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Cardiopulmonary hemodynamics and pharmacokinetics after hepatic intraarterial infusion of 5-fluorouracil (5-FU)*

An experimental study in the pig

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Summary. Reported 5-FU-induced cardiac side effects may be explained by drug-induced hemodynamic changes and/or by direct myocardial toxicity due to regional drug uptake. This question was studied in 11 animals given constant infusions and 6 animals given bolus 5-FU infusions into the hepatic artery. Six animals, which received normal saline infusion, served as controls. A second aim was to study possible pulmonary drug clearance. Aortic, pulmonary arterial, and coronary sinus plasma 5-FU concentrations were determined during constant and after the bolus infusions of 5-FU. The V5 ECG, aortic, pulmonary arterial, and right atrial pressures were recorded continuously, and cardiac output and coronary sinus blood flow were recorded intermittently in all animals. No significant alterations in hemodynamic variables were seen during constant infusion. After the bolus infusion, an increased arterio-mixed venous oxygen content difference was recorded. Pharmacokinetic data after 3-min infusions indicated pulmonary drug uptake and release; during constant infusions, the data indicated myocardial drug uptake. As there were no alterations in myocardial oxygen demand or supply or in systemic hemodynamics during this myocardial drug uptake, it is likely that the cardiotoxicity is related to the direct effects of the drug on cardiac myocytes.

Introduction

5-Fluorouracil is probably one of the most commonly used cytostatic agents for the treatment of solid tumors in various organs, including primary and secondary liver cancer [12]. Common drug-related side effects are myelosuppression, nausea, vomiting, and stomatitis [3]. Cardiotoxicity has been an infrequently reported side effect of 5-FU treatment [14–16]. Chest pain, ECG abnormalities, and enzyme evidence of myocardial necrosis are among the reported cardiac side effects. It is reasonable to postulate that the side effects are secondary to drug actions upon the systemic or coronary vascular beds or, alternatively, are due to the consequences of myocardial cell damage.

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The pharmacokinetics of 5-FU have been described in several previous investigations [5, 11, 18]. Pulmonary clearance has been discussed mostly because of the high total body clearance of 5-FU [5]. In a recent study of cancer patients, given 5-FU into the hepatic artery, we reported data indicating a drug clearance by the cardiopulmonary circulation [2]. The aim of the present investigation was to evaluate the effect of 5-FU on systemic, pulmonary, and coronary hemodynamics and myocardial oxygenation and their relationships to regional myocardial 5-FU pharmacokinetics in the pig.

Materials and methods

In this study 23 pentobarbital-anesthetized female pigs (Swedish landrace) weighing between 40 and 70 kg were used. After i.v. pentobarbital induction, a tracheostomy was carried out and the animals were attached to a volume-cycled ventilator. Ventilation was maintained by oxygen-enriched air (fraction of inspired oxygen = 30%). Anesthesia was maintained by continuous i.v. pentobarbital infusion at 15 mg/kg per hour. End-tidal carbon dioxide tension was kept around 4.0 kPa. Under fluoroscopic guidance, catheters were placed in the thoracic aorta via the femoral artery, in the pulmonary artery, and in the coronary sinus via the external jugular vein. After laparotomy, a catheter was inserted into the hepatic artery. Pressure transducers (Siemens-Elema 746/51) were placed at midchest level and calibrated by water standards. The V5 ECG, aortic, pulmonary arterial, and right atrial pressures were recorded continuously during the study period on a Mingograph 82 recorder. Cardiac output and coronary sinus blood flow were determined by the bolus and retrograde continuous infusion thermodilution techniques, respectively [7, 9]. A list of abbreviations referring to hemodynamic variables and their derivations is presented in Tables 1 and 2.

Eleven animals received constant infusions of 5-FU at 0.02 mg kg/min over 2 h (mean total dose = 120 mg) into the hepatic artery, and six animals serving as controls were given approximately 60 ml normal saline into the same vessel over 2 h. Blood was sampled from the pulmonary artery, the aorta, and the coronary sinus for 5-FU analysis at 10-min intervals from 60 to 120 min after the start of the drug infusion. In addition, blood was sampled from the pulmonary artery, the aorta, and the coronary sinus for measurement of oxygen content, in association with the

hemodynamic measurements made before laparotomy and 60 and 120 min after the start of the infusion. Blood sampling and hemodynamic measurements were identical in the control animals. Six other animals were given bolus infusions of 15 mg/kg 5-FU into the hepatic artery over 3 min (mean total dose = 750 mg). In these animals, blood was sampled for 5-FU analysis from the pulmonary artery, the aorta, and the coronary sinus at 2, 5, 10, 15, 30, and 60 min after the infusion. Blood was also sampled from the pulmonary artery, the aorta, and the coronary sinus for measurement of oxygen content, in association with the hemodynamic measurements carried out prior to the abdominal incision and before as well as 5, 15, 30, and 60 min after the end of the infusion.

