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Uptake of Adriamycin by Sarcoma Transplants in the Rat Kidney: Effects of Renal Arterial vs Systemic Constant Rate Infusion and of Combination with Ricin*

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Abstract—*The uptake of adriamycin (Adm) by normal tissues and by sarcomas transplanted to both kidneys in rats was studied at* 10 min *following constant rate infusion of Adm* 5 mg/kg *body wt into one renal artery, during* 3 *and* 10 min. *Since the selectively infused kidney extracted only about* 20% *of the total dose, the present model provides a direct comparison of systemic versus selective i.a. infusions in each individual. Tumor Adm uptake was about* 6 *times higher on the selectively infused side. Adm uptake by tumor and normal renal tissue was proportional to the concentration* × *time product of Adm in arterial blood, in spite of highly different blood peak concentrations at different infusion rates. Ten-minute systemic intravenous infusion of the Adm dose, with concurrent infusion of ricin,* 3 μg/kg, *into one renal artery tended to increase Adm uptake by the tumors on both sides. This indicates a systemic rather than a local effect of ricin: ricin reduced Adm uptake by red blood cells and normal solid tissues and thus resulted in a delayed Adm clearance from the total plasma volume. In contrast, the relationship between tumor uptake and the concentration* × *time product of Adm in plasma was not affected by ricin, explaining the increased tumor uptake.*

INTRODUCTION

THE RATIONALE of local intra-arterial (i.a.) infusion of cytostatics is based on the concept that a high concentration of the agent in the perfusing blood also gives a high uptake in the tumor tissue. As a possible secondary benefit, the extraction of a major part of the dose at first passage through the selectively infused tissue should entail a lesser impact on non-target tissues.

However, our knowledge of the relationship between blood concentration and tissue uptake *in vivo* is limited for commonly used cytostatics, even for adriamycin (Adm), which has been used therapeutically by selective arterial administration [1–8].

Both in experimental [6] and clinical [7] studies local i.a. infusion gives a higher local uptake of Adm than does systemic administration, as estimated from measurements of recirculating Adm. *In vitro* studies have demonstrated a positive relationship between suspension medium Adm concentration as well as exposure time and the uptake of Adm in Chinese hamster cells and HeLa cells [9].

In apparent contrast, useful pharmacokinetic models based on an assumed tissue blood flow-dependent uptake have been established for predicting long-term tissue Adm concentrations following a systemic administration [10, 11].

However, so far, systematic *in vivo* studies confirming the rationale of local i.a. infusion therapy seem to be lacking.

In the present work we have determined Adm uptake in normal tissue and sarcoma transplants

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in the autoperfused rat kidney receiving Adm by direct renal arterial constant rate infusion and in the contralateral kidney, also with implanted sarcoma, receiving the systemically recirculated Adm only.

As one kidney accounts for approximately 10% of cardiac output, the blood Adm concentration to the autoperfused kidney would be expected to be several times higher than that of the contralateral kidney, depending on renal blood flow and the clearance of Adm from systemic blood.

Using a consistent total dose (5 mg/kg) and varied infusion time (3–30 min), we have correlated the course of Adm concentration in the perfusing blood to the uptake of Adm by tumor and normal tissue in both kidneys at 10 min post-infusion.

A recent report [12] might suggest increased uptake of Adm in mouse leukemic cells in the presence of ricin, a cytotoxic plant lectin.

Therefore we have studied Adm uptake by normal tissues and tumors during systemic intravenous (i.v.) infusion of Adm combined with a selective infusion of ricin into the renal artery of the autoperfused kidney.

In both types of experiment the Adm concentration in red blood cells, plasma and solid tissues are included. It may be pertinent to emphasize that conclusions drawn from these acute experiments with high Adm concentrations may not readily be extended to conditions of very slow infusions of a total Adm dose similar to the present one.

MATERIALS AND METHODS

Inbred Lister rats of both sexes, body weight 180–280 g, were kept on a diet of corn pellets and water.

Transplantable 20-methylcholanthrene-induced sarcomas were implanted in both kidneys [13]. Seven to eight days later the animals were anesthetized with pentobarbital-Na, tracheotomized and placed on a heating pad with thermostatic control via a rectal thermometer, keeping the body temperature at 37–38°C.

