Growth Inhibition of a Rat Colon Tumor by L-Canavanine

Deborah A. Thomas, Gerald A. Rosenthal, David V. Gold, and Kenneth Dickey

ABSTRACT

The effects of L-canavanine, a higher plant nonprotein amino acid, on the growth of a rat colon carcinoma were assessed. The 1 and 10% lethal dose values following a single s.c. injection in Fischer rats were 4.75 and 5.57 g/kg, respectively. Rats received s.c. injections of a 10% (v/v) tumor cell suspension. When the tumors reached a size of 500 to 1000 mm³, the rats received canavanine, 2.0 g/kg or 3.0 g/kg s.c. daily for 5 or daily for 9 days. Control animals received a 0.9% NaCl solution.

Administration of canavanine, 2.0 g/kg for 5 days produced a treated versus control of 23%; the treated versus control for 9 days was 14%. The 3.0-g/kg dosing regimen resulted in a treated versus control value of −13% after 5 days and −8% after 9 days. The negative values indicated regression of the tumor. The reduction in tumor volume, expressed as the percentage of regression, was 22% in animals receiving canavanine, 3.0 g/kg daily for 5 days and 60% in the 3.0-g/kg-daily-for-9-days treatment group.

Cumulative toxicity caused death in 2 of 5 animals in the 3.0-g/kg-for-9-days treatment group; the average weight loss was 31%. The 3.0-g/kg-for-5-days treatment also produced undesirable cumulative toxicity as indicated by a weight loss of 19%. Cumulative toxicity was reduced greatly when canavanine was administered at a dose level of 2.0 g/kg for 5 days (weight loss of 13%).

Analysis of the relationship of caloric deprivation to tumor growth reduction established that canavanine-mediated curtailment of tumor growth was not caused by reduced food intake and its associated loss in body weight.

Histological examination of tissues from rats receiving canavanine, 2.0 or 3.0 g/kg daily for 5 or 9 days failed to reveal lesions in any of the examined tissues, except for varying degrees of pancreatic acinar atrophy. All other tissues appeared normal. The white and red blood cell values of canavanine-treated rats were also normal following 1, 3, or 6 injections of canavanine, 2.0 or 3.0 g/kg.

The results indicated that canavanine induced marked growth inhibition of the rat colon carcinoma. Our experiments also disclosed that further studies must be conducted to optimize the dosing schedule to enhance drug efficacy and to reduce its cumulative toxicity.

INTRODUCTION

L-Canavanine, 2-amino-4-(guanidinooxy)butyric acid, is a nonprotein amino acid synthesized by many leguminous plants (1). The cytotoxic and insecticidal properties of this arginine analogue have been demonstrated in numerous organisms (2). An important basis for the antimitabolic properties of canavanine resides in the inability of the arginyl-tRNA synthetases of canavanine-sensitive species to discriminate adequately between L-canavanine and L-arginine. This limitation results in the erroneous incorporation of canavanine into proteins (2) that can cause structural and functional protein aberrations (3, 4).

Canavanine toxicity may result from the formation of aberrant proteins involved in DNA replication and transcription and RNA synthesis. Schachtele and Rogers (5) demonstrated that canavanine caused a marked reduction in RNA synthesis in Escherichia coli; canavanine-dependent inhibition of RNA synthesis was also observed in the alga, Chlamydomonas reinhardtii (6), where it was attributed to canavanyl protein formation that attenuated transcription. Larvae of the tobacco hornworm, Manduca sexta, treated with canavanine exhibited reduced RNA polymerase activity (2), whereas canavanine treatment of Semliki Forest virus prevented RNA polymerase synthesis (7). Canavanine also disrupts the reactions of DNA metabolism, as demonstrated by reduced DNA synthesis in herpes simplex exposed to canavanine (8). Significant substitution of arginine by canavanine, with an isoelectric point of 8.12, can decrease the basicity of arginine-rich histones and alter DNA function or genomic expression. Inhibition of histone synthesis has been demonstrated in HeLa cells (9) and cultured hamster and mouse cells (10).

Green et al. (11) have reported that canavanine prolongs the life of mice bearing L1210 leukemic cells, indicating that canavanine does exhibit antitumor properties. It was also shown to enhance the lethal effects of irradiation on a human tumor cell line (12). Other studies with monkey kidney cells (13, 14) established the selectivity of this arginine analogue in decreasing DNA replication of transformed as compared to normal cells. The ability of canavanine to attenuate growth of a solid tumor in vivo has not been investigated. The present study on canavanine-mediated inhibition of rat colon tumor growth in vivo was instituted to assess its potential value as an anticancer agent.

MATERIALS AND METHODS

Animals and Tumor Cell Lines. Male Fischer rats, weighing 150–175 g, were obtained from Harlan Sprague-Dawley, Inc., Indianapolis, IN. Rats were housed 5 to a cage in polycarbonate cages with sawdust bedding. They received Purina Rodent Laboratory Chow No. 5001 and tap water ad libitum throughout the experiments.