5-FU analysis. The blood samples were immediately centrifuged for 5 min at 3000 rpm and stored at −80° C until analyzed. After thawing, the plasma samples were deproteinized and analyzed by HPLC. The HPLC system consisted of a C18-μ Bondapak column, 30 cm × 3.9 mm, and a Waters model 600 A solvent delivery system. A UV-detector operating at 254 nm was used for detection of 5-FU.

Pharmacokinetic evaluation. Pulmonary uptake/release (mg/min) was calculated as CO × ($C_{PA} - C_A$), where CO is the cardiac output (ml/min), and C_{PA} and C_A (ng/ml) are the concentrations of 5-FU in the pulmonary arterial and aortic plasma, respectively. The area under the plasma concentration curve (AUC) was calculated according to the trapezoidal rule.

Statistics. The Wilcoxon matched-pairs signed-rank test was used for the comparision of two related samples. Independent samples were compared with the Mann-Whitney *U*-test. A *P*-value less than 0.05 was considered statistically significant. All results are presented as means ± SEM.

Table 1. Hemodynamic parameters (mean ± SEM) before and during 2-h constant rate, hepatic arterial infusions of 5-FU[a]

	Preoperative	Postlaparotomy	30 min	60 min	120 min
MAP	117.4± 5.8	110.1± 6.8	105.2±11.5	108.8± 8.2	106.3± 9.4
MPAP	19.6± 1.0	20.3± 1.2	19.2± 0.9	20.8± 1.8	20.6± 1.1
PCWP	10.6± 0.8	9.1± 0.6	9.2± 0.8	10.5± 0.6	9.5± 0.5
HR	107.4± 5.4	113.4± 6.0	114.3± 7.4	114.4± 4.8	121.6± 6.0
CO	5.3± 0.4	4.9± 0.4	5.2± 0.1	5.0± 0.3	5.0± 0.2
SV	49.4± 3.2	43.8± 3.7	48.0± 5.4	44.1± 2.6	44.6± 5.4
SVR	31.4± 3.3	31.5± 3.0	20.0± 0.8	29.7± 2.7	28.6± 2.7
PVR	2.4± 0.1	3.3± 0.4	2.6± 0.3	3.0± 0.5	3.2± 0.3
A-PAO_2-d	44.3± 6.4	42.3± 4.9	30.8± 5.7	42.2± 6.3	45.0± 3.1
VO_2	233.9±25.2	220.2±24.6	157.6±26.3	219.1±36.5	232.6±24.0

[a] *Abbreviations:* MAP, mean arterial pressure (mm Hg); MPAP, mean pulmonary arterial pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg); HR, heart rate (beat per min); CO, cardiac output (l/min); SV, stroke volume (ml); SVR, systemic vascular resistance [mm Hg (l/min/m^2)]; PVR, pulmonary vascular resistance [mm Hg (l/min/m^2)]; A-PAO_2-d, arterio-mixed venous oxygen content difference (ml O_2/l); VO_2, oxygen consumption (ml O_2/min)

Table 2. Hemodynamic parameters (mean ± SEM) before and during 2-h constant rate, hepatic arterial infusions of 5-FU[a]

	Preoperative	Postlaparotomy	30 min	60 min	120 min
MVO_2	9.7 ± 2.6	9.6 ± 2.5	–	9.2 ± 2.8	10.0 ± 3.3
MVO_2/HR	0.09± 0.03	0.09± 0.01	–	0.09± 0.03	0.08± 0.03
CSF	91 ±22	106 ±28	86±24	109 ±32	118 ±35
MO_2-extr	89.3 ± 1.0	89.7 ± 1.0	–	88.3 ± 0.9	87.8 ± 0.8

[a] *Abbreviations:* MVO_2, myocardial oxygen consumption (ml O2/min); CSF, coronary sinus blood flow (ml/min); MO_2-extr, myocardial oxygen extraction (%)