An extracorporal flow circuit was established according to Fink and Brody [14] from the right carotid artery to an aortic pouch, having the left renal artery as the only outlet, i.e. as a selective arterial route to the left kidney. Total renal blood flow (RBF) was measured with a flow probe (Nycotron, model 1607) and a Nycotron electromagnetic flowmeter. Mean arterial blood pressure (AP) and heart rate, as measured with a Hewlett-Packard transducer connected to a side branch of the shunt, were recorded together with RBF on a Hewlett-Packard recorder [15].

A catheter was introduced into the left carotid artery for blood sampling. Another catheter was inserted in the right femoral vein for infusions. The abdominal wall was closed and the animals were allowed 0.5–1 hr recovery after surgery.

In the first series of experiments, consisting of 18 rats, 5 mg/kg body weight of Adm together with 3 μCi of [^{3}H]-Adm (courtesy of Farmitalia, Milan) was infused at a constant rate for 3–30 min into the shunt. The drugs were stored in crystalline form and dissolved in 1.3 ml of 0.9% saline immediately prior to infusion.

During and after Adm infusion the renal tubular fluid would presumably contain a higher Adm concentration in the left as compared to the right kidney. To minimize this difference a post-infusion period of 10 min was allowed before the renal circulation was stopped on both sides by tightening snares prepositioned around the renal pedicles.

A total of 6–7 timed blood samples, 100 μl each, were drawn from the left carotid artery during and following the infusion, the extracted blood volumes being replaced with saline. During the experimental period an additional 2 ml of saline was infused to avoid a low urine flow.

Following the stop of renal circulation a 1-ml arterial blood sample was drawn and centrifuged for determination of Adm in plasma and red blood cells. All blood samples, a sample of the infusate, representative tissue samples from both kidneys and tumors together with tissue samples from the heart, spleen, liver and skeletal muscle were analyzed for radioactivity (Packard Tri-Carb 460 CD liquid scintillation system). A standard preparative procedure and correction for quenching were used.

Pilot experiments indicated that urine appearing in ureteral catheters towards the end of the post-infusion period had Adm concentrations that were similar on both sides and lower than in simultaneously sampled renal tissue. Thus the present model gives a valid comparison of tissue Adm uptake in right and left kidneys.

In the second series of experiments the autoperfused kidney model was used in 8 Lister rats with sarcoma transplants in both kidneys, and in 5 Sprague-Dawley rats without tumors (body weight 230–350 g): Adm, 5 mg/kg, was infused during 10 min into a femoral vein (instead of into the extracorporal shunt). Concurrently, 3 μg/kg ricin dissolved in 1.1 ml 0.9% saline was infused at a constant rate into the shunt, i.e. selectively to the left kidney. This dosage of ricin corresponds to the LD_{50} in mice according to earlier reports on the synergistic effect between ricin and Adm [12, 16]. All other procedures were the same as described above.

The time course of Adm in systemic arterial blood was calculated from the timed blood samples from the left carotid artery. The time course of Adm to the selectively infused left kidney was calculated from the infusion rate for Adm, the RBF and the corresponding systemic (recirculating) Adm concentration.

For statistical evaluation unpaired Student's *t*- and Mann-Whitney's *U* tests were used. The results are presented as mean ± S.E., unless otherwise stated.

RESULTS

Steady hemodynamic conditions were established before Adm infusion: mean AP was 111± 4 mm Hg, and the range of RBF in the autoperfused kidney was 3.2–5.8 ml/min/g kidney weight.

Ten-minute infusion

On the selectively infused left side, the renal arterial concentration of Adm increased during infusion due to recirculating Adm (Fig. 1) but also in part due to a decrease of RBF induced by Adm as previously described [17]. The left renal arterial concentration was 5–6 times higher than the systemic peak concentration of Adm (Fig. 1).

The first post-infusion half-time of Adm in systemic arterial blood was less than 2 min, the next was 3–3.5. Subsequently, the blood clearance of Adm appeared to be considerably prolonged, the concentration being 20% of the peak at 10 min after completed infusion (Fig. 1).

The mean concentration × time product for Adm to the selectively infused kidney was 481± 71 μg min/ml, which is 6.2 times the value in the systemic blood (77 ± 6 μg min/ml).

The intact part of the left kidney extracted 20 ± 3% of the Adm dose, whereas 3 ± 0% was taken up by the right kidney. Thus 17% of the dose was extracted by the selectively infused kidney during first renal passage.

