

## Pharmacokinetics of 5-fluorouracil and its penetration into pancreatic juice in dogs

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**KEY WORDS** fluorouracil; pancreatic juice; pharmacokinetics

**AIM:** To study the pharmacokinetic behavior of 5-fluorouracil (5-FU) in pancreatic juice in dogs and its correlation with 5-FU in plasma, and to evaluate its penetration characteristics. **METHODS:** After placing a pancreatoc-drainage tube, 8 dogs were injected 5-FU 250 mg iv. Blood and pancreatic samples were collected and the 5-FU concentrations were determined by HPLC. The pharmacokinetic parameters were obtained with statistical analysis. **RESULTS:** The mean slopes of the terminal phase ( $K_{10}$ ) in plasma and pancreatic juice were  $9.4 \text{ h}^{-1}$  and  $10.2 \text{ h}^{-1}$ , respectively ( $P > 0.05$ ). The pharmacokinetic behaviors of 5-FU in plasma and pancreatic juice fitted a nonlinear model. Its penetration index was  $3.39 \pm 2.84$ . The penetration of 5-FU from blood to pancreatic juice was relatively rapid, demonstrating a consistently higher concentration in pancreatic juice than in plasma. **CONCLUSIONS:** The elimination phase of 5-FU in plasma was similar to that in pancreatic juice, indicating that they were in the same kinetic compartment.

Pancreatic cancer is a kind of gastrointestinal neoplasm with characteristics of concealed clinical manifestation, rapid development and poor prognosis<sup>[1]</sup>. 5-Fluorouracil (5-FU), mitomycin C, and streptozocin are commonly used in the treatment of pancreatic cancer, but their results are unsatisfactory.

It was revealed that there was a barrier for some of antibiotics in their distribution into pancreas, a so called blood-pancreas barrier, which may caused

concentration of drugs lower than expected<sup>[2-5]</sup>. But it was rarely reported whether such a barrier existed for chemotherapeutic agents and little information was available regarding the ease of drug transport into the pancreas. Therefore a series of investigations were undertaken to evaluate the pharmacokinetic and pharmacodynamic behavior of these agents in plasma and pancreatic juice in our laboratory. One of them, 5-FU was reported here.

### MATERIALS AND METHODS

**Subjects** Eight mongrel dogs (5 F and 3 M; weighing  $17.9 \pm 1.9 \text{ kg}$ , range 13 - 19 kg) were selected and had pancreatoc-drainage tube surgically being inserted for fluid collection<sup>[6,7]</sup>.

**Drug and administration** Sterile ampoules of 5-FU for clinical injection were obtained from Shanghai Xudonghaipu Pharmaceutical Co, China (0.25 g/10 mL, lot 960307). A single dose of 250 mg 5-FU was injected iv in a 5-min infusion.

**Sample collection** Blood samples were obtained in heparinized tubes from the femoral vein before and at 2, 10, 20, 30, 40, 55, 75, and 95 min after medication. Pancreatic juice samples were collected before and at 5 min, 10-min interval from 5 - 45 min, and 20-min interval from 45 - 105 min after dosing, with each blood sampling time at the mid-point. The plasma and pancreatic juice samples were stored at  $-70 \text{ }^{\circ}\text{C}$  until assay.

**Assay** The concentrations of 5-FU in plasma and pancreatic juice were determined by an RP-HPLC assay with a sensitivity of  $10 \mu\text{g}\cdot\text{L}^{-1}$  and a linearity from  $0.1 - 10 \text{ mg}\cdot\text{L}^{-1}$ . Sample processing was a simplified modification of the original assay<sup>[8]</sup>. Instead of a triplicate liquid-liquid extraction, a specimen  $100 \mu\text{L}$  was extracted into 1.5 mL of *n*-propyl alcohol-ether (25:75, vol/vol) and then evaporated to dryness under  $\text{N}_2$ . The residue was reconstituted with mobile phase and  $25 \mu\text{L}$  of supernatant was injected onto the column.

**Data analysis** A computer program PCNONLIN (SCI, v.4.2; KY, USA) was used to obtain the major pharmacokinetic parameters of 5-FU in plasma and pancreatic juice. The slopes of the terminal phase of both plasma and pancreatic juice curves were estimated by a least-squares regression

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analysis.

The dynamic penetration ratio from plasma to pancreatic juice was measured by the concentration in pancreatic juice vs the simultaneous plasma concentration. The mean penetration index (PI) was obtained by dividing the area under the pancreatic juice curve ( $AUC_{pf}$ ) by the area under the plasma curve ( $AUC_p$ ), which was obtained by trapezoidal rule.

The differences of above parameters were evaluated by ANOVA and a paired-samples *t*-test.

## RESULTS

The plasma and pancreatic juice concentrations of 5-FU vs time as well as its penetration ratio were shown in Fig 1. Their pharmacokinetic parameters were listed in Tab 1.

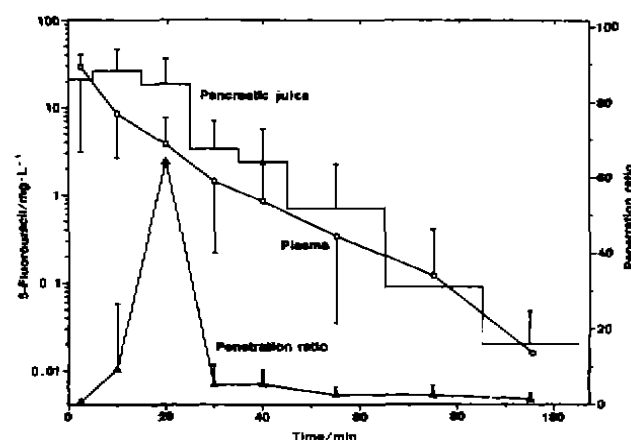


Fig 1. Plot of 5-FU in plasma, pancreatic juice, and its penetration ratio after iv 250 mg in 8 dogs.

