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ORIGINAL ARTICLE

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Effect of carcinomatosis and intraperitoneal 5-fluorouracil on peritoneal blood flow modulated by vasopressin in the rat as measured with the ^{133}Xe-clearance technique

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Abstract *Purpose*: Intraperitoneal administration of 5-fluorouracil for the treatment of gastrointestinal malignancies results in a greater total drug exposure in the peritoneal fluid than in plasma. Drugs are eliminated from the peritoneal cavity mainly by capillaries leading to the portal venous system and to a lesser extent by lymphatics. The drug itself and the presence of peritoneal carcinomatosis may affect elimination of the drug. The ^{133}Xe-clearance technique allows the influence of a vasoactive agent on the peritoneal blood flow to be estimated with minimal invasiveness. The aim of the present study was to explore whether intraperitoneal 5-FU or peritoneal carcinomatosis affects the peritoneal blood flow and its reactivity to intravenous vasopressin, as measured indirectly with the ^{133}Xe-clearance technique. *Methods*: The animals used in this study were 63 Wistar-Fu (W-Fu) rats and 67 Lister-Hooded (LH) rats. On day 0, either 5-FU at 25 mg/kg body weight in 25 ml/kg isotonic saline was instilled intraperitoneally, or 1×10^5 syngeneic tumour cells were inoculated intraperitoneally. On days 1, 2 and 3 in the 5-FU-treated rats, and on days 12–16 in rats inoculated with tumour cells, peritoneal blood flow was analysed with the ^{133}Xe-clearance technique, before and during intravenous infusion of vasopressin at 0.07 IU/min/kg body weight. *Results*: The basal ^{133}Xe-clearance before administration of vasopressin was similar in all groups except in the LH rats treated with 5-FU in which it was significantly lower. Infusion of vasopressin induced a significant decrease in ^{133}Xe-clearance of the same magnitude in controls and in tumour-bearing rats. In the rats given intraperitoneal 5-FU, vasopressin did not reduce the ^{133}Xe-clearance the first day after administration of 5-FU. *Conclusions*: Intravenous vasopressin at 0.07 IU/min/kg decreased peritoneal blood flow as measured indirectly with the ^{133}Xe-clearance method. Intraperitoneal 5-FU abrogated the reduction in peritoneal blood flow with intravenous vasopressin the first day after treatment. In contrast, the presence of peritoneal carcinomatosis did not influence peritoneal blood flow, nor the effect of vasopressin

Keywords Vasopressin · Xenon-133 · Intraperitoneal · Carcinomatosis · 5-fluorouracil · Peritoneal blood flow

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Introduction

The intraperitoneal (i.p.) route of administration of chemotherapeutic drugs gives a pharmacological advantage in treating tumours confined to the abdominal cavity [2, 16, 13]. There is evidence of clinical responses to i.p. chemotherapeutic drug administration for ovarian, gastric and pancreatic cancer [1, 10, 18]. The ratio of total drug exposure (area under the concentration × time curve, AUC) for the peritoneal cavity relative to that for plasma is determined by the clearance of the drug from the peritoneal cavity relative to its clearance from the systemic circulation. Reduced splanchnic blood flow, as achieved with vasopressin, may further enhance the i.p. drug exposure [13].

Drugs given i.p. are administered according to body weight or body surface area without considering the impact of tumour growth or of the drug per se in the abdominal cavity, but both these factors may affect the splanchnic blood flow and thereby also the kinetics of the drug.

The radionucleotide xenon-133 (^{133}Xe) is an inert gas tracer used for organ blood flow measurements through inhalation, injection directly into the tissue, or via the arterial supply [8, 17]. The ^{133}Xe-clearance technique gives a reasonable estimation of changes in peritoneal blood flow [19]. The aim of the present study was to explore whether i.p. 5-fluorouracil (5-FU) or peritoneal carcinomatosis affects the peritoneal blood flow and its reactivity to intravenous (i.v.) vasopressin, as measured indirectly with the ^{133}Xe-clearance technique.

Materials and methods

Animals

The animals used in this study were 63 Wistar-Fu (W-Fu) rats (ALAB Möllegård, Denmark) and 67 Lister-Hooded (LH) rats (Scanbur, Stockholm, Sweden). The animals were maintained on a standard pellet and water diet under a day and night 12-h rhythm. The mean weights (and SD) of the W-Fu and LH rats were 266 ± 38 g and 243 ± 56 g, respectively. All handling and measurements of the animals were performed while the animals were under anaesthesia with an i.p. injection of 3 ml/kg body weight of midazolam (5 mg/ml), fentanyl citrate (0.3 mg/ml) and fluanisone (10 mg/ml) diluted in sterile water (Jansen Animal Health, Belgium). At the conclusion of the experiment the rats were killed with an i.v. injection of pentobarbital sodium.

