Effect of Low Molecular Weight Dextran on Hepatic Metastases in the Rabbit

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SUMMARY

The administration of low molecular weight dextran resulted in an increase in hepatic metastases in rabbits receiving intraportal inoculations of V2 carcinoma cells. This effect is similar to that observed previously in our laboratory following intraportal injection of Walker tumor cells in the rat. Although the mechanism whereby dextran produces such an effect on tumor growth is unclear, the findings do not appear to be related to an anaphylactoid reaction due to dextran. They further emphasize the importance of local ("soil") factors in metastasis formation since the effect observed on hepatic metastases apparently differs from that purported to occur in the lung. The increase in hepatic metastases in two species following dextran administration provokes caution concerning its use in patients undergoing surgery for neoplastic disease.

INTRODUCTION

In the course of obtaining information relative to the effect of a variety of hemarheologic alterations on experimental metastasis formation we observed (3) that the incidence and size of hepatic metastases were increased with administration of low, medium, and high molecular weight dextrans. It was proposed that these findings might be consequent to the increase in circulating blood volume resulting from the dextran infusion. Reasons for such a consideration were presented. Recently, however, Wood et al. (10) have challenged this explanation. Since they failed to alter the frequency of pulmonary metastases in the rabbit by dextran treatment, they suggested that our findings obtained in the rat may have been the consequence of a species-specific reaction to dextran which has been described in that animal (1, 7). In spite of our failure to observe such a response in our studies, it was deemed advisable to reassess the effect of low molecular weight dextran on experimental liver metastasis in another species. Consequently, the rabbit has been employed in these investigations. We are unaware of any reports indicating an anaphylactoid response to dextran in this animal.

MATERIALS AND METHODS

New Zealand female rabbits weighing 1–2 kg housed in individual cages and fed Purina laboratory chow and water ad libitum were employed. Tumor cell suspensions from V2 carcinomas propagated in this laboratory for many generations were prepared so that there were 50,000 cells/ml of either normal saline or low molecular weight dextran (Rheomacrodex, Pharmacia Laboratories, Upsala, Sweden, Lot No. 301164), molecular weight 40,000, 10% w/v in normal saline. Animals were randomized into 14 groups with 3 in each, and all groups were treated similarly. One member (A) was injected via a jugular vein with low molecular weight dextran (15 ml/kg body weight), and one hour later under anesthesia (Diabutol) was inoculated intraportally with 1 ml (50,000 cells) of a cell suspension in dextran. A second animal (B) of the group received a jugular vein injection of normal saline (15 ml/kg body weight) followed in an hour by an intraportal tumor cell inoculation (1 ml) prepared in saline. The third rabbit (C) received no jugular vein inoculation prior to the intraportal injection of a similar number of tumor cells in saline. Each of the 3 animals was injected with tumor cells from the same tumor. A different tumor was employed for each of the 14 groups. All groups were sacrificed 8 weeks following injection, and a complete autopsy was done on every animal. Animals dying prior to sacrifice were likewise examined. Tumor growth in livers of each animal in a group was evaluated and compared with that in livers of the other 2 in the same group. Size and number of nodules and degree of replacement of liver were taken into consideration. Only when the extent of tumor in one liver was obviously greater than in the other was there judged to be a difference. Lungs were examined for metastases and, when present, were arbitrarily graded as 1+ when they contained a few scattered small nodules, 3+ when all lobes were extensively involved, and 2+ when the amount of tumor was intermediate.

RESULTS

All animals in 11 of the 14 groups survived until sacrifice. In 9 of the 11 sets rabbits receiving dextran demonstrated more liver tumor than did those members which were either injected with saline or were uninoculated prior to intraportal tumor cell injection (Table 1). In one set (No. 8), while the liver of the dextran animal was almost completely replaced by tumor and the saline and uninfused control rabbit had in-

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numerable large and small discrete nodules involving all lobes, the amount of tumor was so great in all that there was considered to be no difference between them. Only in one set (No. 12) was the amount of tumor in livers of the saline and uninfused controls greater than that found in the livers of the dextran-treated animal. In 2 of the 3 sets in which a nondextran-treated member died prior to sacrifice, more liver tumor was present in the dextran animal than in its surviving control. Whereas livers of all 14 animals injected with dextran contained tumor, 6 of 13 receiving saline and 5 of 12 uninfused controls were free of implants. When single or multiple nodules occurred in several members of a set, they were usually more numerous and/or larger in the dextran animals (Fig. 1, Set 4). In several groups the difference was striking (Fig. 2, Set 7).

In 6 of the 11 complete sets it was judged that the livers of saline animals had more tumor than did those in uninfused animals. In 2 sets the opposite was found, and in 3 sets no significant difference was discernible.

Lung metastases were slightly more prominent in the dextran-infused animals. Whereas 43% of those animals demonstrated such tumor, 30% of the saline-injected and 16% of the noninfused controls had metastases. In general, lung tumors were found in those animals having the most extensive hepatic involvement with tumor.

None of the animals in this investigation demonstrated anaphylactic manifestations. Blood pressures were monitored in 6 normal rabbits via femoral artery catheters during and following administration of dextran in the amounts employed in these studies. No significant alteration of blood pressure was observed in any animal. Histologic examination of livers from these animals revealed no abnormality. Sinusoidal congestion was not present.

DISCUSSION

The present findings in the rabbit are coincident with our previous observations in the rat that low molecular weight dextran enhances the incidence and growth of hepatic metastases, and they minimize the possibility that findings in the rat were the result of an anaphylactoid response to the dextran. None of the rabbits in this study exhibited such a reaction.