Table 3. Hemodynamic parameters (mean ± SEM) during 2-h constant rate, hepatic arterial infusions of normal saline

	Preoperative	Postlaparotomy	30 min	60 min	120 min
MAP	118.7± 7.1	112.5±10.3	108.8±11.2	108.5±11.8	107.7±11.8
MPAP	19.7± 1.3	20.8± 1.1	18.3± 0.6	18.5± 0.7	18.3± 0.5
PCWP	10.0± 1.3	9.5± 0.9	8.8± 0.9	8.7± 0.7	8.3± 0.6
HR	123.0± 9.9	126.5± 8.0	122.5± 5.9	115.2± 5.1	120.6± 4.0
CO	5.4± 0.5	5.0± 0.4	4.4± 0.6	4.5± 0.5	4.4± 0.5
SV	44.8± 4.4	40.5± 4.1	39.0± 5.6	38.7± 3.9	32.9± 2.5
SVR	27.4± 3.5	27.1± 3.3	31.3± 4.6	30.4± 4.6	30.7± 5.1
PVR	2.3± 0.3	2.9± 0.3	2.6± 0.3	2.9± 0.3	3.0± 0.4
A-PAO_2-d	36.9± 1.3	38.7± 1.9	39.6± 5.5	40.6± 1.5	42.8± 2.8
VO_2	190.3±18.2	192.3±11.7	–	175.1±20.6	183.8±24.3

Table 4. Hemodynamic parameters (mean ± SEM) during 2-h constant rate, hepatic arterial infusions of normal saline

	Preoperative	Postlaparotomy	30 min	60 min	120 min
MVO_2	8.3 ± 2.2	7.0 ±0.9	–	6.5 ±0.6	6.8 ±0.7
MVO_2/HR	0.07± 0.01	0.06±0.01	–	0.06±0.01	0.06±0.06
CSF	86 ±15	76 ±8	68±7	65 ±4	67 ±6
MO_2-extr	80.4 ± 3.0	78.7 ±3.4	–	32.6 ±1.8	33.7 ±1.9

Table 5. Hemodynamic parameters (mean ± SEM) after 3-min hepatic arterial bolus infusions of 5-FU

	Preoperative	Postlaparotomy	2 min	5 min	15 min	30 min	60 min
MAP	157.0± 5.0	140.0± 7.0	139.0±6.0	137.0± 6.0	134.0± 5.0	131.0± 5.0	125.0± 8.0
MPAP	19.3± 0.9	16.7± 0.8	17.8±1.2	19.0± 1.6	18.8± 1.7	17.7± 1.3	16.3± 2.3
PCWP	8.0± 0.6	7.2± 0.3	8.2±1.4	8.5± 1.6	8.3± 1.5	8.0± 1.5	7.5± 2.0
HR	140.0± 6.1	120.0± 8.2	118.0±7.8	118.0± 7.8	120.0± 8.1	124.0± 8.2	123.0±20
CO	4.6± 0.3	3.8± 0.1	4.0±0.2	3.9± 0.2	3.8± 0.2	3.7± 0.2	3.6± 0.3
SV	33.6± 3.5	32.3± 2.5	34.8±2.9	33.2± 2.7	32.2± 2.9	30.6± 3.1	30.0± 6.0
SVR	38.0± 3.3	40.1± 1.6	37.4±1.2	38.9± 1.5	38.5± 1.3	38.8±31.3	38.0± 4.9
PVR	2.8± 0.2	2.8± 0.2	2.7±0.4	3.1± 0.4	3.2± 0.3	3.0± 0.3	2.8± 1.0
A-PAO_2d	43.1± 2.7	43.4± 2.8	–	47.5± 2.2	47.1± 3.4	51.6± 3.5	55.3±11
VO_2	195.0±11	165.0±14	–	183.0±12	178.0±18	192.0±20	200 ±60

Table 6. Hemodynamic parameters (mean ± SEM) after 3-min hepatic arterial bolus infusions of 5-FU

	Preoperative	Postlaparotomy	5 min	15 min	30 min	60 min
MVO_2	10.7 ± 1.6	9.3 ± 1.7	9.2 ± 1.6	10.2 ± 2.0	9.0 ± 1.6	9.2 ± 2.1
MVO_2/HR	0.08± 0.01	0.08± 0.02	0.08± 0.02	0.09± 0.02	0.08± 0.02	0.08± 0.01
CSF	107 ±14	93 ±15	91 ±14	103 ±18	87 ±14	83 ±15
MO_2-extr	91.0 ± 1.5	84.7 ± 2.9	85.1 ± 2.8	85.1 ± 2.4	85.7 ± 2.5	85.8 ± 1.4