Xenon clearance measurement

A catheter was placed in the carotid artery and connected to a continuous blood pressure monitor (Patient Data Monitor 565A, Kone Instrument, Spånga, Sweden), and a venous cannula was inserted in the tail vein. To maintain adequate circulatory volume and a mean arterial blood pressure (MAP) above 80 mmHg during the experiment, a subcutaneous injection of 10 ml/kg of isotonic saline was given every 30 min. The rats were placed on a heat pad to maintain a body temperature above 36.0°C. Body temperature was recorded throughout the experiment by a rectal recorder probe.

^{133}Xe (10–50 µl, 10–15 MBq) was promptly injected percutaneously into the abdominal cavity. The injected volume was adjusted to the actual activity to give 200–500 counts per second. ^{133}Xe activity was recorded with a well collimated NaI (Tl)-scintillation detector (diameter 5 cm) centred externally 1 cm above the abdominal wall, thus covering the major part of the abdominal cavity. The collector was connected to a multichannel analyser. Pulse height discrimination was used and the energy window was set at 30 keV symmetrically around the 81 keV gamma peak from ^{133}Xe, and incoming pulses were recorded in 10-s intervals. The initial pulse rate was 200–500 counts per second and the background radiation was 3–7 counts per second, and hence negligible. In repeated studies of blood flow, small residues of xenon, with an activity less than 10 counts per second, could remain in the tissue due to previous injections. The endpoint of the analysis was chosen at 600 s after injection of ^{133}Xe since the k-values in this part of the curve were close to zero.

After recording the basal ^{133}Xe clearance, 0.07 IU/min/kg body weight of vasopressin (Ferring, Malmö, Sweden) was infused into the tail vein with an infusion pump (Terumo Syringe Pump, model STC-521, Terumo, Tokyo, Japan) for 10 min, and an identical recording was performed.

Control experiment

When the experiments were performed, ^{133}Xe-clearance without using i.v. vasopressin was analysed in one or two rats each day, in total 8 W-Fu and 21 LH rats. These animals were given a similar volume of isotonic saline i.v. instead of vasopressin.

Sham experiment

Randomly, in 8 W-Fu and 14 LH rats, not subjected to i.p. tumour cell inoculation or 5-FU, ^{133}Xe-clearance was analysed before and during i.v. vasopressin administration.

Intraperitoneal 5-FU experiment

5-FU (25 mg/kg; Flurablastin, Pharmacia, Stockholm, Sweden) in 25 ml/kg isotonic saline was given i.p. to 24 W-Fu and 16 LH rats without tumours on day 0. On days 1, 2 and 3, peritoneal blood flow was analysed with the ^{133}Xe-clearance technique, before and during i.v. vasopressin administration.

Intraperitoneal tumour experiment

On day 0, 23 W-Fu and 16 LH rats were inoculated i.p. at a fixed umbilical site with a suspension of 1 ml (1×10^5 cells) nitrosoguanidine-induced syngeneic adenocarcinoma of the colon (NGW) [22] or a 3-methyl-diaminobenzidine-induced syngeneic hepatoma (Hep), respectively [11]. The cells were prepared by homogenizing harvested tumours. On days 12–16, peritoneal blood flow was analysed with the ^{133}Xe-clearance technique, before and during i.v. vasopressin administration. After conclusion of the ^{133}Xe-clearance measurements, the abdomen was opened and the tumour volume was determined according to a three point scale as described by Ottow et al. [20] with modification. Thus, a small tumour volume was fewer than four pin-point tumour foci with a diameter of less than 1 mm, a medium tumour volume was when peritoneum was visible between

Table 1 Absolute values of ^{133}Xe-clearance (k_3) before and during i.v. vasopressin administration in control and sham-treated rats. The results are presented as means ± SE. Control animals received saline during infusion (*n.s.* not significant)

Rat	Treatment	No. of rats	k_3 before	k_3 during	*P* value[a]
W-Fu control	Saline	8	0.36 ± 0.03	0.38 ± 0.04	n.s.
W-Fu sham	Vasopressin	8	0.34 ± 0.04	0.19 ± 0.04	0.033
LH control	Saline	21	0.35 ± 0.03	0.30 ± 0.04	n.s.
LH sham	Vasopressin	14	0.35 ± 0.06	0.14 ± 0.03	0.0046

[a]ANOVA during vs before i.v. vasopressin administration

tumours, and a large tumour volume was when the tumour had replaced most of the peritoneal cavity.

