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Experimental report

Effects of intra-abdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration

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Increased hydrostatic pressure in solid tumor nodules decreases the penetration of chemotherapy into cancerous tissue. This is true for both i.v. and i.p. chemotherapy. The purpose of this study was to determine the influence of increasing intra-abdominal pressures on the pharmacokinetics and tissue distribution of doxorubicin administered i.p. Four groups of 10 Sprague Dawley rats were given i.p. doxorubicin (4 mg/kg) during 60 min combined with no pressure (control), 10, 20 and 30 mm Hg pressures. During the course of i.p. chemotherapy, peritoneal fluid and blood were sampled. Two other groups of 10 rats received the same dose of i.p. doxorubicin during 10 min combined with no pressure and 30 mm Hg pressure. At the end of experiments animals were sacrificed and tissue samples were collected. Doxorubicin concentrations in peritoneal fluid, plasma and tissues were determined by HPLC. Pharmacokinetic studies showed that increased intra-abdominal pressures of 10, 20 and 30 mm Hg did not alter peritoneal fluid AUCs, the plasma AUCs and the peak ratios of i.p. doxorubicin when compared to the control group (no pressure). A subset analysis of high intra-abdominal pressure groups (20 and 30 mm Hg) versus control group showed statistically significant differences in peritoneal fluid AUCs, plasma AUCs and AUC (peritoneal fluid/plasma) ratios. For all groups, the highest tissue concentrations of doxorubicin were found in tissues associated with the parietal peritoneum: the bladder, the abdominal wall and the diaphragm. After 10 min of i.p. chemotherapy, the group treated with 30 mm Hg pressure showed a significant increase of doxorubicin concentrations in these tissues as compared to the control group. This significant increase of tissue doxorubicin concentrations was not found after 60 min of pressure with i.p. chemotherapy; prolonged intra-abdominal pressure was associated with a high incidence of intestinal ischemia. In conclusion, intra-abdominal pressure of 20 and 30 mm Hg significantly decreased the AUC ratios of i.p. doxorubicin but concomitantly increased tissue uptake of doxorubicin in bladder, diaphragm and abdominal wall during the first 10 min of i.p. administration. These findings may have significance in the design of improved strategies to increase tissue concentrations of chemotherapy delivered by an i.p. route.

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Key words: Doxorubicin, intraperitoneal chemotherapy, intra-abdominal pressure, pharmacokinetics.

Introduction

The peritoneal cavity is a common site of tumor dissemination for various gastrointestinal malignancies and ovarian malignancies. Intraperitoneal chemotherapy combined with cytoreductive surgery has been described as a therapeutic option in the management of these malignancies when the spread of cancer is confined to the peritoneal cavity.[1–3] The advantage of i.p. chemotherapy is that a high concentration can be achieved locally. For selected chemotherapy agents, the concentration differential between the peritoneal cavity and the systemic circulation arises because the rate of movement of the drug from the peritoneal cavity into plasma (peritoneal clearance) is generally slow relative to the total body clearance.[4] This pharmacological process rests in the specific characteristics of the peritoneal plasma barrier which maintains a continuous high ratio of chemotherapeutic drug concentration between the peritoneal cavity and plasma.[5–7]

The major factors determining the theoretical and practical limitations of i.p. therapy are the pharmacologic properties of the peritoneal plasma barrier and the ability of cytostatic drugs to penetrate intra-abdominal tissues. The tissue penetration of i.p. chemotherapeutic agents depends on drug characteristics (concentration, time of exposure, molecular weight, lipophilicity) and tissue characteristics (tissue geometry, surface exposed to drug, hydrostatic pressure, blood perfusion, lymphatic drainage, permeability of tissue cell membrane). Numerous studies have been performed to analyze the pharmacokinetics of i.p. chemotherapy.[7–9] The distribution of cytostatic drugs

into tumor tissue delivered by the i.p. route has also been widely examined.[10–13] However, little information is available on drug distribution in the different intra-abdominal tissues after i.p. chemotherapy given with intra-abdominal pressure.

The present study was initiated to investigate whether the pharmacokinetics and tissue distribution of adriamycin would be modified by increasing the intra-abdominal pressures. We used a rat model of i.p. chemotherapy delivered with four different intra-abdominal pressures. The long-term objective of these studies was to develop a model to overcome the increased hydrostatic pressure in solid tumor nodules that hinders the penetration of chemotherapy into cancerous tissue.

