Anti-Cancer Drugs 1998, 9, pp. 685–688

Clinical paper

Penetration kinetics of 5-fluorouracil into pancreatic fluid in post-pancreatoduodenectomy patients

Zhu Zhu, Qiang Fu, Charles H Nightingale,[1] Yu-Pei Zhao,[2] Quan Liao[2] and Da-Kui Li
Departments of Pharmacy and [2]Surgery, Peking Union Medical College (PUMC) Hospital, PUMC, Chinese Academy of Medical Sciences, Beijing 100730, PRC. Tel: (+86) 10 65296537; Fax: (+86) 10 65296536/65124875. [1]Pharmacy Research, Hartford Hospital, Pharmacy School, University of Connecticut, Hartford, CT 06102, USA.

Our aim was to investigate the pharmacokinetic behavior of 5-fluorouracil (5-FU) in pancreatic fluid and to evaluate its penetration characteristics in post-pancreatoduodenectomy patients. After completing the external drainage of the pancreatic duct during pancreatoduodenectomy surgery, eight patients were administered 1.0 g 5-FU i.v. by a 5 min infusion after the eighth day post-surgery on average. Blood and pancreatic fluid were collected, and the 5-FU concentrations were determined by HPLC assay. Their pharmacokinetic parameters were obtained by PCNONLIN and statistical analysis was performed. The C_{max} was 20.03 ± 18.25 mg/l in pancreatic fluid with a T_{max} of 15.6 ± 9.5 min following i.v. administration and 49.69 ± 20.75 mg/l in plasma. 5-FU in plasma and pancreatic fluid were all in conformity with a non-linear model with a K_m of 1098.08 ± 1426.57 and 11.08 ± 6.38 mg/l, respectively. The concentrations in pancreatic fluid were similar to that observed in plasma with an average penetration index up to 1.01 ± 0.49. It is suggested therefore that 5-FU is capable of penetrating from blood into the pancreas as evidenced by the observed pancreatic concentrations. [© 1998 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, pancreatic fluid, pancreatodudeonectomy, penetration index, pharmacokinetics.

Introduction

Pancreatic cancer is one of the major leading causes of cancer death in the US. Surgical resection does not significantly change its clinical outcome. Combination chemotherapy has a partial response but overall survival remains low. 5-Fluorouracil (5-FU) is one of the chemotherapeutic agents commonly used in the treatment of pancreatic cancer, but clinical outcomes have not been completely satisfactory.[1]

The efficacy of 5-FU penetration into the pancreas needs to be identified. In our previous experiments in dogs, we observed that the elimination of 5-FU in plasma and pancreatic fluid had similar pharmacokinetic behavior and were consistent with a non-linear process, suggesting that the blood-pancreas barrier may not influence the diffusion of 5-FU from blood into the pancreas. The higher concentrations of 5-FU in pancreatic fluid compared to plasma after administration may play a positive role in chemotherapy.[2]

We therefore decided to study the pharmacokinetics of 5-FU in post-pancreatodudeonectomy patients in order to determine if the previously reported findings in dogs also occurred in human.

Materials and methods

Subjects

Eight patients who had been diagnosed as adenocarcinoma of the pancreas were enrolled in this study after providing written informed consent as required by the Ethical Committee in our hospital. They had external drainage of the pancreatic duct during WHIPPLE pancreatoduodenectomy (Table 1).

Drug and administration

Sterile injection ampoules of 5-FU for clinical use were obtained from Shanghai Xu-dong-hai-pu Pharmaceutical (Shanghai, PRC) (0.25 g/10 ml, lot 960307). A single dose of 1.0 g 5-FU was administered i.v. as a 5 min infusion.

Correspondence to Z Zhu

Table 1. Patients enrolled in the study

Name	Sex	Diagnosis	Sampling post-operative (day)	Pancreatic fluid flow during sampling (ml)			
				1st h	2nd h	3rd h	mean
LZH	M	carcinoma of ampulla	12	12.54	13.1	8.4	11.35
LQH	F	carcinoma of head of pancreas	14	3.1	3.24	4.32	3.55
CGE	F	carcinoma of head of pancreas	8	4.068	4.38	3.42	3.96
DZW	M	chronic pancreatitis, tumor of head of pancreas	5	17.888	6.3	6.75	10.31
ZX	M	mass of lower billiary duct, chronic pancreatitis	5	30.3	28.5	25.8	28.20
WZ	M	carcinoma of lower billiary duct	5	6.304	7.92	9.6	7.94
WC	M	carcinoma of ampulla	6				
WSH	M	carcinoma of head of pancreas	4				

Sample collection

Blood samples were obtained in heparinized tubes from the femoral vein before drug administration, and at the following times after administration: 2, 10, 20, 30, 40, 55, 75 and 95 min. Simultaneously pancreatic fluid samples were collected before and at the following times after dosing: 5 min, 10 min intervals from 5 to 45 min, and 20 min intervals from 45 to 105 min, with each blood sampling time at the mid-point of the pancreatic fluid sampling interval. The plasma and pancreatic fluid samples were harvested and then stored at −70°C until assay.