On a per weight basis, the tumors extracted proportionally the same amount of Adm offered on both sides, 14 ± 2% of normal tissue uptake in the left and 15 ± 4% in the right kidneys. Tumor diameter averaged 4 mm.

Accordingly, the Adm uptake was 6–7 times higher on the selectively infused side, for normal renal tissue ($P < 0.001$) as well as for the tumors ($P < 0.001$) (Fig. 1).

As observed in pilot experiments, the concentration of Adm in urine sampled during the last 3 min of the post-infusion period from the left kidney was 117 ± 32% (S.D.) of that obtained from the right kidney, on average 71 μg/ml. The difference in recovery of Adm between the kidneys could therefore not be due to Adm in tubular fluid.

Considering left and right kidneys together, a statistically significant linear relationship between tissue uptake and blood concentration × time product was obtained ($P < 0.001$) as demonstrated in Fig. 2. As the infusion rate was consistent, a negative correlation of Adm uptake to RBF ($P < 0.01$) is implied.

Also for the tumors (Fig. 3), the concentration dependency of Adm uptake was statistically significant ($P < 0.01$).

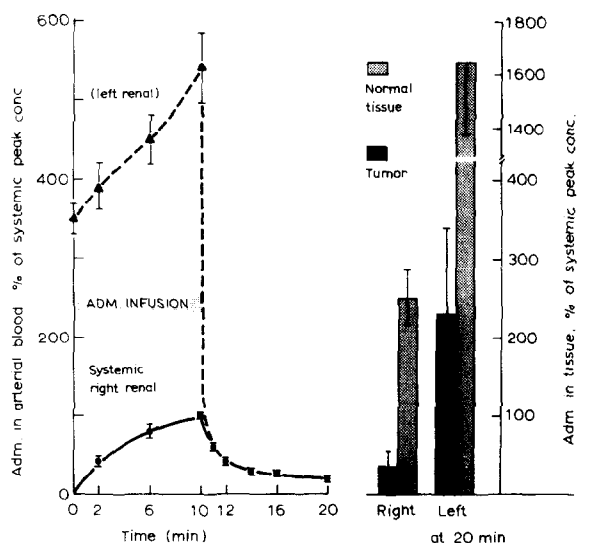

Fig. 1. Left panel: the time course of adriamycin (Adm) concentration in the selectively infused left renal artery and in systemic arterial blood; right panel: recovery of Adm in normal renal tissue and in sarcoma transplants of both kidneys. All data are normalized with respect to peak concentration in systemic arterial blood.

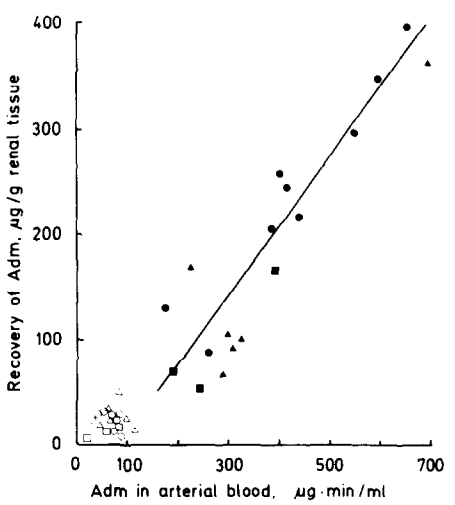

Fig. 2. Recovery of adriamycin (Adm) in normal renal tissue after selective infusion of 5 mg/kg body weight into the left renal artery as related to the concentration × time product of Adm in arterial blood. Infusion times: 3 min (triangles); 10 min (circles); and 30 min (squares). Closed symbols: left kidneys; open symbols: right kidneys.

Varied infusion time

Figure 4 compares the course of blood Adm concentration in 3-, 10- and 30-min infusion experiments, all animals given the same total dose. In spite of markedly different peak concentrations in the left renal artery as well as in systemic blood, significant differences in blood Adm were not obtained at 10 min after completed infusion (Fig. 4).

At all infusion rates the uptake of Adm in normal renal tissue of the selectively infused kidney was linearly related to the concentration × time product (Fig. 2).

The tumor uptake of Adm was similar at 3- and 10-min infusion times (34 ± 10 μg/g vs 32 ± 5), while the uptake in normal renal tissue was non-significantly lower at the 3-min infusion time (176 ± 50 μg/g vs 233 ± 29, $P > 0.1$).

The tumor to normal tissue uptake ratio was similar at all infusion rates.