Material and methods

Animals

Sixty Sprague-Dawley male rats (3–5 months old) weighing between 310 and 380 g were obtained from a single breeding colony (Harlan Sprague-Dawley, Indianapolis, IN). Animals were individually housed, and they were allowed free access to food and water.

Surgical procedures

Rats were anesthetized with an intramuscular injection of sodium phenobarbital (60 mg/kg). One catheter (polyethylene tubing 0.58 mm diameter; Becton Dickinson, Cockeysville, MD) was inserted into the left femoral vein for blood sampling. Another catheter (silicone tubing 5mm diameter; Spectrum, Houston, TX) was placed through the abdominal wall into the peritoneal cavity for drug injection and peritoneal fluid sampling. Intra-abdominal pressure was achieved by placing a pressure cuff 5 cm wide (Baxter, McGraw Park, IL) around the abdominal cavity of rats. The intra-abdominal pressure was controlled by a slit catheter (Howmedica, Rutherford, NJ) set into the abdominal cavity through the abdominal incision. The slit catheter was connected to an interstitial pressure monitor (Howmedica). See Figure 1.

Experimental design

At the start of each experiment, doxorubicin (Ben Venue, Bedford, OH) was slowly infused through the peritoneal catheter. All rats received doxorubicin at a dose of 4 mg/kg diluted in 50 cm^3 of 5% dextrose solution (Abbot, North Chicago, IL). To determine the possible effect of intra-abdominal pressure on adriamycin pharmacokinetics and tissue concentration, the animals were randomized into different groups. Four groups of 10 rats were given i.p. adriamycin during 60 min combined with four different intra-abdominal pressures: no pressure (control), 10, 20 and 30 mm Hg. For each rat, 1 ml of peritoneal fluid and 0.6 ml of blood were collected at specific intervals (0, 5, 10, 20, 30, 40, 50 and 60 min) during 1 h after the initiation of i.p. chemotherapy. The venous catheter was flushed with heparinized saline after blood sampling and all rats were given a saline infusion (10 ml/kg) for fluid replacement during the experiment. At the end of the procedure (60 min), the abdomen was reopened and the appearance of the small intestine was monitored for each group. Intestinal vascular congestion was assessed by the discoloration of intestinal loops. Rats were then sacrificed and tissues (liver, spleen, omentum, small bowel, abdominal wall, diaphragm and

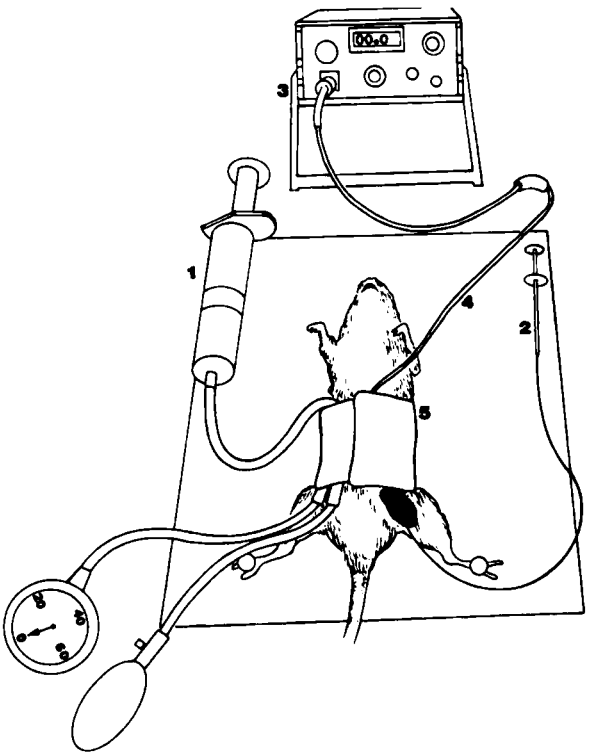

Figure 1. Intra-abdominal pressure in rat model. (1) Peritoneal fluid samples through the silicone catheter. (2) Blood samples through the intrafemoral catheter. (3) Intra-abdominal pressure monitor. (4) Pressure monitoring catheter. (5) Pressure cuff.

bladder) were sampled. The doxorubicin concentration in peritoneal fluid, plasma and tissue samples was analyzed by HPLC.