Sample assay

The concentrations of 5-FU in plasma and pancreatic fluid were determined by a reverse-phase HPLC assay established in our laboratory[3] with a sensitivity of 10 μg/l and a linearity range of 0.1–10.0 μg/l. The inter-run coefficients of variation were 0.5167 ± 0.0367 (CV 7.10% at 0.50 μg/ml, n=6) and 7.8683 ± 0.376 (CV 4.78% at 8.0 μg/ml, n=6). The intra-run coefficients of variation were 0.4904 ± 0.0183 (CV 3.73%, n=8) and 7.8601 ± 0.1742 (CV 2.22%, n=8).

Data analysis

The major pharmacokinetic parameters of 5-FU in plasma and pancreatic fluid were measured by non-linear curve fitting software (PCNONLIN SCI, version 4.2) to fit a pharmacokinetic model to data. The last four points on the concentration-time profile were defined as the terminal phase. The slopes of both the plasma and pancreatic fluid terminal portions of these curves were estimated by a least-squares regression analysis.

The dynamic penetration ratio (PR) was calculated by the concentration in pancreatic fluid versus the simultaneously obtained plasma concentration. The penetration index (PI) was obtained by dividing the area under the pancreatic fluid curve $(AUC)_{pf}$ by the area under the plasma curve $(AUC)_p$, which were both obtained by using the trapezoidal rule.

The elimination of 5-FU is an enzyme-saturated non-linear process which may be expressed by the Michaelis-Menten output model with the elimination rate equal to $-dC/dt = V_m{}^*C_p/(K_m + C_p)$, in which V_m is the maximum elimination rate and K_m is the Michaelis constant.[4] The 5-FU concentrations in plasma were fitted to a non-linear model with bolus input and Michaelis-Menten output. Its transposition in pancreatic fluid was fitted to a first-order input, Michaelis-Menten output non-linear process.

Statistical differences in the above parameters were evaluated by an ANOVA.

Results

The plasma and pancreatic fluid concentrations of 5-FU versus time from patients post-administration are shown in Figure 1. Their pharmacokinetic parameters are listed in Table 2.

The 5-FU concentrations in pancreatic fluid were slightly higher than the simultaneous concentrations in plasma and had a PI of 1.01 ± 0.49. The non-linear pharmacokinetic characteristics of 5-FU were again observed in these patients as demonstrated by a plot of V_d versus $C_{max\text{-}p}$ (Figure 2). This indicates that the kinetic model previously described in dogs also appears to explain 5-FU kinetics in the patients.[4]

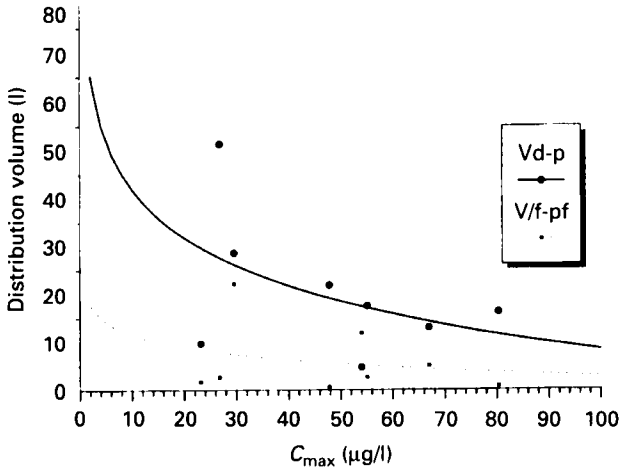

Figure 1. Mean concentration–time curves of 5-FU in plasma, pancreatic fluid and its PR in patients following a single dose of 1.0 g i.v. (n = 8). (●) Plasma, (Δ) pancreatic juice, (–) PR.

Table 2. Pharmacokinetic parameters of 5-FU in plasma versus pancreatic fluid in patients (n = 8, mean ± RSD)

Pharmacokinetic parameters	Plasma	Pancreatic fluid
C_{max} (mg/l)	48.00 ± 20.34	32.90 ± 8.43[b]
T_{max} (min)	–	15.63 ± 9.51
V_d (l/kg)	20.37 ± 14.48	5.89 ± 7.56
V_{max} mg/l/h	5691.81 ± 7932.23	1700.19 ± 2058.34
$K_{M\ (mg/l)}$	1098.08 ± 1426.57	11.08 ± 6.38
$AUC_{0-\infty}$ (mg·h·l^{-1})	12.33 ± 6.01	10.09 ± 1.77[b]
PI[a]	–	1.01 ± 0.49

[a]The penetration index of 5-FU, AUC in pancreatic fluid versus AUC in plasma.
[b]$p > 0.05$.