Mathematics

The mathematical model for analysis of the ^{133}Xe-clearance curves was regarded as a single compartment with: $A(t) = Ce^{-k3t}$, where (t) is the activity in the organ at time t, C is a coefficient which can be calculated from the initial conditions in the compartment, and k_3 is the elimination rate [19].

Calculations and statistics

The results are given as means and standard errors of the mean (SEM). The different groups were compared using Student's *t*-test for paired samples and ANOVA. The relative values of ^{133}Xe-clearance (k_3) during vs before i.v. vasopressin administration were compared to the value of 1 using Student's *t*-test for paired samples. *P* values less than 0.05 were considered significant.

Ethical considerations

This study was approved by the Animal Ethics Committee of the Medical faculty of Umeå University.

Results

Before administration of vasopressin, MAP was of the same magnitude (88 ± 1 mmHg) in all groups, except in the tumour-bearing LH rats in which it was significantly lower (79 ± 5 mmHg, $n = 16$, $P = 0.0016$). The difference was most prominent comparing all groups with the LH group with the largest tumour burden (MAP 66 ± 5 mmHg, $n = 6$, $P = 0.0006$). There was a highly significant increase in MAP up to 151 ± 2 mmHg ($P < 0.001$) during vasopressin administration infusion in all rats.

The basal ^{133}Xe-clearance before administration of vasopressin was of the same magnitude in all groups (0.35 ± 0.04), except in the LH rats given 5-FU i.p., in which the clearance was significantly lower (0.22 ± 0.02), both compared to W-Fu rats treated with 5-FU and LH sham-treated rats ($P = 0.0081$ and $P = 0.0015$, respectively, Student's unpaired *t*-test; Tables 1 and 2).

Table 2 Absolute values of ^{133}Xe-clearance (k_3) before and during i.v. vasopressin administration in 5-FU-treated rats. The results are presented as means ± SE (*n.s.* not significant)

Rat	Day	No. of rats	k_3 before	k_3 during	*P* value[a]
W-Fu	1–3	24	0.34 ± 0.04	0.23 ± 0.03	0.027
	1	7	0.30 ± 0.05	0.28 ± 0.03	n.s.
	2	9	0.38 ± 0.08	0.24 ± 0.06	n.s.
	3	8	0.31 ± 0.05	0.17 ± 0.03	0.029
LH	1–3	16	0.22 ± 0.02	0.16 ± 0.03	n.s.
	1	5	0.23 ± 0.05	0.15 ± 0.03	n.s.
	2	7	0.19 ± 0.03	0.12 ± 0.01	0.052
	3	4	0.25 ± 0.04	0.24 ± 0.09	n.s.

[a]ANOVA during vs before i.v. vasopressin administration

There was a statistically significant reduction in ^{133}Xe-clearance in absolute values during vasopressin administration in the W-Fu rats given i.p. 5-FU ($P = 0.027$). The relative values revealed a numerical decrease to 0.81 ± 0.11 ($P = 0.10$). A subgroup analysis identified a significant reduction in the ^{133}Xe-clearance in W-Fu rats on day 3 after the i.p. administration of 5-FU (Table 2). In all LH rats given i.p. 5-FU there was no reduction in the ^{133}Xe-clearance in either absolute or relative values. A borderline decrease was found on day 2 after the i.p. administration of 5-FU. In relative values this decrease was significant ($P = 0.026$; Table 3).

In the tumour-bearing rats, the basal ^{133}Xe-clearance in W-Fu and LH rats (0.38 ± 0.02 and 0.31 ± 0.06, respectively) was of the same magnitude as in the sham-treated group (0.34 ± 0.04 and 0.35 ± 0.06, respectively; Tables 1 and 4). The relative values of ^{133}Xe-clearance was significantly lower during i.v. vasopressin administration than before in all rats with tumour (Table 5).