Other studies reported relative to the influence of dextran on metastasis formation have primarily been concerned with its effect on tumor growth in lung. Results have been variable. While Griffen and Aust (6) noted a decreased incidence of lung metastases in mice following low molecular weight dextran administration, they observed that when metastases did occur they were more numerous and larger than in control animals. Alexander and Altemeier (2) reported that low molecular weight dextran had no beneficial effect in preventing metastases in wounds from hematogenously disseminated tumor cells. In fact, "slightly more metastases were found in animals treated with low molecular weight dextran than in control animals." Schatten et al. (9) found that clinical dextran (average molecular weight 75,000) when given prior to V2 tumor cell inoculation markedly reduced the number of lung and liver metastases and increased the survival time of rabbits. In their investigations tumor cells were inoculated via the femoral vein rather than the portal vein which was used in this study. Moreover, their observation that as many as 80% of control animals developed liver metastases following inoculation of tumor cells via a systemic vein has not been our experience in either rabbits or rats so injected. Liver metastases under such circumstances have been a rarity. Wood et al. (10), as previously noted, failed to observe an alteration of pulmonary metastases in rabbits treated with dextran, and Garvie and Matheson (5) demonstrated that high molecular weight, as well as low molecular weight dextran, promoted the development of lung metastases in rats following intravenous injection of Walker tumor cells. The latter investigators, as we, failed to note any untoward reaction to dextran in rats, but they conceded the possibility that anaphylaxis may have been present but unrecognized. Microscopic evidence of increased cell sedimentation rates suggested to them that dextran affected the aggregation of tumor cells. They concluded that intravascular agglomeration of these cells with their increased arrest in the lung resulted in the enhancement of metastases. Previous studies by us (4) employing 51Cr-labeled tumor cells

<p>| Table 1 |
|----------------|----------------|----------------|----------------|
| Set | Group A, dextran (cm) | Group B, saline (cm) | Group C, uninfused (cm) | Liver tumor comparison | Lung tumors |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Size (cm)</th>
<th>No.</th>
<th>Size (cm)</th>
<th>No.</th>
<th>Size (cm)</th>
<th>Dextran</th>
<th>Saline</th>
<th>Uninfused control</th>
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<tr>
<td>1</td>
<td>2</td>
<td>2.0-3.0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.9</td>
<td>A &gt; C &gt; B</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>0.1-1.0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>A &gt; B &gt; C</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1.5-2.0</td>
<td>Died</td>
<td>1 day</td>
<td>1</td>
<td>2.0</td>
<td>A &gt; C</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>1.0-5.0</td>
<td>3</td>
<td>1-0.45</td>
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<td>0</td>
<td>A &gt; B &gt; C</td>
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</tr>
<tr>
<td>5</td>
<td>Replaced</td>
<td>1</td>
<td>1.5</td>
<td>Died</td>
<td>1 day</td>
<td>1.0</td>
<td>A &gt; B &gt; C</td>
<td>1+</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>3.0</td>
<td>14</td>
<td>1.0-2.5</td>
<td>Died</td>
<td>1 day</td>
<td>B &gt; A</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
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<td>1.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>A &gt; B &gt; C</td>
<td>1+</td>
</tr>
<tr>
<td>8</td>
<td>Replaced</td>
<td>3.0</td>
<td>&gt;15</td>
<td>1.0-2.8</td>
<td>&gt;15</td>
<td>0.5-2.7</td>
<td>A = B = C</td>
<td>3+</td>
</tr>
<tr>
<td>9</td>
<td>0.4-2.5</td>
<td>5</td>
<td>1.0-1.3</td>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>A &gt; B &gt; C</td>
<td>3+</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>A &gt; B &gt; C</td>
<td>2+</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>0.3-0.5</td>
<td>0</td>
<td>0</td>
<td>Died</td>
<td>30 day (neg)</td>
<td>A &gt; B</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>0.5</td>
<td>Almost replaced</td>
<td>5</td>
<td>1.4-4.0</td>
<td>B &gt; C &gt; A</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>1.0-1.5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.8</td>
<td>A &gt; C &gt; B</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>A &gt; B &gt; C</td>
<td>1+</td>
</tr>
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</table>

Effect of dextran on experimental hepatic metastasis in the rabbit.
failed to reveal evidence indicating that the augmentation of metastases noted with dextran was due to an increase in number of tumor cells trapped in the liver. This variability is also emphasized by the comprehensive studies of the effect of low, medium, and high molecular weight dextrans on pulmonary metastases of a variety of experimental tumors in rats and mice by Rudenstam (8). These divergent findings may be in part due to differences in routes of administration of tumor cells and dextran, loci of metastasis formation, as well as the species and tumors employed. Other variables, such as effects of anesthesia, positions of the rabbit, and different lots of dextran employed may likewise play a role.

It is of interest that a slightly greater number of metastases was observed in this study in rabbits infused with saline than in uninfused controls. We had previously observed (3) a relationship between tumor growth and an increase in circulating blood volume resulting from the administration of low molecular weight dextran, plasma, or saline.

These studies further emphasize the importance of local ("soil") factors in considering metastatic mechanisms. They also emphasize that the findings in one model system utilized to obtain information relative to metastases in one organ (lung) are not necessarily applicable to that of another (liver). Despite the mechanism involved, the finding of increased hepatic metastases following dextran administration in two species suggests that employment of these agents during or after surgery for neoplastic disease may be unwise.

ACKNOWLEDGMENTS

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REFERENCES

Fig. 1, Set 4. Effect of dextran on hepatic metastasis in the rabbit.

Fig. 2, Set 7. Effect of dextran on hepatic metastasis in the rabbit.
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