In all tissues receiving systemic Adm, fairly similar Adm uptakes were found at the different infusion rates.

Combination of adriamycin and ricin

As compared to experiments with Adm alone, significant differences in arterial pressure, heart rate and renal blood flow were not observed in the present acute experiments.

Figure 5 (upper panel) shows the recovery of Adm in plasma, red blood cells and different tissues, as determined 10 min after completed infusion, comparing the experiments with and without ricin.

After the simultaneous infusions of Adm and ricin, blood clearance of Adm was retarded as compared to experiments with Adm alone ($P \sim 0.1$).

Accordingly, a higher plasma Adm concentration was obtained in the ricin-infused animals: at 10 min post-infusion, 0.60% of the total Adm dose was recovered per g plasma as compared to 0.25% when ricin was not present ($P \sim 0.08$). Furthermore, the Adm uptake by red blood cells was reduced in the presence of ricin from 0.22 ± 0.06% of total Adm/g to 0.07 ± 0.02% ($P \sim 0.08$), the corresponding change of red cells to plasma partition being statistically significant ($P < 0.01$).

The reductions of Adm uptake by other normal tissues were slight ($P > 0.1$).

In the tumors, a non-significantly higher average concentration of Adm was found on the left side selectively infused with ricin as compared to the right side (1.02 ± 0.28% of total Adm dose/g tumor vs 0.87 ± 0.18%, $P > 0.1$). However, considering all 16 tumors of the ricin experiments together, their Adm uptake was doubled compared to the 18 tumors receiving recirculating Adm alone (0.93 ± 0.16% of total dose/g tumor vs 0.37 ± 0.08%, $P < 0.05$). Relating Adm uptake to the time × concentration product in arterial blood gave a similar pattern (Fig. 5, middle panel), with the exception that tumor uptake was not significantly increased by ricing ($P > 0.1$).

DISCUSSION

Validity of the experimental model

We chose the present kidney model in order to have paired host organs with single arteries, thereby obtaining comparison of local arterial

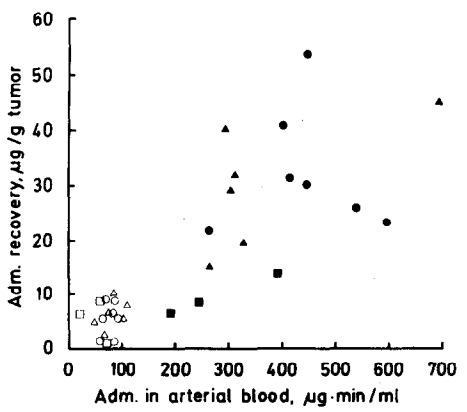

Fig. 3. Recovery of adriamycin (Adm) in sarcoma transplants in the kidneys after selective infusion of 5 mg/kg *body weight into the left renal artery. Symbols as in Fig. 2.*

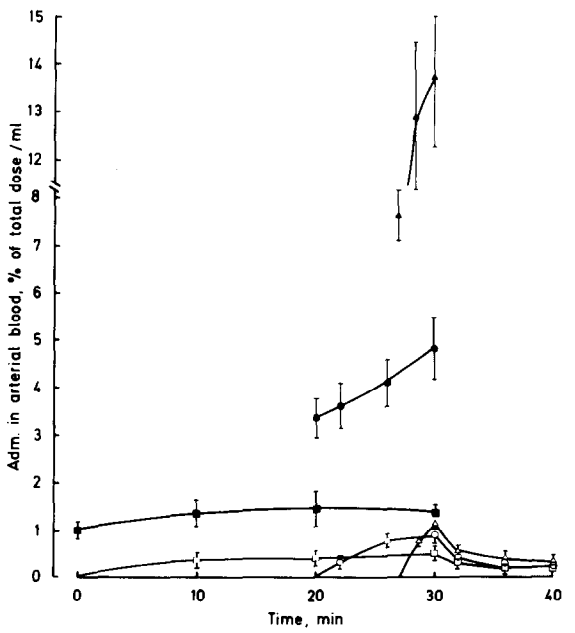

Fig. 4. Course of Adm blood concentration during and after selective infusion of 5 mg/kg *body weight into the left renal artery. Infusion times:* 3 min *(triangles);* 10 min *(circles); and* 30 min *(squares). Closed symbols: concentration in the left renal artery; open symbols: concentration in systemic arterial blood. Bars indicate ± S.E.*

