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ORIGINAL RESEARCH

Pharmacokinetics of four 5-FU preparations administered rectally to rats and rabbits

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Abstract

AIM: To compare the pharmacokinetic characteristics of four preparations of fluorouracil (5-FU) administered rectally using a rat model.

METHODS: Concentrations of 5-FU were measured in plasma, the rectal wall and mesentery lymph tissues of rats and rabbits by high performance liquid chromatography. Differences between the main pharmacokinetic parameters were compared by statistical analysis.

RESULTS: The 5-FU concentrations in the rectal wall and mesenteric lymph tissues were significantly higher than the concentration in blood following rectal administration for all four of the preparations ($P < 0.01$). The drug level in the rectal wall was higher in the animals received delivery of an emulsion, compared to those who received delivery as a suppository ($P < 0.05$). Moreover, the animals who received a lipophil-based suppository had lower plasma level of drug than those who received a hydrophil-based suppository, and the animals who received the simple (o/w) emulsion had lower plasma level than those who received the complex (w/o/w) emulsion. The differences found in the rat model were confirmed in rabbits ($P < 0.01$).

CONCLUSION: The lipophil-based suppository and the simple emulsion of 5-FU might be more suitable for rectal administration for treatment of rectal cancers.

Key words: Fluorouracil/phamarcokinetics; Rectal administration; Rectal neoplasms/drug therapy

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INTRODUCTION

Fluorouracil (5-FU) is one of the most effective medicines for chemotherapy of large bowel cancer; unfortunately, intravenous administration does not allow for a sufficiently high concentration to reach the cancer tissues and is associated with frequent serious toxic reactions and side effects[1]. However, a higher 5-FU concentration in cancer tissues accompanied by a relative lower level in plasma could be obtained if the drug is administered rectally[2]; as such, this strategy would also reduce the risk of adverse reactions, such as arrest of bone marrow functions.

We generated four different preparations of 5-FU for rectal administration, and compared their pharmacokinetic characteristics in the rat and rabbit whole animal systems.

MATERIALS AND METHODS

Animals

Female and male rats (weight range: 150-200 g) and rabbits (weight range: 2-3 kg) were provided by the animal facility of North Sichuan Medical College.

Compounds

5-FU raw drug (lot number: 910732) was procured from the manufacturer, Shanghai 12th Pharmaceutical Factory. All reagents used in the study were of AR grade.

Preparations

Crystalline grain (o.d. 10 μm) was generated by the solvent-transformation method. The hydrophil-based (polyethylene glycols) suppositories (HBS) and lipophil-based (semi-synthetic fatty glyceride) suppositories (LBS), each containing 250 mg 5-FU (for rabbits) or 25 mg (for rats), were generated by the heating-melt method. Two kinds of emulsions containing 5-FU (5%) (wt/vol)) were generated using an aqueous solution, namely the simple (o/w) emulsion (SE)

Table 1 Comparison of tissue concentrations in rats among the four 5-FU preparations ($\bar{x} \pm s$, $n = 5$)

Group	Concentration		
	Plasma (mg/L)	Rectal wall (mg/g)	Mesenteric lymph nodes (mg/g)
HBS	27.10 ± 15.06[c]	71.97 ± 21.64[b]	75.92 ± 21.81[b]
LBS	16.60 ± 15.03	46.82 ± 20.84[b]	41.93 ± 17.22[b]
SE	14.39 ± 9.40	154.11 ± 46.54[a,b]	41.29 ± 15.30[b]
CE	19.47 ± 8.71[c]	156.60 ± 42.31[a,b]	46.45 ± 13.41[b]

[b]$P < 0.01$ *vs* plasma level; [a]$P < 0.05$ SE group *vs* HBS group, CE group *vs* LBS group; [c]$P > 0.05$ HBS group *vs* LBS group, CE group *vs* SE group. HBS: hydrophil-based (polyethylene glycols) suppositories; LBS: Lipophil-based (semi-synthetic fatty glyceride) suppositories SE: Simple (o/w) emulsion; CE: Complex (w/o/w) emulsion.