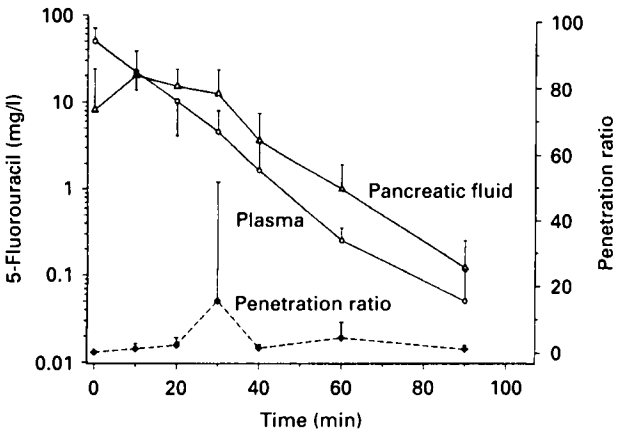

Figure 2. The plot of distribution volume versus the maximum concentration of 5-FU in patients.

Discussion

The modified HPLC assay for 5-FU in biological fluids was sensitive, reproducible and reliable, with an intra-run and inter-run coefficient of variation of less than 5%. The average sampling time was 8 days post-surgery, with a range of 4–14 days after surgery (Table 1).

It is important for this investigation that external drainage of the pancreatic duct during the WHIPPLE pancreatoduodenectomy resulted in the placement of an appropriate size drainage tube. Appropriate technique for anastomosis and fixation of the tube is necessary for successful pancreatic fluid collection. To ensure this, all our operations were conducted by the same group of surgeons so that the quality of the operation was consistent among the patients.

The secretion of pancreatic fluid was in excess of 50 ml/day from the third day post-surgery and 100–300 ml/day while biological samples were collected. Generally in healthy adults the exocrine pancreas secretes about 1–2 l/day of alkaline pancreatic juice, which contains water, electrolytes and enzymes necessary for digestion.[5] However, only 0–30 ml/day was secreted within the first days after pancreatic trauma in these patients. Several factors might be related to individual differences for 5-FU's distribution, such as quantity of pancreas that was surgically removed, the original secretion function of pancreas, and the type and site of carcinoma.

The process of drug penetration into pancreatic fluid actually involves two steps, i.e. from blood into pancreatic tissue and from tissue into the fluid. It was difficult to collect tissue sample versus time from patients, thus the drug in the pancreatic fluid represents the penetration of 5-FU from blood into the pancreatic tissue and this penetration should be the only way that the drug can get into pancreatic fluid. This study suggests that the blood-pancreas barrier does not adversely influence the penetration of 5-FU in these patients.

The prognosis for unresectable advanced gastric cancer patients, especially with wide-spread metastasis in the peritoneal cavity, is very poor. Chemotherapy as a systemic therapy is often selected in such cases. Therefore, measurement of local drug concentrations in pancreatoduodenectomy patients may be helpful to predict the penetration of chemotherapeutic agents in both resectable and unresectable patients.

In summary, the pharmacokinetics of 5-FU in both plasma and pancreatic fluid in pancreatoduodenectomy patients was investigated. The concentrations in pancreatic fluid were as high as in plasma with an average PI up to 1.01 ± 0.49. It is suggested here that 5-

FU may penetrate from blood into the pancreas as evidenced by the observed pancreatic fluid concentrations in patients.

References

1. Wanebo HJ, Vezeridis MP. Pancreatic carcinoma in perspective. A continuing challenge. *Cancer* 1996; **78** (suppl 3): 580–91.
2. Zhu Z, Fu Q, Nightingale CH, Zhao YP, *et al.* The pharmacokinetics of 5-fluorouracil and its penetration into pancreatic fluid in dogs. *Acta Pharmacol Sinica* 1998; **19**: 7–9.
3. Meng X, Chen LY. An improved high-performance liquid chromatographic method for determination of 5-fluorouracil in human plasma. *Chin J Clin Pharmacol* 1985; **1**: 188–193.
4. Shargel L, Yu ABC. *The applied biopharmaceuticals and pharmacokinetics,* 3rd edn. Norwalk CT: Appleton & Lange 1993: 375–9.
5. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pancreatitis. In: *Pharmacotherapy—a pathophysiology approach,* 3rd edn. Stamford, CT: Appleton & Lange 1996: 815.

(Received 21 April 1998; revised form accepted 18 June 1998)