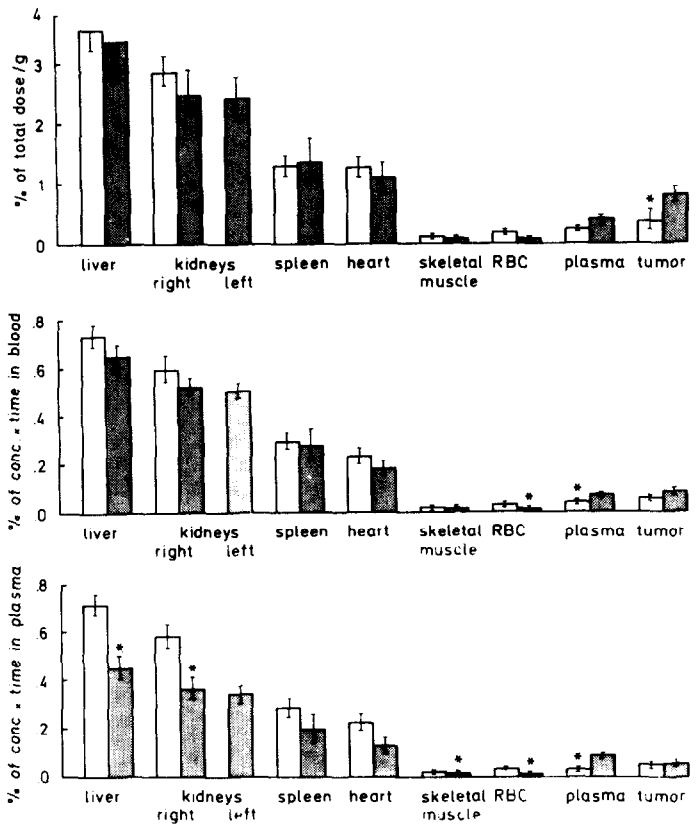

Fig. 5. Recovery of adriamycin (Adm) in blood and solid tissues (the right kidneys only) 10 min *after ended infusion of* 5 mg/kg *body weight into the left renal artery for* 10 min *(open columns), compared to the recovery following the same dose given systemically during the simultaneous infusion of* 3 μg/kg *ricin into the left renal artery (hatched columns). The plasma × time product (low panel) is calculated on the assumption that the red cell to plasma partition of Adm as observed* 10 min *post-infusion is representative for the entire uptake period (cf. discussion). Bars indicate ± S.E. Asterisks denote* $P < 0.05$.

and systemic administration within the same animals. Its main drawback would be that a difference in filtered Adm in the two kidneys might falsely be interpreted as difference in tissue uptakes. We therefore allowed an 10-min post-infusion period to obtain a tubular fluid derived from equal blood Adm concentrations in both kidneys (Fig. 1). This was verified by the observation of similar Adm concentrations in urine from both kidneys at 10 min after completed infusion when the tissue samples were taken.

Pilot experiments indicated that approximately 0.02% of the total dose of Adm appeared in the urine during the last 3 min of the post-infused period. This is in accordance with earlier comparable results: 0.01% during 5 min following a systemic injection of Adm in hamster [18] and 0.06% during 20 min in man [19].

Clearly, Adm in the tubular fluid did not appreciably affect the estimated difference in the Adm uptake by the two kidneys. On the other hand, the Adm concentration was in the same order of magnitude in urine and tumor tissue. However, since the tumors do not contain glomeruli or renal tubules, the Adm concentrations obtained must reflect uptake from the blood-perfusing tumor capillaries.

Close arterial versus systemic infusion of adriamycin

At 10 min infusion, the selectively infused kidney extracted 20% of the total dose, as compared to 3% for the contralateral kidney. An uptake of approximately 3.5% of the total dose may thus be predicted for the contralateral kidney if the whole dose had been given intravenously. The present experimental model therefore provides a valid comparison of tissue Adm uptake during local and systemic infusion in each experiment. Evidently, non-target tissues would take up practically equal amounts of Adm at local i.a. and systemic modes of administration.

The rapid clearance of Adm from systemic blood agrees reasonably well with previous results: a plasma half-time of 4–7 min was observed after a 90-sec i.v. infusion in man [20]. In rabbits, 5–6 blood half-times [21] and approximately 10 plasma half-times [22] have been obtained during 30 min after an i.v. bolus injection. In mice, 5 plasma half-times during 10

min after i.v. bolus injection of Adm has been reported [23].

