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Flow dependence of metoprolol elimination in isolated perfused rat liver[1]

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ABSTRACT The effect of blood flow rates on hepatic elimination of metoprolol (Met) was studied in a recirculating isolated perfused rat liver system with a constant infusion of Met into the reservoir. This design ensures that, at a steady state, the elimination rate of Met is a constant. The results showed that at flow rates of 10, 20, and 30 ml·min^{-1}, the concentrations of Met entering the liver (C_{in}) were 7.6, 5.0, and 3.4 μg·ml^{-1} and the concentrations leaving the liver (C_{out}) were 1.2, 2.0, and 2.7 μg·ml^{-1}, while the logarithmic average concentrations in hepatocytes ($\bar{C}$) were 3.4, 3.2, and 3.0 μg·ml^{-1}, respectively. It is concluded that the hepatic elimination of Met is flow-dependent, which is in accordance with the 'parallel tube' model.

KEY WORDS metoprolol; liver; regional perfusion; pharmacokinetics

Liver blood flow is important for the hepatic elimination of iv administered substrates under certain circumstances. The elimination rate of metoprolol (Met) was effected by changing the hepatic blood flow rate[1]. But the enzymatic elimination physiological model of Met was yet unknown. The present investigation dealt with the relationship between the elimination of Met and the blood flow rate, and the physiological elimination model of Met.

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MATERIALS AND METHODS

Reagents Met (Sigma); dextran and bovine serum albumin powder (Shanghai Institute of Biochemistry). Other reagents were all of AR grade.

Liver perfusion See reference [2].

Procedures Met 0.5 mg was added to the perfusion medium before the experiment to shorten the initial period of equilibration. Met was given into the reservoir by a calibrated syringe pump with a flow rate of about 0.03 ml·min^{-1}.

All experiments consisted of 3 trial periods of 45 min each. Five 1.0-ml samples of the medium were taken every 5 min during the last 20 min of each period from the inlet medium and the outlet medium.

In 7 experiments the flow rate of the medium was adopted high-low (30—20—10 ml·min^{-1}) in 3 successive periods and low-high (10—20—30 ml·min^{-1}) in 6 experiments. In 4 control experiments the flow rate was kept constant, ranging from 10 to 30 ml·min^{-1}. This design permits evaluation of possible changes in the function of the liver during the experiment.

Analysis of Met in blood See reference [2].

Mathematical models of hepatic elimination kinetics At steady state, the elimination rate of drug (v) is equal to the hepatic blood flow rate (Q) multiplied by the difference between the concentration of drug entering the liver (C_{in}) and the concentration of drug leaving the liver (C_{out}). Thus

$$v = \text{constant} = Q \cdot (C_{in} - C_{out}) \quad (1)$$

Two well defined models have been widely used to predict the effect of changes in blood flow and drug metabolizing enzyme activity on the hepatic clearance of drugs. The 'well-stirred' model predicts that at a given elimination rate the outlet concentration is flow-independent;

$$v = (V_{max} \cdot C_{out}) / (K_M + C_{out}) \quad (2)$$

Where V_{max} is the maximal elimination rate and K_M the Michaelis constant. But the 'parallel tube' model predicts that both inlet and outlet concentra-

tions will change:

$$v=(V_{max}\cdot\hat{C})/(K_M+\hat{C})^{[3]} \quad (3)$$

Where $\hat{C}=(C_{in}-C_{out})/\ln(C_{in}/C_{out})$ is the logarithmic average concentration of drug in hepatocytes. This model, the relationship between v and $\hat{C}$ is flow-independent.

Statistical analysis If a single factor analysis of variance was significant ($P<0.05$), the differences between individual pairs of means were evaluated by Q test.

RESULTS

The average C_{in} and C_{out} of Met in 7 experiments with high-low flow rates of the medium and the concentration in 6 experiments with low-high flow rates. It was seen that the C_{out} was lower during the low flow rate than during the high flow rate. The difference was highly significant ($P<0.01$). The C_{in} were higher in the low flow rate periods than in the high flow rate periods in all experiments ($P<0.01$).