Discussion

Optimal chemotherapy delivery to the tumour depends on regional drug concentration, tumour perfusion, tissue uptake of drug, metabolism and timing. In treatment of cancer restricted to the abdominal cavity, the i.p. route is interesting since the local concentration of cytostatics can be held much higher than with the i.v. route. In humans, the peritoneal plasma AUC ratio for 5-FU ranges from 117 to 1066 [6, 23, 21, 12]. 5-FU is to a large

Table 3 Relative values of ^{133}Xe-clearance (k_3) during vs before i.v. vasopressin administration in 5-FU-treated rats. The results are presented as means ± SE (*n.s.* not significant)

Rat	Day	No. of rats	During/before	*P* value[a]
W-Fu	1–3	24	0.81 ± 0.11	n.s.
	1	7	1.04 ± 0.24	n.s.
	2	9	0.74 ± 0.19	n.s.
	3	8	0.68 ± 0.16	n.s.
LH	1–3	16	0.81 ± 0.10	n.s.
	1	5	0.82 ± 0.17	n.s.
	2	7	0.68 ± 0.11	0.026
	3	4	1.02 ± 0.32	n.s.

[a]Student's paired *t*-test ratio during/before vs 1

extent cleared in the liver giving low systemic concentrations and hence holding side effects down. Vasopressin (lysin-8-vasopressin) is a vasoactive drug which significantly constricts the splanchnic vessels [9]. In a rat model, vasopressin at 0.07 IU/min/kg body weight i.v. has been shown to reduce the peritoneal blood flow [19], and consequently the peritoneal microcirculation should be decreased. To increase the uptake of 5-FU in colorectal hepatic metastases in rat, vasopressin given via the hepatic artery has been tested [4]. Drugs are transported from the peritoneal cavity by intraabdominal lymphatics and by capillaries leading to the portal venous system. Due to the much higher blood flow rate of the portal route this route of clearance dominates [21, 3]. Decreased splanchnic blood flow may reduce this clearance, thereby raising the dose intensity of the drug in the abdominal cavity and intraabdominal lymphatic tissue without increasing systemic toxicity, provided that total body clearance is unchanged.

In the present study, a decreased peritoneal blood flow as measured indirectly with the ^{133}Xe-clearance method, was achieved using i.v. vasopressin. It was significantly reduced in the W-Fu and LH sham-treated groups to 63% and 50%, respectively (Table 6). ^{133}Xe-clearance was measured 1, 2 and 3 days after 5-FU i.p. administration. In W-Fu rats there was no effect on the basal ^{133}Xe-clearance values, but in LH rats these values were reduced to approximately two-thirds from 0.35 to 0.22 (Tables 1 and 2). When vasopressin was then given, the LH rats started from a lower ^{133}Xe-clearance level. In both rat strains i.v. vasopressin failed to produce a reduction in ^{133}Xe-clearance 1 day after i.p. administration of 5-FU.

Table 5 Relative values of ^{133}Xe-clearance (k_3) during vs before IV vasopressin for rats with IP carcinomatosis. The results are presented as means ± SE (*n.s.* not significant)

Rat	Tumour volume	No. of rats	During/before	*P* value[a]
W-Fu	All tumours	23	0.56 ± 0.06	< 0.0001
	Small	9	0.66 ± 0.13	0.029
	Medium	11	0.56 ± 0.04	< 0.0001
	Large	3	0.27 ± 0.02	0.00042
LH	All tumours	16	0.34 ± 0.06	< 0.0001
	Small	5	0.23 ± 0.06	0.0002
	Medium	5	0.36 ± 0.08	0.0011
	Large	6	0.43 ± 0.12	0.0053

[a]Student's paired *t*-test ratio during/before vs 1

Table 6 Relative values of ^{133}Xe-clearance (k_3) during vs before i.v. vasopressin administration in control and sham-treated rats. The results are presented as means ± SE (*n.s.* not significant). Control animals received saline during infusion

Rat	Treatment	No. of rats	During/before	*P* value[a]
W-Fu control	Saline	8	1.08 ± 0.30	n.s.
W-Fu sham	Vasopressin	8	0.63 ± 0.13	0.026
LH control	Saline	21	0.92 ± 0.11	n.s.
LH sham	Vasopressin	14	0.50 ± 0.09	< 0.0001

[a]Student's paired *t*-test ratio during/before vs 1

There was no difference in MAP before or during vasopressin infusion in the 5-FU-treated W-Fu and LH rats (89 ± 2 and 91 ± 3 mmHg, respectively) compared to the sham-treated W-Fu and LH rats (92 ± 3 and 95 ± 4 mmHg, respectively), indicating that there was no general circulatory vasoconstrictive effect of 5-FU in either rat strain, which is agreement with earlier findings [15]. A local effect of the drug within the abdominal cavity was possible. In fact, inflammatory morphological changes have been shown in the peritoneum after i.p. instillation of 10–20 mg/kg 5-FU in a rat model [5]. Our interpretation of the results is that i.p. 5-FU might initially to some extent affect the peritoneal blood flow, thus influencing the kinetics of the drug. A speculative explanation for the difference in reduction of basal ^{133}Xe-clearance between W-Fu and LH rats could be a different sensitivity of vessels in the peritoneal cavity to 5-FU. As