Similarly, the present Adm uptake by tissues is well in line with most previous results obtained after i.v. bolus injection of the present dose (5 mg/kg) in mice [24, 25]. Approximately twice the present tissue concentrations were obtained after an i.v. injection of 25 mg/kg to hamsters [18]. In contrast, 5–8 times higher initial uptake of Adm in heart and kidney was observed in rats after an i.v. bolus injection of 10 mg/kg [26].

The uptake of Adm by the autoperfused renal tissue and sarcoma transplant was 6–7 times higher than that obtainable by systemic infusion at all infusion rates.

On account of the rapid post-infusion clearance of Adm from the blood, tissue Adm concentration may not increase from the levels obtained 10 min after completed infusion [24–26]. During the following hours the decrease in Adm will be fairly proportional in all types of normal tissues, in spite of highly variable tissue to plasma Adm concentrations [23–26]. The time course of Adm in tumors is less well known, but the concentration is reported to be maintained between 2 and 16 hr after administration in a transplantable sarcoma in mice [24]. Thus it is likely that a relatively high Adm concentration, as obtained by selective infusion, will prevail. This assumption is supported by our recent observation of a significantly greater delay of tumor growth in rat kidneys following close i.a. infusion of Adm as compared to renal tumors receiving its Adm via systemic i.v. infusion [27].

The uptake of Adm by tumors was about 15% of that in normal renal tissue. As the local blood flow in the present type of tumor is about 20% of renal tissue flow [28, 29], a flow-dependent Adm uptake might be assumed. However, an apparent flow-dependent uptake might well relate to tissue capillarity, which again may be fairly closely related to tissue blood flow.

Conceivably, local Adm uptake might be improved by using a rapid i.a. bolus injection of the dose, i.e. by a higher peak concentration in arterial blood. However, this is clearly not the case: tissue uptake was proportional to the concentration × time product (Fig. 2), in spite of a three times higher average peak concentration at 3 min than at 10 min infusion (Fig. 4).

This supports the idea of reducing the local arterial blood flow artificially during selective Adm infusion in order to achieve a prolonged relatively high concentration of Adm to the tumor [30]. However, it is uncertain to what extent tumor blood flow persists when flow is substantially lowered in the host artery. As tumor blood flow is susceptible to changes in perfusion pressure [31], central parts of the tumor, which may have a relatively high interstitial pressure [32], might be let without blood flow if the perfusion pressure is reduced. Vasoconstrictor agents would appear to be more suitable for reducing host organ flow since tumor blood flow may be relatively less affected [28, 29] and since vasoconstriction has been observed to reduce tumor interstitial pressure [33].

Experiments with ricin

The simultaneous systemic infusion of Adm and selective i.a. infusion of ricin to one kidney was done in order to assess whether the combination might increase the uptake of Adm by rapidly proliferating cells, as suggested in an earlier report on concurrent dosage of ricin and Adm in leukemic mice [12].

With ricin there was a consistent and significant reduction of red cell to plasma Adm concentration ratio and a substantial increase of Adm recovery in the tumors on both sides. It is notable that Adm uptake was similar in the left and right kidneys, in spite of selective ricin administration to the left kidney.

We interpret the results (Fig. 5) as indicating that ricin reduces or delays Adm uptake by the red blood cells and normal solid tissues, resulting in a higher plasma Adm concentration as compared to experiments with Adm alone. The higher plasma Adm may possibly explain the larger Adm uptake by the tumors; as such an indirect effect of ricin on tumor Adm uptake was not anticipated, we measured the red cell to plasma concentration ratio at 10 min post-infusion only. However, on the assumption that this ratio is representative for the duration of the Adm uptake period, the tumor uptake vs plasma concentration × time product corresponds to that of the experiments without ricin on both sides (Fig. 5, lower panel).

This interpretation is supported by the finding of similar Adm uptake in both kidneys in spite of selective ricin administration to the left one. Why tumor uptake *per se* thus may be unaffected by ricin is an open question.

According to this hypothesis, tumor uptake of other agents than Adm may be affected by ricin, depending on uptake mechanisms involved.

The significantly increased plasma Adm concentration in the presence of ricin might in part explain the marked synergistic effect of ricin and Adm on mouse leukemic cells *in vivo* [12].

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