Results

Hemodynamics

Eight animals given constant infusions of 5-FU were included in the hemodynamic studies, and three animals were excluded due to long preparation time. The hemodynamic variables measured and calculated in these, in the control animals, and in six animals given the 3-min 5-FU infusions are outlined in Tables 1–6. No significant drug effects were observed in animals given constant infusion of 5-FU or saline. The only significant effect observed after the 5-FU bolus infusion was an increase in arterio-mixed venous oxygen content, measured 30 and 60 min postinfusion (+19% and +28%, respectively, $P < 0.05$), compared with the postlaparotomy value (Table 5). At 30 min postinfusion the increase included five animals and at 60 min, all six animals.

Pharmacokinetics

Pharmacokinetic data were available from nine animals given the constant 5-FU infusion. During this infusion the mean 5-FU concentration was 2.2±1.4 nmol/ml in the aorta, 2.1±1.6 nmol/ml in the pulmonary artery, and 1.5±0.7 nmol/ml in the coronary sinus. The concentration gradient over the myocardium was significant ($P < 0.001$) (Fig. 1).

The 5-FU elimination curves following the 3-min infusions in six animals are shown in Fig. 2. The mean aortic and pulmonary artery 5-FU concentrations at 5 min after the infusion were 149±27 and 121±25 nmol/ml, respectively ($P < 0.05$). There was a tendency toward higher concentrations in the pulmonary artery than in the aorta at 10 and 15 min postinfusion ($P = 0.058$ at 10 min). No significant differences between aortic and coronary sinus 5-FU concentrations were observed. The mean aortic, pul-

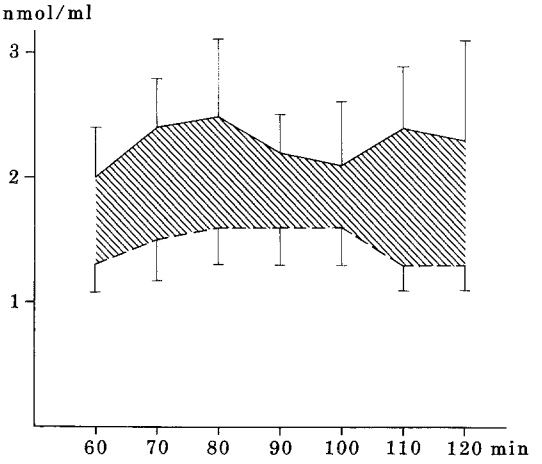

Fig. 1. Mean (± SEM) concentrations of 5-FU in aortic (———) and coronary sinus (– – – – –) plasma during constant drug infusions

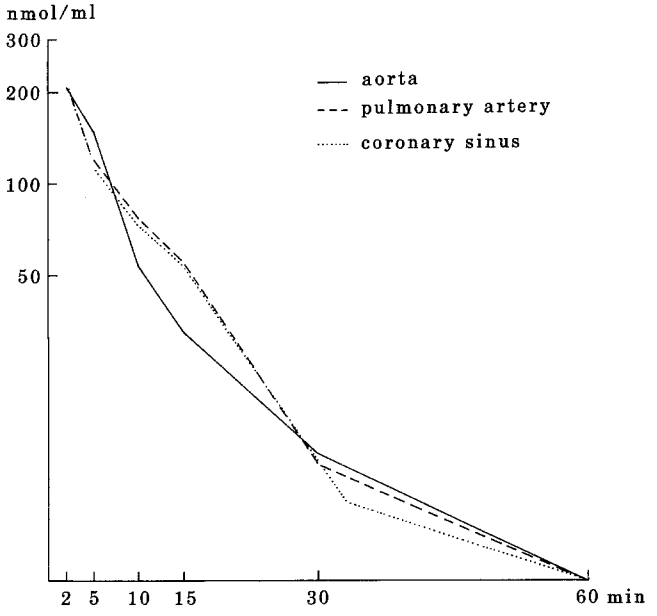

Fig. 2. Mean concentrations of 5-FU in aortic (———), pulmonary arterial (– – – –), and coronary sinus (. . . . .) plasma after bolus drug infusions

monary arterial, and coronary sinus AUC values were 2371 ± 331, 2041 ± 341, and 2238 ± 235 nmol/min per milliliter, respectively. The difference between aortic and pulmonary arterial AUC was significant ($P < 0.05$). The mean pulmonary uptake/release of 5-FU was -1.0 ± 35.0, -13.3 ± 12.0, 11.6 ± 15.1, 10.7 ± 12.7, and -1.1 ± 5.1 mg/min at 2, 5, 10, 15, and 30 min, respectively. Values at 5 min were significantly different from those measured at 10 and 15 min postinfusion ($P < 0.01$).