Experiments were conducted with a rat colon carcinoma obtained from Dr. Jerrold Ward of NIH. The tumor was induced by injection with 1,2-dimethylhydrazine over a period of 13 wk (15). A primary adenocarcinoma was found in the ascending colon. Histological examination revealed that a majority of the tumors had signet ring cells suspended in mucus. Cords of undifferentiated epithelial cells and some areas of cells attempting to form glands were also observed. Transplantation of this tumor by trocar, over a period of generations, yielded a mucinous tumor of mostly undifferentiated cells. Heterogeneity was evident in that focal areas of gland formation could be noted. This tumor produced carcinoembryonic antigen-like glycoproteins as well as an organ-specific colonic mucin (16). The tumor was maintained by successive passages in male Fischer rats by s.c. injection. Tumors were evident 8 to 10 days after injection; the doubling time in vivo for tumor volume was 3 to 4 days.

Preparation of Chemicals and Injections. L-Canavanine was isolated from acetone-defatted jack bean seeds, Canavalia ensiformis, purified by ion-exchange chromatography, and crystallized from ethanol-water (17). The crystalline canavanine was treated with decolorizing charcoal and recrystallized as described (17). Elemental analysis, melting point

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3 D. Gold, unpublished observation.

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determination, and automated amino acid analysis of a highly concentrated canavanine solution were conducted periodically. These determinations confirmed that our preparative procedures consistently yielded material of approximately 99% purity. Doses for injection were prepared by dissolving canavanine in 0.9% (w/v) NaCl (pH 8.1).

Treatment of Rats Bearing Colon Tumors with Canavanine. Prior to chemotherapy studies, tumors were excised, minced, and homogenized in sterile 20 mM sodium phosphate (pH 7.2) containing 0.1% (w/v) NaCl. A 10% (w/v) tumor suspension (0.5 ml) was injected s.c. into the left flank of the experimental animal; tumors were evident within 8 to 10 days. Canavanine injections were initiated between 2 and 3 wk after implantation, when the tumors attained a size by caliper measurement of 500 to 1000 mm³. The initial tumor weight averaged 0.5% of the rat body weight. Tumor volume was estimated by the formula

\[ \text{Vol} = \frac{l \times w^2}{2} \]

where \( l \) = length and \( w \) = width of the tumor in mm.

For each experiment, the tumor-bearing rats, randomized into groups of 5 animals, were given s.c. injections of canavanine, either 2.0 or 3.0 g/kg on a daily schedule for 5- or for 9-day period. The control groups received a 0.9% (w/v) NaCl solution on the same dosing schedules as the treated animals. To prevent direct contact with the tumor, canavanine was injected into the right flank of all experimental animals. At 24-h intervals throughout the experiments, tumors were measured first followed immediately by the administration of the appropriate dose of canavanine or NaCl solution. Two days after receiving the final treatment, animals were sacrificed and tumors were excised and weighed individually. Tumor response to canavanine treatment was calculated as

\[ \frac{\text{Final tumor wt}}{\text{Initial tumor wt of controls}} \times 100 \]

In experiments where tumor regression was observed, the percentage of regression was calculated by the formula

\[ \% \text{ regression} = \frac{1 - \left( \frac{\text{Final tumor wt}}{\text{Initial tumor wt of controls}} \right) \times 100}{\text{Initial tumor wt}} \]

Evaluation of Reduced Food Intake on Rat Colon Tumor Growth. Rats were housed individually in suspended wire cages to prevent the experimental animal access to its fecal pellets. As in all canavanine treatment studies, when the tumors reached a size of 500 to 1000 mm³, the rats were randomized, 5/group, into a series of restricted feeding regimens: Purina rat chow, 10 or 5 g/day or food ad libitum (control group). To verify that tumor response to canavanine treatment occurred as in prior experiments, another group of rats, fed ad libitum, received daily injections of canavanine, 3.0 g/kg. All treatments were conducted daily for 5 days. Tumor volume, food intake, and body weight were measured daily, just prior to treatment. Animals were sacrificed, and tumors were excised and weighed individually at the end of the experiment.

Collection and Analysis of Tissue and Blood Samples. Two days after the 5- and 9-day canavanine treatments were concluded at dose levels of both 2.0 and 3.0 g/kg, rats were sacrificed for gross necropsy examination. Tissue samples (brain, liver, kidney, lung, heart, spleen, stomach, small intestine, cecum, colon, urinary bladder, pancreas, adrenal glands, testicles, and tumor) were fixed in neutral, buffered formalin. After fixing, 5-μm sections were stained with hematoxylin and eosin and examined microscopically.