The calculated values of $\hat{C}$ tended to be somewhat higher in the low flow rate periods than that in the high flow rate periods ($P>0.05$) (Tab 1).

Tab 1. Metoprolol concentrations ($mg\cdot L^{-1}$) at different perfusion flow rates in recirculating isolated liver. $n=13$ livers, $\bar{x}\pm s$. $^bP>0.05$, $^cP<0.01$, *vs* 10 $ml\cdot min^{-1}$.

Flow rate	10 $ml\cdot min^{-1}$	20 $ml\cdot min^{-1}$	30 $ml\cdot min^{-1}$
C_{in}	7.6±1.7	5.0±1.2[c]	3.4±0.9[c]
C_{out}	1.2±0.4	2.0±0.5[c]	2.7±0.6[c]
$\hat{C}$	3.4±0.8	3.2±0.6[b]	3.0±0.7[b]

DISCUSSION

C_{out} was increased from 1.2 to 2.7 $\mu g\cdot ml^{-1}$, with the flow rates varying from 10 to 30 $ml\cdot min^{-1}$ (Tab 1). The results showed that C_{out} was flow-dependent. According to eqution (2), at a given elimination rate, C_{out} is flow-independent. The predictions of the 'well-stirred' model were thus not consistent with the experimental data. The 'well-stirred' model was more successful at predicting the pharmacokinetics of lignocaine and propranolol, because the protein binding ratios of lignocaine and propranolol were about 99 %[4,5], but the ratio of Met only about 12%[6]. The changes in C_{in} and the changes in C_{out} consequent upon the change of hepatic blood flow rate were well predicted by the 'parallel-tube' model. According to this model, $\hat{C}$ should not be modified by changes in hepatic blood flow rate. The changes in $\hat{C}$ were unsignificant in different blood flow rates (Tab 1). At a given elimination rate, the higher the hepatic flow rate, the higher the C_{out}. It was reported that food intake, known to increase the hepatic flow rate, should increase the blood concentration of Met given *po*[7]. This is in agreement with the 'parallel-tube' model. So it was concluded that the elimination of Met is consistent with the 'parallel-tube' model. But the physiological conditions in the intack liver are much more complex than any described model. Further studies are required to know the relationship between enzyme content, perfusion rates and transit times.

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离体大鼠肝灌流美托洛尔消除的流量依赖性

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A 摘要 用离体大鼠肝灌流方法，研究了稳态时美托洛尔的代谢模型，灌流量分别为10，20和30 ml·min^{-1}时；流入肝脏的浓度分别为7.6，5.0和3.4 μg·ml^{-1}；流出肝脏的浓度分别为1.2，2.0和2.7μg·ml^{-1}；肝窦平均浓度分别为3.4，3.2和3.0 μg·ml^{-1}. 提示流入和流出浓度呈流量依赖性，与'平行管'模型相符，而与'充分搅拌'模型不符.

关键词 美托洛尔；肝脏；局部灌注法；药物动力学

药代动力学

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Platelet activation by platelet aggregation factor from *Eisenia foelide*[1]

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ABSTRACT A platelet activating factor from earthworm, *Eisenia foelide* (EPAF, 25.9 μmol·L^{-1}), induced human platelet aggregation and 5-HT (maximal release of 89 % at EPAF 74.1 μmol·L^{-1}) was detected during this process. Neither creatine phosphate/creatine phosphate kinase (CP/CPK) nor aspirin completely inhibited the EPAF-induced platelet aggregation. In the presence of fibrinogen, EPAF (55.6 μmol·L^{-1}) induced the aggregation of human platelet which had been thrombin-treated and degranulated. Results indicated that EPAF was a potent platelet agonist and the EPAF-induced platelet aggregation was ADP- and TXA_2-independent.

KEY WORDS platelet activating factor; Oligochaeta; snake venoms; phosphocreatine; creatine kinase; aspirin; serotonin; thromboxane A_2

ADP receptor antagonist and aspirin had been applied to classify strong and weak platelet agonists[1] and aggregation pathway of platelet aggregating factor[2,3]. A platelet aggregating factor from *Eisenia foelide* (EPAF)

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