given as an infusion of 10 mg verapamil over 5 min, and a solution of deuterated [D_3]-verapamil was administered orally as 40 mg 0.5 h after the intravenous dose. For the estimation of verapamil pharmacokinetics, 16 venous blood samples were taken over the ensuing 24 h. As well, on both occasions, 0.5 mg/kg indocyanine green was given as a bolus dose with blood samples being taken over 40 min. Finally, before shunt surgery only, antipyrine was administered orally as a solution containing 10 mg/kg body weight and saliva samples taken for 48 h. Throughout the time course of verapamil administration, the ECG was monitored and the change in P-R interval was used as a measure of effect. [D_3]-verapamil (2,8-bis(3,4-dimethoxyphenyl)-6-methyl-2-isopropyl-6-azaocitanil) was trideuterated in the methoxy group para to the 'quaternary' carbon. Isotopic purity was 98%. Previous experiments in this laboratory showed that this label produced no isotopic effect. Verapamil and [D_3]-verapamil were analysed in plasma by mass fragmentography (Spiegelhalder & Eichelbaum, 1977) with d_7 -verapamil deuterated in the isopropyl group as the internal standard. Antipyrine in saliva was measured by HPLC (Eichelbaum & Spannbrucker, 1976). Indocyanine green in plasma was measured spectro-

photometrically. The distribution of verapamil between plasma and erythrocytes was determined by incubating the drug in blood at 37°C and measuring the resultant plasma concentration. The verapamil plasma concentration-time data on both occasions was subjected to non-linear least squares regression analysis using the NONLIN (Metzler, 1969) program on an IBM 370/125 computer system. From the coefficients and exponents of the best fit model, the following pharmacokinetic parameters were calculated using standard methods (Wagner, 1976); the volume of the central compartment (V_c), the volume of distribution at steady state (V_{dss}), the area volume of distribution ($V_{d\beta}$), the terminal elimination half-life ($T_{1/2\beta}$) and total plasma and blood clearance (Cl_p, Cl_b). Bioavailability was assessed by a comparison of the area under the plasma concentration-time curves oral to intravenous taking into account the dose difference. For the oral area, the trapezoidal rule was employed with extrapolation to infinity by dividing the last plasma concentration by the terminal slope. Indocyanine green and antipyrine clearance were calculated by dividing the dose by the area under the curve, the former being corrected for the haematocrit to obtain a blood clearance value.

After the construction of the shunt, the physical characteristics of the patient remained unchanged when compared with those before the shunt, these characteristics included body weight, haemoglobin, haematocrit, and serum albumin. Figure 1 shows the plasma concentration-time profile for verapamil in this patient before and after shunt surgery. As seen, the concentrations after intravenous administration were almost identical thus resulting in pharmacokinetic parameters which differed by less than 5% (Table 1) with no obvious trend. However, as seen in Figure 1, the oral time curves were completely different such that the bioavailability more than doubled, from 38% before the shunt to 81.5% after the shunt (Table 1). Whereas verapamil blood clearance remained the same, indocyanine blood clearance decreased by 63% (Table 1) consistent with a reduction in liver blood flow. The antipyrine clearance before the shunt was 20.8 ml/min, confirming the severe liver cirrhosis in this patient.

Before shunt surgery the maximum change in the P-R interval of 90 ms occurred at 1 h after oral verapamil dosing. After shunt surgery the time of maximum effect was the same but it increased to 125 ms and remained above the pre-shunt values for over 6 h.

Figure 1 Plasma concentrations of verapamil administered intravenously (○, ●) and orally (□, ■) before (open symbols) and after (closed symbols) construction of a mesocaval shunt.

Table 1 Pharmacokinetic characteristics of verapamil and indocyanine green in a patient before and after mesocaval shunt surgery.

Parameter	Before shunt	After shunt
V_c (l/kg)	1.84	1.94
V_{dss} (l/kg)	7.18	7.44
$V_{d\beta}$ (l/kg)	8.56	8.75
$T_{1/2\beta}$ (h)	15.67	15.28
Cl_p (ml/min)	391.20	383.90
Cl_b (ml/min)	429.90	421.90
Bioavailability (%)	38.17	81.50
ICG clearance (ml/min)	447.61	165.15
Antipyrine clearance (ml/min)	20.00	—

These response results being consistent with the increase in bioavailability.

In normal subjects, verapamil has a high systemic blood clearance of approximately 1300 ml/min and a low bioavailability of ~20% (Eichelbaum *et al.*, unpublished data). Since the drug is almost completely absorbed (Schomerus, Spiegelhalder, Stieren & Eichelbaum, 1976), this low bioavailability could be due to either hepatic or gut-wall 'first-pass metabolism'. The increased bioavailability and reduced blood clearance of verapamil in this cirrhotic patient before shunt surgery, compared with normal patients is consistent with previous reports in cirrhotic patients with other highly cleared drugs (Neal, Meffin, Gregory & Blaschke, 1979). After shunt surgery in this patient the almost complete bioavailability is we believe due to the shunt transferring all the absorbed drug past the liver and into the systemic circulation. This increased bioavailability corresponds to about 82%, the remaining 18% can be accounted for as stomach absorption since the oral dose was given in solution form and peak concentrations occurred after 15 min. Absorption from the stomach would produce some first-pass metabolism as the mesocaval shunt did not incorporate venous return from the stomach.