Blood samples were collected from rats receiving canavanine, 2.0 or 3.0 g/kg daily at least 48 h before treatments began and also 24 h after the first, third, and sixth canavanine injections. WBC and RBC were determined using the Unopette Test 5856 (Becton-Dickinson, Rutherford, NJ).

Determination of LD₀, LD₁₀, and LD₅₀. LD₀, LD₁₀, and LD₅₀ were determined following single s.c. injections. Nine dose levels plus a control group were evaluated; each group contained 9 rats. The following doses (g/kg) were used: 3, 4, 5, 6, 6.5, 7, 7.5, 8, and 9. Animals were observed for 7 days following injection, by which time all rats had either died or had recovered from the canavanine treatment. The effects of these dose levels ranged from no mortality to 100% mortality. Data were calculated and analyzed by probit analysis (18).

RESULTS

Histomorphology. Microscopic examination of stained tumor sections from control animals revealed that the s.c. transplants consisted of pleomorphic undifferentiated epithelial cells arranged primarily in cords or clusters of varying widths. A variable fibrous stroma was present throughout the tumor. Numerous mitotic figures were observed. Attempts at forming tubular structures were widespread, resulting in numerous foci with multiple layers of epithelial cells surrounding a lumen or a single layer of epithelial cells surrounding a lumen. Staining with periodic acid-Schiff revealed that moderate numbers of lumens and numerous individual epithelial cells contained mucin. Unlike the typical mucinous adenocarcinoma pattern or signet ring pattern (19, 20), these tumors, because of multiple passages and atypical sites of growth, did not exhibit the extensive accumulation of mucin nor were signet ring cells seen floating in mucin. Occasional isolated signet ring cells were present.

Tumor sections from control animals bearing tumors greater than 1 cm diameter revealed scattered necrotic foci. Larger and older tumors contained coalesced necrotic areas that at times consisted of more than 25% of the total volume of the tumor. These necrotic areas resulted presumably from the loss of blood supply as the tumor enlarged. Two days after the final canavanine injection, tumors from rats treated with canavanine, 2.0 or 3.0 g/kg for 5 or 9 days were excised and prepared for histological evaluation. These tumors had fewer and smaller necrotic foci than tumors from control animals. This was ascribed to the fact that treated tumors, much smaller than the control tumors, did not outgrow their blood supply to the same extent as did the control tumors. Canavanine-treated tumors also contained more attempts at glandular differentiation than control tumors. Mitotic patterns in treated tumors were similar to those of control animal tumors.

Histological examination of selected tissue samples from rats treated with canavanine, 2.0 or 3.0 g/kg daily for 5 or 9 days revealed varying degrees of pancreatic acinar atrophy, leaving fibrous stroma. Islet cells were prominent and appeared to be normal. All other tissues examined exhibited no microscopic lesions.

We also examined the WBC and RBC values of animals treated with canavanine, 2.0 or 3.0 g/kg. There were no differences in either of these blood parameters between treated and control animals following 1, 3, or 6 daily canavanine injections.

Treatment of Rat Colon Tumors with L-Canavanine. LD₀, LD₁₀, and LD₅₀ values with their 95% confidence limits were 4.75 g/kg (3.55 and 5.36 g/kg), 5.57 g/kg (4.67 and 6.03 g/kg), and 6.77 g/kg (6.33 and 7.18 g/kg), respectively. In all experiments, rats bearing the colon tumors were treated with daily doses of canavanine less than the single-dose LD₀. Standard doses below the LD₀ were selected because our experiments involved repeated administration; this repetitive regimen enhanced the toxicity of canavanine in rats.\(^\text{5}\) In experiments using

\(^{\text{4}}\) The abbreviations used are: T/C%, percentage of treated versus control; LD₀, LD₁₀, LD₅₀, L₀, 1, 10, or 50% lethal dose.

\(^{\text{5}}\) Unpublished observation, D. Thomas and G. Rosenthal.
all dosing schedules, tumor growth inhibition was statistically significant (P < 0.0025 in all cases) (Table 1).

The greatest antitumor response was observed in rats treated with canavanine, 3.0 g/kg daily for 5 or 9 days. These treatments, as indicated by the negative T/C% values in Table 1, caused the tumor to decrease in size. To determine the magnitude of tumor volume reduction, the percentage of regression was calculated by comparing final to initial tumor weight. These values indicated that the 3.0-g/kg-for-5-days treatment produced a 22% loss of tumor volume while the 3.0-g/kg-for-9-days dosing schedule caused a 60% diminution of the tumor. Although the 2.0-g/kg dosing regimens did not cause the tumor to recede, they did elicit significant growth inhibition, as demonstrated by T/C% values of 23% for the 5-day canavanine treatment (Table 1, Experiment 1) and 14% for the 9-day treatment (Table 1, Experiment 2).

