Heptyl Aldehyde-Sodium Bisulfite: Toxicity and Effect on Spontaneous Mammary Carcinoma in Mice

Frank Garai, M. D.

(From the Department of Pathology, Manhattan Eye, Ear, and Throat Hospital, New York, N. Y.)

(Received for publication November 16, 1940)

For the past 2 years we have observed the action of intraperitoneally or subcutaneously injected solution of heptyl aldehyde-sodium bisulfite upon mice of 3 inbred strains. All the animals had spontaneous mammary carcinoma at the time when the injections were started (Table I).

The spontaneous tumors were treated when they reached an average size of 1 cm. diameter. As tumors grow at different rates in the various strains, the

### Table I: Mice of C3H, Dba, and Paris R3 Strains Injected with Heptyl Aldehyde-Sodium Bisulfite

<table>
<thead>
<tr>
<th>No. of mice</th>
<th>Strains</th>
<th>No. of injections intraperitoneally</th>
<th>No. of injections subcutaneously</th>
<th>Average age of mice in months</th>
<th>Size of tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>C3H</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>0.5-1.5 cm. in diameter</td>
</tr>
<tr>
<td>25</td>
<td>Dba</td>
<td>15</td>
<td>10</td>
<td>11</td>
<td>0.5-1.5 cm. in diameter</td>
</tr>
<tr>
<td>50</td>
<td>Paris R3</td>
<td>30</td>
<td>20</td>
<td>8</td>
<td>0.5-1.5 cm. in diameter</td>
</tr>
<tr>
<td>15</td>
<td>Control mice, no tumor</td>
<td>15</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

...peritoneally in mice without any local irritation or ulceration.

Injections were never made into the tumor or near the site of the tumor.

The toxicity of this compound was determined by intraperitoneal or subcutaneous injections in healthy mice, and intravenous injection in healthy rabbits.

Since the heptyl aldehyde-sodium bisulfite contains the equivalent of 52 per cent its weight of heptyl aldehyde all doses mentioned hereafter are calculated as heptyl aldehyde.

We found that the minimal lethal dose was 666 mgm. of heptyl aldehyde per kilo of body weight while injections of 400 mgm. per kilo produced transitory toxic symptoms. The minimum dose which produces liquefaction of spontaneous mouse tumors was found to be 166 mgm. per kilo.

This dose corresponds to 5 mgm. of heptyl aldehyde per 30 gm. mouse. The 1st injection was 3 mgm.; the 2nd, 4 mgm.; the 3rd was 5 mgm. This last dose was kept up for the remainder of the treatment. The injections were given every 2nd day regularly to 100 mice of the above-mentioned strains, each one afflicted with spontaneous mammary carcinoma. As the result of injections of the compound every 2 days for from 40 to 60 days, each animal, in accordance with its period under treatment, received from 86 to 136 mgm. of heptyl aldehyde.

A puncture section of the tumor was made on each mouse before the 1st injection of heptyl aldehyde-sodium bisulfite.

Generally, after the 1st or 2nd injection a decided expansion of the tumor occurred in all cases. After several injections the response of the tumors was not uniform. In some cases, liquefaction occurred; in other cases, regression of the tumor was noticed, and in others, hemorrhages in the tumors were observed. In those instances where liquefaction or hemorrhage occurred, fluid was aspirated from the tumor with large-gauge needles. Pathological examination of these fluids disclosed large numbers of tumor cells in each case.
In some cases where the tumors were somewhat more advanced, necrotization of the tumor tissue occurred, accompanied by a splitting of the skin and a complete dislodging of the tumor as a whole. In these instances the falling out of the tumor was occasionally followed by sufficient hemorrhage to cause the death of the animal. In other instances where no fatal hemorrhage took place suturing of the skin failed to prevent the occurrence of secondary infection, which was always fatal.

When the tumors were approximately 0.5 cm. in diameter and some hope of total regression seemed reasonable, the animals were kept under treatment for an average of 60 days, with the usual injection every 2nd day. While it was noticed that the growth of the treated tumors was retarded in comparison with the untreated control tumors of the same strain, the mice eventually succumbed. The control animals with untreated tumors died approximately 21 days earlier than the treated animals.

There were no differences in the reactions of the tumors in each strain to the heptyl aldehyde-sodium bisulfite compound.

Autopsies were made on every treated animal and pathological examination of sections from the tumor, kidneys, and liver disclosed the cause of the deaths. The tumors were more or less necrotized, but a partial or total destruction of the tissues of the kidneys and liver of all of the treated animals were the most striking features.

There were no strain differences in the resistance of the mice to the toxic action of the compound upon kidneys and liver. Associated with this was a partial retardation of the growth of spontaneous tumors in mice. However it is well known that any procedure which affects the general health of an animal may retard the growth of an associated tumor. The effect on the kidneys and liver may have been caused by absorption of toxic substances from the destruction of the tumor during treatment, but 15 controls with no tumor showed similar destructive effects in their kidneys and livers as a result of similar chemical treatment. Strong reports no toxic results and favorable tumor reactions in mice receiving heptyl aldehyde-sodium bisulfite injections. We do not confirm these results.

**CONCLUSION.**

The destructive action of continued doses of heptyl aldehyde-sodium bisulfite upon the kidneys and liver far outweighs its effect upon the growth of spontaneous tumors, insofar as any application of this product to the chemotherapy of cancer is concerned.

Nevertheless, we feel that studies with heptyl aldehyde compounds in relation to spontaneous tumors opens up a definitely attractive field for further experimentation with compounds of this type.

We are indebted to the Department of Pathology of the Manhattan Eye, Ear, and Throat Hospital, New York City, for generous cooperation.

To Dr. A. A. Eggston, Director of this Department, we owe a special debt of gratitude for his study and description of the sections.

**REFERENCE**

Heptyl Aldehyde-Sodium Bisulfite: Toxicity and Effect on Spontaneous Mammary Carcinoma in Mice

Frank Garai

Cancer Res 1941;1:144-145.