Two groups of 10 rats were added to the experiment in order to evaluate the influence of intra-abdominal pressure on tissue concentration of adriamycin during the early phase of i.p. chemotherapy. These rats received i.p. doxorubicin during only 10 min. The first group received i.p. chemotherapy alone. The second group received i.p. chemotherapy with 30 mm Hg intra-abdominal pressure. All rats were sacrificed 10 min after the initiation of i.p. chemotherapy for tissue sampling.

Adriamycin assays by HPLC

Adriamycin levels were determined using a modification of the method of Israel *et al.*[14] The HPLC system consisted of a Shimadzu LC7A instrument equipped with a SPD-6AV detector (set at 495 nm UV) along with a C-R6A Chromopac data processor. A reversed phase column (250 × 4.6 nm) of Dynamax 300A 5 μm silica was used, coupled to a guard column of the same chemical consistency. The mobile phase consisted of a mixture of acetonitrile (35% v/v) in 0.1% ammonium formate buffer (pH 4) ran isocratically at 0.9 ml/min. Sample injections were 50 μl. All solvents used were HPLC grade (Fisher Scientific, Norcross, GA).

Tissue extraction. A piece of tissue (300–500 mg) was dried of surface moisture, and then accurately weighed and homogenized in approximately 10 times its volume of methanol:chloroform (3:2). The homogenate was then transferred to a 15 ml polypropylene centrifuge tube and centrifuged at 3000 r.p.m. for 10 min. The organic solution was transferred to another polypropylene tube and vacuum extracted at 45°C under a stream of nitrogen. The residue was resuspended in 1 ml of the mobile phase and filtered through a 0.45 μm nylon filter for HPLC injection.

Plasma extraction. Blood samples were centrifuged and the plasma was separated from the cells. Then, 300 μl of plasma was treated with 5 ml methanol:chloroform (3:2) and mixed thoroughly. After centrifugation, the organic phase was transferred to another polypropylene tube and blown down under nitrogen. The residue was resuspended in 300 μ of the mobile phase and filtered for HPLC injection.

Peritoneal fluid extraction. Peritoneal fluid samples were diluted with mobile phase and filtered before HPLC injection.

Statistical procedures

To obtain the area under the curve (AUC) of peritoneal fluid versus time and plasma versus time, a computer program LAGRAN-S[15] was used. The peritoneal fluid AUCs, the plasma AUCs and the (peritoneal fluid/plasma) AUCs ratio of all groups were compared according to two different statistical analyses. In the final analysis, pharmacokinetic data of each pressurized group was compared to that of the control group. In the second analysis, an aggregate of high pressure groups consisting of the group treated with 20 mm Hg and the group treated with 30 mm Hg were compared to the control group.

Doxorubicin concentrations in tissues were compared between the control (no pressure) group and each of the pressurized groups at 60 min and 10 min. All statistical analyses were conducted by the Wilcoxon Rank test using SAS for Windows, version 6.8 (SAS Institute, Cary, NC). For all statistical procedures, values for $p < 0.05$ were taken as significant.

Results

Adriamycin levels in peritoneal fluid and plasma

The peritoneal fluid and plasma pharmacokinetics of doxorubicin are shown in Figure 2. The mean (±SD) peak peritoneal fluid levels were 28.8 (±2.9) μg/ml for the control group, 30.1 (±2.3) μg/ml for the group treated with 10 mm Hg, 29.3 (±2.1) μg/ml for the group treated with 20 mm Hg and 28.3 (±1.4) μm/ml for the group treated with 30 mm Hg. The peritoneal fluid concentrations decreased rapidly during the first 5min for all groups. The doxorubicin concentration in peritoneal fluid of the control group and the group treated with 10 mm Hg remains higher than that of the group treated with 20 mm Hg and the group treated with 30 mm Hg (Table 1).