Table 2 Main pharmacokinetic parameters in rabbits after rectal administration of four 5-FU preparations ($\bar{x} \pm s$, $n = 3$)

Group	T1/2 (h)	Vd (L)	AUC [(mg·g)/L]	Cmax (mg/L)	Tmax (h)
HBS	1.19 ± 0.52	2.25 ± 1.01	95.41 ± 45.21[b]	39.56 ± 19.02	0.84 ± 0.41
LBS	1.92 ± 0.80	16.90 ± 7.44	20.44 ± 9.82	8.56 ± 3.70	0.55 ± 0.29
SE	4.54 ± 1.75	22.98 ± 10.51	35.60 ± 15.03	9.95 ± 3.97	0.40 ± 0.17
CE	2.10 ± 0.98	3.00 ± 1.42	126.19 ± 73.35[b]	30.48 ± 15.24	0.99 ± 0.49

[b]$P < 0.01$ HBS group *vs* LBS group, CE group *vs* SE group. HBS: hydrophil-based (polyethylene glycols) suppositories; LBS: Lipophil-based (semi-synthetic fatty glyceride) suppositories SE: Simple (o/w) emulsion; CE: Complex (w/o/w) emulsion.

and the complex (w/o/w) emulsion (CE).

Instruments and requirements of assay

High performance liquid chromatography (HPLC) was carried out with the chromatographic column-Zorbax ODS (Gilson Corporation, France) using the following parameters: 4.6 mm × 150 mm; graininess 5 μm; mobile phase, phosphate buffer solution (0.025 mol/L, pH 3.0); and flow rate, 1 mL/min.

Experiments

Twenty rats were randomly divided into four groups, with total weight balanced in each. The rats in the four groups were rectally administered 5-FU as HBS, LBS, SE or CE at a dose of 25 mg. In order to prevent leakage of the drug solution from the anus, the orifice was clipped closed after the drug delivery. At 1 h post-delivery, blood samples (2 mL each) were drawn from the tail vein and the rats were sacrificed for immediate tissue harvesting (rectal and mesenteric lymph nodes). The rectal tissues were first cleaned by distilled water and blotted on filter paper, then 30 mg were weighed out for the subsequent analyses. The blood samples (containing heparin) were centrifuged and 1 mL plasma was collected for analysis. The 5-FU concentrations in the tissues and plasma were determined by HPLC assay as previously described but with slight modification[3].

Twelve rabbits were randomly divided into four groups and rectally administered 5-FU as HBS, LBS, SE or CE at a dose of 250 mg. At 0.5, 1, 1.5, 2, 4 and 6 h post-delivery, blood samples (1.5 mL) were drawn from the posterior auricular arteries and processed for analysis as described above.

RESULTS

Data for the main pharmacokinetic parameters are presented in Tables 1 and 2.

DISCUSSION

5-FU is one of the most common anticancer drugs used in clinical practice today, and its strong killing effects on cancer cells are well recognized. Specifically, 5-FU damages proliferating cells, thereby reducing the tumor mass in size and preventing tumor cells from spreading and undergoing metastasis. However, if the drug is administered intravenously, its curative effects are inadequate because it achieves a lower concentration in the rectal wall and mesenteric lymph nodes and instead has a relatively higher concentration in blood[4]. High blood concentrations lead to serious side effects that preclude the patients' ability to tolerate the treatment.

In this study, the 5-FU concentrations in the rectal wall and mesenteric lymph nodes were significantly higher than that in blood at 1 h after administration to rats, for all four of the different preparation types ($P < 0.01$). Comparison of the four types of preparations showed that the emulsions provided higher levels of 5-FU in the rectal wall than did the suppositories ($P < 0.05$). The drug concentrations in the blood was higher in the rats given HBS than in those given LBS, and higher for CE than for SE ($P > 0.05$). The differences were confirmed in the rabbit system as well ($P < 0.01$).

Thus, LBS and SE provided higher 5-FU concentrations in the rectal wall and mesenteric lymph nodes, and a lower concentration in blood. Rectal administration can reduce toxic and side effects and increase anticancer effects; therefore, the two preparations, LBS and SE, are more suitable for clinical application.

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