Tab 1. Pharmacokinetic parameters of 5-FU in plasma and pancreatic juice in 8 dogs.  $\bar{x} \pm s$ .

Pharmacokinetic parameters	Plasma	Pancreatic fluid
$C_{max}/mg \cdot L^{-1}$	$29.3 \pm 11.1$	$37.1 \pm 15.9$
$T_{max}/h$	—	$0.17 \pm 0.14$
$K_{10}/h^{-1}$	$9.4 \pm 5.9$	$10.2 \pm 7.1$
$K_p/h^{-1}$	—	$38.4 \pm 36.4$
$V_d/L \cdot kg^{-1}$	$0.61 \pm 0.11$	$0.18 \pm 0.14$
$V_{max}/mg \cdot L^{-1} \cdot h^{-1}$	$1\ 064 \pm 1\ 057$	$2\ 109 \pm 1\ 689$
$K_M/mg \cdot L^{-1}$	$159.6 \pm 176.1$	$254.0 \pm 300.3$
$AUC_{0-180}/mg \cdot h \cdot L^{-1}$	$4.2 \pm 2.8$	$9.5 \pm 5.2$
PI	—	$3.39 \pm 2.84$

$K_p$  = Total penetration rate constant of 5-FU from blood to pancreas plus from pancreas to fluid.

PI = Penetration Index =  $AUC_{pf}/AUC_{plasma}$ .

The pharmacokinetic behavior of 5-FU in plasma

was fitted to a nonlinear model with bolus input and Michaelis-Menten output. Its transposition in pancreatic juice was fitted to a 1st-order input Michaelis-Menten output nonlinear process<sup>[9]</sup>

The 5-FU concentrations in pancreatic juice were higher than its simultaneous level in plasma. The mean penetration index was  $3.39 \pm 2.84$ .

## DISCUSSION

The modified HPLC assay for 5-FU in biological fluids was sensitive, reproducible, and reliable, with the intraday and interday coefficient of variation less than 5%. No potentially medication concomitant use with 5-FU was found to interfere this assay.

5-FU in pancreatic juice was consistent higher than its corresponding blood level obtained simultaneously after reaching its peak concentration in pancreatic (Fig 1), as those reported<sup>[10,11]</sup>. The statistic difference between AUC ( $P < 0.05$ ) proved that a mechanism of specific binding or an active transformation in pancreas might be involved in distribution and elimination of 5-FU. The elimination phase of 5-FU in pancreatic juice vs time was parallel with that in blood and showed no difference in their slopes ( $P > 0.05$ ), indicating that 5-FU in the blood and pancreatic juice was in the same kinetic compartment.

A plot of apparent distribution volume ( $V_d$ ) and the area under curve (AUC) vs the plasma peak concentration ( $C_{max}$ ), did not appear to be linear, and the elimination of 5-FU in both blood and pancreatic juice followed the same non-linear pattern.

Since there were no statistical difference ( $P > 0.05$ ) for the maximum elimination rate constant ( $V_m$ ) and the Michaelis-Menten constant ( $K_m$ ) in the two biological fluids, it could be concluded that 5-FU in blood was in the same compartment as that in pancreatic juice.

The penetration ratio was  $3.8 \pm 1.6$  from 0.5 – 1.5 h after administration ( $P > 0.05$ ), indicating that the penetration would be over-estimated if only a penetration ratio near the  $C_{max}$  was obtained. The over-estimation would mislead the evaluation of drug penetration behavior. Clinical efficacy must be considered along with the actual concentration of a drug at the local area. It was important to find out that the

blood-pancreas barrier did not adversely influence the penetration of 5-FU into the pancreas in dogs. Further investigation in patients regarding its permeation into pancreatic juice was ongoing.

It was difficult to collect tissue sample vs time. The available concentrations so far are not actual concentrations at actual tumor sites<sup>[12,13]</sup>. Thus the drug in pancreatic juice may represent penetration of 5-FU from blood into pancreatic tissue and this penetration should be the only way that drug can get into pancreatic juice.

In summary, the eliminations of 5-FU in both plasma and pancreatic juice displayed similar pharmacokinetic behavior and were consistent with a nonlinear process. It was suggested here that the blood-pancreas barrier did not influence the diffusion of 5-FU from blood into pancreas. The higher concentrations of 5-FU in pancreatic juice than plasma post iv administration might play a positive role in chemotherapy.

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## 5-氟脲嘧啶对狗胰液的穿透性及其药物动力学

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关键词 氟脲嘧啶; 胰液; 药物动力学 穿透性

目的: 研究胰液中 5-氟脲嘧啶(5-FU)的药物动力学行为及其与血药浓度的关系, 并评价其穿透胰液特性. 方法: 杂种狗 8 只, 手术放置胰外引流管后单剂量静注 5-FU 250 mg. 采集血和胰液并用 HPLC 法测定药物浓度. 计算药物动力学参数并作统计学分析. 结果: 血浆和胰液中 5-FU 的平均  $K_{10}$  分别为  $9.4 \text{ h}^{-1}$  和  $10.2 \text{ h}^{-1}$  ( $P > 0.05$ ). 血中和胰液药物消除均符合非线性模型, 穿透指数为  $3.39 \pm 2.84$ . 5-FU 由血浆向胰液穿透较迅速, 胰液中的药物浓度持续高于同期血药浓度. 结论: 胰液中药物消除与血液相似, 二者为同一动力学房室.