In the plasma, the mean peak levels were 0.24 (±0.06) μg/ml for the control group, 0.23 (±0.07) μg/ml for the group treated with 10 mm Hg, 0.27 (±0.06) μg/ml for the group treated with 20 mm Hg and 0.28 (±0.07) μg/ml

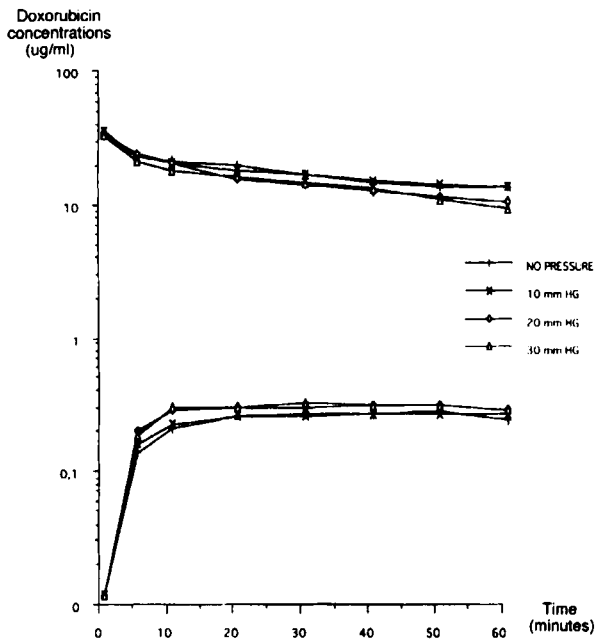

Figure 2. Influence of intra-abdominal pressure on peritoneal fluid and plasma concentrations of doxorubicin.

for the group treated with 30 mm Hg. These peak plasma levels were achieved at 50 min for the control group, at 40 min for the group treated with 10 mm Hg and the group treated with 20 mm Hg, and at 30 min for the group treated with 30 mm Hg (Table 2). The peak peritoneal fluid/peak plasma ratio for i.p. doxorubicin was 121 (±17) for the control group, 129 (±23) for the group treated with 10 mm Hg, 108 (±19) for the group treated with 20 mm Hg and 102 (±12) for the group treated with 30 mm Hg. There was no significant difference between peak ratios of control group and pressurized groups.

Area under the curve

The mean AUCs of doxorubicin concentrations in peritoneal fluid, plasma and peritoneal fluid/plasma ratio are shown in Table 3. AUC for peritoneal fluid doxorubicin concentrations was 903.7 (±224) for the control group, 909.3 (±192) for the group treated with 10 mm Hg pressure, 809.1 (±82) for the group treated with 20 mm Hg pressure and 767.6 (±147) for the group treated with 30 mm Hg pressure. When each of the pressurized groups was compared with the control group, no significant difference of AUC was found. When high pressure groups (20 and 30 mm Hg) were compared to the control group, there was a significant difference of peritoneal fluid AUC ($p = 0.01$). Doxorubicin left the peritoneal cavity slightly more quickly when high pressure was applied.

AUC for plasma doxorubicin concentrations was 11.5 (±2) for the control group, 12.4 (±3.2) for the group treated with 10 mm Hg pressure, 14.9 (±2.7) for the group treated with 20 mm Hg pressure and 15.2 (±5) for the group treated with 30 mm Hg pressure. The group treated with 20 mm Hg and the group treated with 30 mm Hg exhibited an increase of plasma AUC. When each of the pressurized groups was compared to the control group, no significant difference of AUC was found. When high pressure groups (20 and 30 mm Hg) were compared to the control group, there was a significant difference of

Table 1. Doxorubicin concentrations (μg/ml) in peritoneal fluid (mean ± SD)

Pressure	0 min	5 min	10 min	20 min	30 min	40 min	50 min	60
No pressure	28.8 ± 2.9	19.9 ± 3.3	18.4 ± 4.5	16.7 ± 4.2	14.4 ± 4.1	12.8 ± 4.1	11.8 ± 3.4	11.5 ± 2.7
10 mm Hg	30.1 ± 2.3	19.3 ± 4.0	17.8 ± 4.2	15.9 ± 3.6	14.6 ± 3.3	13.0 ± 3.1	12.0 ± 2.8	11.5 ± 2.8
20 mm Hg	29.3 ± 2.1	20.1 ± 4.0	17.3 ± 3.0	13.8 ± 1.6	12.3 ± 1.6	10.8 ± 1.7	9.9 ± 1.7	9.1 ± 2.1
30 mm Hg	28.3 ± 1.4	18.0 ± 3.2	15.8 ± 3.0	14.0 ± 3.1	12.8 ± 3.0	11.4 ± 3.4	9.5 ± 2.8	8.0 ± 3.0

Table 2. Doxorubicin concentrations (μg/ml) in plasma (mean ± SD)