Discussion

Hemodynamics

It has previously been shown that the format of anesthesia used in the present investigation results in constant plasma pentobarbital concentrations [13]. Thus, it is unlikely that interference with alterations in plasma pentobarbital levels would alter the results in this study. Our hemodynamic findings in the pig are in agreement with data previously presented by Spremulli et al. [17]. In the latter study, blood pressure and ECG were measured after i.v. bolus injections of various adenosine analogues, including 5-FU, into sodium amytal-anesthetized rats. Although several adenosine analogues depressed heart rate and blood pressure, 5-FU did not cause any changes in the hemodynamic variables.

In the present study, 30 and 60 min following the bolus infusion of 5-FU the arterio-mixed venous oxygen difference was significantly increased (19% and 28%, respectively). Since cardiac output, arterial oxygen content, and blood pH remained constant, this observation indicates an increased total body oxygen use, possibly due to an oxygen-dependent metabolism of 5-FU. Two primary cytotoxic mechanisms for 5-FU have been demonstrated: inhibition of thymidylate synthetase [6] and incorporation into RNA [4]. Approximately 90% of the 5-FU is metabolized [19]; this metabolism is considered to involve an initial reduction of the pyrimidine ring by dihydrouracil dehydrogenase followed by degradation to urea [11]. None of these events has, however, previously been shown to be oxygen-dependent.

Pharmacokinetics

A high initial pulmonary drug uptake would decrease acute systemic toxicity following a bolus infusion. Measurements taken 2 min after termination of the bolus infusion of 5-FU, as in the present study, would not be expected to include peak plasma drug concentrations occuring during initial drug distribution. Therefore, a possible first-pass uptake of 5-FU by the lungs and/or the heart could not be studied. The variations in aortic-pulmonary arterial 5-FU concentration gradients with time and the difference between the aortic and pulmonary arterial AUCs do, however, indicate that the lungs act as a temporary storage site for the drug, which is then redistributed into the systemic circulation. Liss and Chadwick [10] have i.v. injected 200 mg/kg radiolabelled 5-FU in rats and found concentrations of radioactivity in both the myocardium and the lungs higher than those observed in the blood, up to 96 h postinjection. Their data suggest both myocardial and pulmonary drug uptake. In our animals given bolus infusions, however, we could not confirm an active myocardial drug uptake from 2 to 60 min following bolus administration of the drug. It is, however, possible that 5-FU was extracted by the heart over the first 2 min, resulting in a saturation of the myocardium. This suggestion is supported by the active uptake of 5-FU observed in animals given 5-FU as a constant infusion. Since the myocardium receives about 5% of the cardiac output, the observed myocardial elimination includes only a minor part of the total body 5-FU clearance.

The hepatic elimination of 5-FU differs according to dose rate and route of administration. During continuous portal or jugular venous infusions of 5-FU in the dog, approximately 10% and 75%, respectively, of the drug has been eliminated by the liver [8]. After jugular venous infusion, about 15% of the extrahepatic elimination has occurred in the prehepatic splanchnic area [8]. Several studies have indicated a nonlinear elimination of 5-FU [5, 18]. Thus, the hepatic extraction ratio of 5-FU declines with increasing dose, indicating a saturable process. In man, this hepatic extraction ratio has been estimated to be 0.26–0.48 and 0.56–0.87 following high and low doses, respectively [1, 18].

Different etiologies for 5-FU-induced cardiotoxicity have been proposed, including coronary artery spasm, pulmonary hypertension following pulmonary artery spasm, increased platelet aggregation, or direct toxic effects of 5-FU on the myocardium [16]. In the present study, 5-FU did not produce hemodynamic changes that significantly altered the peripheral determinants of myocardial oxygen demand/supply ratio or regional vascular tone. Since a myocardial drug uptake was observed, future studies on 5-FU-related cardiotoxicity should focus on potentially harmful effects of the drug on cardiac myocytes.

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