Table 4 Absolute values of ^{133}Xe-clearance (k_3) before and during i.v. vasopressin administration for rats with carcinomatosis. The results are presented as means ± SE (*n.s.* not significant)

Rat	Tumour volume	No. of rats	k_3 before	k_3 during	*P* value[a]
W-Fu	All tumours	23	0.38 ± 0.02	0.20 ± 0.02	< 0.0001
	Small	9	0.35 ± 0.04	0.22 ± 0.04	0.023
	Medium	11	0.37 ± 0.03	0.21 ± 0.02	< 0.0001
	Large	3	0.46 ± 0.09	0.12 ± 0.03	0.033
LH	All tumours	16	0.31 ± 0.06	0.10 ± 0.02	0.00032
	Small	5	0.29 ± 0.06	0.07 ± 0.02	0.015
	Medium	5	0.24 ± 0.03	0.09 ± 0.03	0.0061
	Large	6	0.39 ± 0.07	0.13 ± 0.03	0.030

[a]ANOVA during vs before IV vasopressin

the i.p. 5-FU-treated LH rats had a lower basal ^{133}Xe-clearance, a further reduction with i.v. vasopressin could be difficult to achieve. The ^{133}Xe-clearance during vasopressin infusion in W-Fu rats on the third day after the i.p. 5-FU infusion returned to absolute values similar to those in the W-Fu sham-treated group. In relative values there was a numerical trend over the days following i.p. 5-FU infusion towards a reduction in the ^{133}Xe-clearance during vasopressin infusion (1.04–0.74–0.68). This indicates that 5-FU would have more acute inflammatory and/or vasoconstrictive effects rather than causing persistent damage to the vessels.

This reduced sensitivity to the effect of vasopressin on ^{133}Xe-clearance after i.p. 5-FU suggests that a pharmacological improvement in 5-FU kinetics with vasoconstrictors is not supported. The implication of this has to be evaluated in pharmacokinetic studies.

Peritoneal carcinomatosis is considered the terminal stage of tumour progression. Thus it may affect the physiological properties of the peritoneum and its arterial and lymphatic vessels, thereby influencing the drug exchange. In a rat model with carcinomatosis, invasion of the lymphatic lacunae in the diaphragm caused complete obstruction within 3–7 days [14].

In our experiment, MAP was significantly lower in LH rats with carcinomatosis. The difference was most prominent in the group with the largest tumour burden. However, vasopressin raised MAP in LH rats with large tumours to levels similar to those in the other groups (148 ± 9 and 151 ± 2 mmHg, respectively), with no difference between the groups. This generally vascular responsiveness to vasopressin did not seem to be lowered by carcinomatosis. In the animals with varying tumour volume in the abdominal cavity, the ^{133}Xe-clearance was of the same magnitude as in the controls, and there was a similar reactivity to vasopressin as in the sham-treated groups in terms of both absolute and relative values. This indicates that carcinomatosis does not affect peritoneal blood flow as measured with the ^{133}Xe-clearance method, nor does it restrict the ability of vasopressin to constrict the intraabdominal vessels and consequently reduce peritoneal blood flow. Blood vessels which feed metastatic tumours lack both smooth muscle and adrenergic receptors, and are therefore unable to respond to vasoactive stimuli [7]. The vasoconstrictive effect of vasopressin on normal vessels could redirect the blood flow towards areas with carcinomatosis, enhancing the drug exposure in tumour tissue.

Conclusion

Vasopressin at 0.07 IU/min/kg body weight i.v. decreased peritoneal blood flow in the rat as measured with the ^{133}Xe-clearance method. 5-FU administered i.p. decreased the basal peritoneal blood flow in LH rats and abrogated the reduction in peritoneal blood flow with vasopressin for 1–2 days in W-Fu and LH rats. The pharmacokinetic advantage of giving 5-FU i.p. was not negatively influenced by the drug itself, since the basal peritoneal blood flow did not increase. The presence of peritoneal carcinomatosis neither influenced the basal peritoneal blood flow, nor the reduction in peritoneal blood flow by i.v. vasopressin. Vasopressin might have a positive effect in directing anticancer drugs towards areas with tumour growth.

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