Pressure	0 min	5 min	10 min	20 min	30 min	40 min	50 min	60 min
No pressure	0 ± 0	0.12 ± 0.04	0.18 ± 0.04	0.22 ± 0.05	0.23 ± 0.04	0.23 ± 0.05	0.24 ± 0.06	0.21 ± 0.04
10 mm Hg	0 ± 0	0.14 ± 0.05	0.19 ± 0.04	0.22 ± 0.05	0.22 ± 0.08	0.23 ± 0.07	0.23 ± 0.08	0.22 ± 0.09
20 mm Hg	0 ± 0	0.17 ± 0.04	0.25 ± 0.07	0.26 ± 0.07	0.27 ± 0.06	0.27 ± 0.06	0.25 ± 0.06	0.25 ± 0.06
30 mm Hg	0 ± 0	0.16 ± 0.06	0.26 ± 0.12	0.26 ± 0.09	0.28 ± 0.07	0.27 ± 0.1	0.27 ± 0.1	0.25 ± 0.11

Table 3. AUC for peritoneal fluid and plasma doxorubicin concentrations: AUC (peritoneal fluid/plasma) ratios are shown in the last column (mean ± SD)

Pressure	AUC peritoneal fluid	p value[a]	p value[b]	AUC plasma	p value[a]	p value[b]	AUC ratio	p value[a]	p value[a]
No pressure	903.7 ± 224			11.5 ± 2.0			80.1 ± 25		
10 mm Hg	909.3 ± 192	NS		12.4 ± 3.2	NS		82.1 ± 26	NS	
20 mm Hg	809.1 ± 82	NS	0.01	14.9 ± 2.7	NS	0.02	56.4 ± 13	0.03	< 0.01
30 mm Hg	767.5 ± 147	NS		15.2 ± 5.0	NS		53.3 ± 19	0.02	

[a]No pressure group versus each of the pressurized group (Wilcoxon rank test).
[b]High pressure groups (20 and 30 mm Hg) versus control group (Wilcoxon rank test). NS, not significant ($p < 0.05$).

Table 4. Doxorubicin concentrations (μg/g) in tissues at 60 min (mean ± SD)

Pressure	Liver	p^a	Spleen	p^a	Small bowel	p^a	Omentum	p^a	Abdominal wall	p^a	Diaphragm	p^a	Bladder	p^a
No pressure	1.10 ± 0.38		1.09 ± 0.73		2.53 ± 0.98		2.93 ± 0.71		6.11 ± 2.20		4.73 ± 3.46		7.03 ± 2.10	
10 mm Hg	1.72 ± 0.95	NS	1.25 ± 0.79	NS	1.53 ± 0.84	0.013	3.44 ± 1.56	NS	5.80 ± 1.84	NS	4.87 ± 1.64	NS	7.27 ± 3.40	NS
20 mm Hg	1.05 ± 0.58	NS	1.22 ± 0.54	NS	2.34 ± 1.09	NS	4.73 ± 3.46	NS	6.22 ± 2.30	NS	4.68 ± 1.24	NS	7.35 ± 2.05	NS
30 mm Hg	0.93 ± 0.56	NS	0.95 ± 0.34	NS	1.55 ± 0.52	< 0.01	3.63 ± 2.51	NS	6.25 ± 1.38	NS	5.23 ± 1.19	NS	7.40 ± 2.67	NS

[a]No pressure group versus pressurized group (Wilcoxon rank test). NS, not significant ($p < 0.05$).

Table 5. Doxorubicin concentrations (μg/g) in tissues at 10 min (mean ± SD)

Pressure	Liver	p^a	Spleen	p^a	Small bowel	p^a	Omentum	p^a	Abdominal wall	p^a	Diaphragm	p^a	Bladder	p^a
No pressure	0.91 ± 0.42		0.52 ± 0.28		0.94 ± 0.34		1.26 ± 0.55		1.85 ± 0.76		1.80 ± 0.53		4.34 ± 2.28	
30 mm Hg	1.00 ± 0.48	NS	0.52 ± 0.18	NS	1.03 ± 0.40	NS	1.26 ± 0.75	NS	4.27 ± 1.34	< 0.01	3.92 ± 1.84	< 0.01	7.82 ± 1.91	< 0.01

[a]No pressure group versus pressurized group (Wilcoxon rank test). NS, not significant ($p < 0.05$).

plasma AUC ($p = 0.02$). High pressure caused an increase in plasma doxorubicin levels.