There would appear to be a discrepancy between indocyanine green and verapamil blood clearance after shunt surgery. Whereas both approach liver

blood flow values in normal patients, and before shunt surgery their clearances were almost identical, after shunt surgery verapamil clearance remained the same whereas indocyanine green clearance was further reduced to 165 ml/min. It may well be that verapamil systemic clearance is no longer blood flow dependent but rather controlled by the activity of the hepatic enzyme system.

An early report in man (Shand & Rangno, 1972) showed that the bioavailability of propranolol in a patient with portal anastomosis was more than complete, though the patient did not serve as his own control. A more recent report in abstract form (Huet, Le Lorier, Pomier & Marlean, 1979) using lignocaine showed no effect on bioavailability as a result of end-to-side portocaval shunt. However, since bioavailability was 98% before shunt surgery no effect is obviously expected.

With the technique used of having a stable labelled form of the drug, we have been able to markedly reduce the blood sampling time and volume and have demonstrated that the bioavailability of a normally high 'first-pass' effect drug, verapamil, is almost complete in a patient after mesocaval shunt surgery, resulting in an increased response. It provides enough evidence to conclude that the low bioavailability in normal subjects is due to extensive hepatic 'first-pass' metabolism. The data also dictates that the oral dose of verapamil needs to be drastically reduced in this type of patient with careful ECG monitoring.

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M. EICHELBAUM, M. ALBRECHT¹, G. KLIEMS¹, K. SCHÄFER & A. SOMOGYI

Departments of Medicine and Surgery¹, University of Bonn, D-5300 Bonn-Venusberg, Federal Republic of Germany

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PHARMACOKINETICS OF TOCAINIDE IN ACUTE MYOCARDIAL ISCHAEMIA

Tocainide is an antidysrhythmic agent similar to lignocaine but with the advantage that it is effective when given orally. There has been extensive investigation of its electrophysiological actions, haemodynamic effects and pharmacokinetics (Harrison, Meffin & Winkle, 1978; Winkle, Meffin, Fitzgerald & Harrison, 1976). Its clinical efficacy in the treatment of chronic ventricular dysrhythmias is documented (Winkle, Meffin & Harrison, 1978; Woosley, McDevitt, Nies, Smith & Wilkinson, 1977), but its use following acute myocardial infarction has not been reported.

We wished to study the pharmacokinetics of tocinide in this clinical situation with a view to determination of suitable dosage regimes that could be used and to note any previously unreported side effects.

Eleven patients (nine male) with proven myocardial infarction were given tocinide prophylactically on admission to the Coronary Care Unit. Acute infarction was suspected from the manner of presentation and accompanying electrocardiographic changes. The diagnosis was confirmed in retrospect for all patients by an elevation of relevant enzyme levels, hydroxybutyric dehydrogenase and aspartate transaminase).

The average age was 57 years (range 32–70) and onset of symptoms was within 10 h (average 8 h) of admission and commencing treatment with tocinide. Patients with evidence of shock, pulmonary oedema, significant bradycardia and conduction defects were excluded.

The first six patients (group 1) were given tocinide 500 mg as a constant intravenous infusion over 30 min. Tocainide 400 mg in tablet form was given at time 0 and at 2 h. The remaining five patients (group 2) were given tocinide 750 mg by infusion over 30 min and 600 mg orally at time 0. Samples of blood were taken at times indicated and tocinide measured by gas chromatography. The results ($\pm$ s.e. mean) are shown in Figure 1. The patients remained in the

Figure 1 Group 1 ($\blacktriangle$) tocinide 500 mg i.v. time 0–30 min, plus 400 mg orally time 0 and 2 h. Group 2 ($\triangle$) tocinide 750 mg i.v. time 0–30 min, plus 600 mg orally time 0.

Coronary Care Unit with continuous electrocardiographic monitoring for the period of the study and generally for 36 h after completion.

The peak plasma concentration obtained after 30 min (Figure 1) was virtually identical for both groups of patients despite different infusion rates. Group 2, who had a larger total dosage of tocinide, maintained a higher level throughout the study. A second and more gradual peak occurred in both groups around 4 h, although the timing of oral administration was different in each group. Thereafter the rate of decline appeared to be the same in both groups. Statistical analysis was not thought to be useful due to the small numbers in each group.

No ventricular dysrhythmia needing therapeutic intervention occurred during the period of the study, although one patient (group 1) developed ventricular tachycardia requiring lignocaine four hours after completion of the study. No change in cardiac conduction occurred during the study other than one patient with inferior infarction who showed inter-