The mean AUC ratio was 80.1 (± 25) for the control group, 82.1 (± 26) for the group treated with 10 mm Hg, 56.4 (± 13) for the group treated with 20 mm Hg and 53.3 (± 19) for the group treated with 30 mm Hg. When each of the pressurized groups was compared to the control group, there was a significant decrease of AUC ratio for the group treated with 20 mm Hg ($p = 0.03$) and the group treated with 30 mm Hg ($p = 0.02$). When high pressure groups (20 and 30 mm Hg) were compared to the control group, there was a significant difference of AUC ratio ($p < 0.01$).

Tissue concentrations

At 60 min. Doxorubicin concentrations in the different tissue samples after 60 min of i.p. chemotherapy are shown in Table 4. For each group, the highest doxorubicin tissue concentrations were found in bladder, abdominal wall and diaphragm. There was no significant difference of doxorubicin concentration between control group and pressurized groups for liver, spleen, omentum, abdominal wall, diaphragm and bladder. There was a significant ($p = 0.013$) decrease of doxorubicin concentration in small bowel for the group treated with 10 mm Hg and the group treated with 30 mm Hg when compared to the control group. The number of rats which presented with intestinal ischemia were, respectively, zero for the control group, six for the group treated with 10 mm Hg, five for the group treated with 20 mm and eight for the group treated with 30 mm Hg.

At 10 min. Doxorubicin concentrations in the different tissue samples after 10 min of i.p. chemotherapy are shown in Table 5. For both groups, bladder, diaphragm and abdominal wall were found to have the highest adriamycin concen-

tration. Rats treated with 30 mm Hg demonstrated a significant increase of doxorubicin concentration in abdominal wall ($p < 0.001$), diaphragm ($p < 0.001$) and bladder ($p = 0.003$). No rats presented with intestinal ischemia.

Discussion

The primary goal of i.p. chemotherapy is to augment the efficacy of chemotherapeutic agents by achieving high levels of drug in the target tissue, while reducing or sustaining the level of systemic toxicity. Once a drug administered i.p. penetrates tissues, its movement occurs by diffusion and convection through the interstitial space.[16] Diffusion is proportional to the concentration gradient in the interstitium and convection is proportional to the interstitial fluid velocity. The latter, in turn, is proportional to the pressure gradient in the interstitium. Different studies have demonstrated that interstitial pressures in tumor tissues are increased and represent a major obstacle to the delivery of macromolecules used for cancer detection and treatment.[17,18] Several physical (radiation, hyperthermia) and chemical (vasoactive drugs) agents have been tested to increase the drug penetration into tissues.[19,20] The goal of this study was to investigate the potential effects of intra-abdominal pressure on pharmacokinetics and tissue concentrations of doxorubicin after i.p. delivery.

In our experiments, rats treated with intra-abdominal pressure exhibited a plasma peak concentration of doxorubicin earlier than rats with no pressure. Intra-abdominal pressure probably accelerated the doxorubicin clearance from the peritoneal cavity. When groups treated with high pressure (20 and 30 mm Hg) were compared to the control group, a significant difference of peritoneal fluid and plasma AUCs was found. However, when each pressurized group was compared to the control group, we did not detect significant differences of drug clearance from the peritoneal cavity into the blood circulation as a result of intra-abdominal pressure. Indeed, there was no significant difference of peritoneal fluid and plasma AUCs between the control group and each pressurized group.

With both statistical analyses, the group treated with 20 mm Hg and the group treated with 30 mm Hg exhibited a significant decreased AUC ratio. Although intra-abdominal pressure of 20 mm Hg or above decreased the peritoneal/plasma concentration ratio, AUC ratio remained superior to 50 for

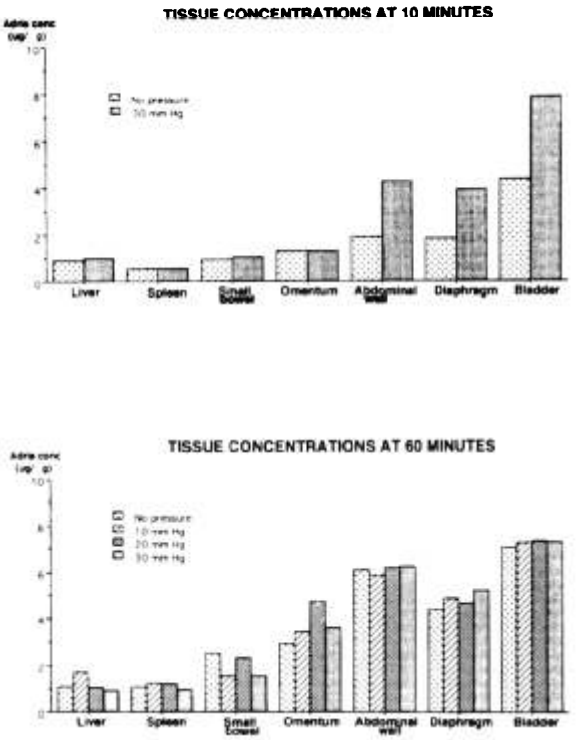

Figure 3. Influence of intra-abdominal pressure on tissue concentrations of doxorubicin after 10 and 60 min of chemotherapy.

all pressurized groups and the pharmacologic advantage of i.p. doxorubicin, as defined by Ozols *et al.*,[21] as the peak peritoneal fluid/peak plasma ratio, remained superior to 100 for all groups. For these reasons, we may conclude that intra-abdominal pressure did not disturb the pharmacokinetic benefits of i.p. delivery of doxorubicin. Such findings correlate previous studies where the influence of lower abdominal pressure (5–6 mm Hg) on the peritoneal clearance of a tracer, such as sucrose or inulin, were tested.[4]

The analysis of doxorubicin tissue distribution showed that the highest concentrations of doxorubicin after i.p. administration were achieved in structures adjacent to parietal peritoneum: the abdominal wall, the diaphragm and the bladder. The variations of doxorubicin tissue distribution found in each group were probably related to the difference of tissue microanatomy and metabolism.[22] The relatively high vascularization and low lymphatic drainage of muscular tissues such as bladder, diaphragm and abdominal wall may induce a high uptake and a decreased elimination of doxorubicin.[23]

At 10 min, intra-abdominal pressure of 30 mm Hg significantly increased the doxorubicin concentration in abdominal wall, bladder and diaphragm. Intra-abdominal pressure may change the physiologic distribution of drug in tissues and the microanatomy of the peritoneal plasma barrier.[5,24] The high intra-abdominal pressure may force the drug deeper into the interstitium. Also, drainage of parietal and visceral tissues may be diminished by compressing the capillaries and lymphatics. The loss of lymphatic and venous drainage may result in higher doxorubicin concentration in tissues since the drug elimination is decreased.

At 60 min, intra-abdominal pressure did not significantly affect doxorubicin concentration in abdominal wall, bladder and diaphragm. The considerable discrepancy between doxorubicin tissue concentrations in rats of the same group may explain the significant decrease of small bowel doxorubicin concentration between the group treated with 10 mm Hg, the group treated with 30 mm Hg and the control group. Another factor that explains this difference of doxorubicin concentrations in small bowel is the high incidence of intestinal ischemia reported in rats treated with pressurized i.p. chemotherapy. Intra-abdominal pressure above 10–12 mm Hg has been shown to collapse the portal vein with resulting stasis of blood flow in the mesenteric bed.[25] This transient intestinal ischemia may alter tissue uptake and drug metabolism.

In conclusion, intra-abdominal pressure of 30 mm Hg increased tissue uptake of doxorubicin in bladder, diaphragm and abdominal wall during the first 10 min of i.p. administration. This was associated with increased plasma doxorubicin suggesting a more rapid movement of drug through the tissues surrounding the peritoneal cavity. However, intra-abdominal pressure did not alter the pharmacologic advantages of i.p. chemotherapy. A high peritoneal/plasma concentration ratio was maintained when i.p. doxorubicin was administered with high intra-abdominal pressure.

Intraperitoneal chemotherapy administered with pressure may be one of many ways that may increase the penetration of chemotherapy into tumor tissues. From a theoretical perspective, increased pressure may be able to force chemotherapy into tumor nodules despite the increased hydrostatic pressure known to exist. However, clinical use of intra-abdominal pressures applied in this experiment requires cautious clinical studies because of the risk of intestinal hypoperfusion.[26] Other experiments using heat, tumor necrosis factor or more penetrating substances may be more appropriate to increase the drug concentration in intra-abdominal tissues.

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