Although the 60% reduction in tumor size following the 3.0-g/kg-for-9-days treatment was the most dramatic response observed, this canavanine dosing regimen was too severe for the rat to make it practical in treatment. Two of 5 animals died on the final day of the experiment and the mean decrease in body weight was 31%. Rats that received canavanine, 3.0 g/kg daily for 5 days (Table 1, Experiment 1) also exhibited regression of the tumor, but the 19 ± 2% (SE) loss in body weight also indicated an unacceptable toxicity with this dosing regimen. The animals of Experiment 3 (Table 1) suffered only a 12 ± 2% loss of body weight following the 3.0-g/kg-for-5-days treatment. These rats were observed for 6 days after canavanine treatment was discontinued; during this time, they began to recoup their initial weight loss. This finding demonstrated the animals' ability to recover from the toxic effects of canavanine when treatment was terminated.

Table 1 Growth inhibition of rat colon tumor by L-canavanine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial tumor wt (mg)</th>
<th>Final tumor wt (mg)</th>
<th>T/C (%)</th>
<th>Body wt net change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 g/kg</td>
<td>979 ± 336d</td>
<td>1320 ± 63</td>
<td>23</td>
<td>-13 ± 2</td>
</tr>
<tr>
<td>3 g/kg</td>
<td>849 ± 190</td>
<td>666 ± 414</td>
<td>-13</td>
<td>-19 ± 2</td>
</tr>
<tr>
<td>Control</td>
<td>773 ± 140</td>
<td>2230 ± 519</td>
<td>+18 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

(5-day treatment + 2 days to end of experiment. Final weight, day 7)

| Experiment 2 |                       |                    |         |                        |
| 2 g/kg | 748 ± 120 | 1450 ± 450 | 14 | -19 ± 3 |
| 3 g/kg | 692 ± 83 | 280 ± 57 | -8 | -31 ± 3 |
| Control | 861 ± 47 | 5870 ± 1160 | +23 ± 2 | |

(9-day treatment + 2 days to end of experiment. Final weight, day 11)

| Experiment 3 |                       |                    |         |                        |
| 2 g/kg | 702 ± 50 | 2560 ± 270 | 33 | -1 ± 1 |
| 3 g/kg | 717 ± 87 | 1300 ± 220 | 10 | -12 ± 2 |
| Control | 711 ± 36 | 6400 ± 410 | +25 ± 2 | |

(5-day treatment + 6 days to end of experiment. Final weight, day 11)

\* Estimated from caliper measurements using the formula

\[ V = \frac{1}{2} \times \text{Vol} \]

\* Actual weight of dissected tumor.

\* T/C% = \frac{\text{final tumor wt} - \text{initial tumor wt of treated tumors}}{\text{final tumor wt} - \text{initial tumor wt of control tumors}} \times 100.

\* Mean ± SE.

Rats that received canavanine, 2.0 g/kg daily for 9 days suffered a decrease in body weight (19 ± 3%) identical to the 3.0-g/kg-for-5-days group. In contrast, the 2.0-g/kg-for-5-days schedule produced a T/C% of 23% (Table 1, Experiment 1) without causing severe toxicity as demonstrated by a mean body weight loss of only 13 ± 2%.

Fig. 1 illustrates the time course of tumor growth following 5- and 9-day canavanine treatments (see Table 1, Experiments 1 and 2). Tumor regression in the 3.0-g/kg group as well as almost complete inhibition of tumor growth in the 2.0-g/kg group was evident in these growth curves. At 5 days, both treatments produced nearly identical tumor inhibition, demonstrating the reproducibility of the canavanine treatments. These growth curves demonstrated that the lower T/C% values for the 9-day treatments as compared to the 5-day treatments (Table 1, Experiments 1 and 2) were due primarily to the continued growth of the control tumor with time and not solely to increased inhibitory activity over the longer treatment period.

Experiment 3 (see Table 1) (Fig. 2) was conducted to monitor tumor growth for 6 days after cessation of canavanine treatment. These growth curves revealed that the rate of tumor growth returned to control values 2 to 3 days after canavanine administration was discontinued. As discussed above, the animals were able to recover their initial weight loss after canavanine treatments were terminated.

Effect of Caloric Restriction on Tumor Growth. The finding that tumor growth inhibition was associated with significant body weight loss raised the question of the contribution of caloric deprivation to the antitumor effects of canavanine. To test this important point, an experiment was instituted to assess the effect of reduced food intake on tumor growth. Careful monitoring of our experimental rats revealed a daily food consumption of approximately 22 g/animal/day. As a result, tumor-bearing rats were maintained on several feeding regimens: food ad libitum (control) and 10 or 5 g/day for 5 consecutive days. A final group received L-canavanine at a dose of 3.0 g/kg/day for 5 days. This group was used to verify that the tumor responded to canavanine treatment as in prior experiments.

The results of this study (Table 2; Fig. 3) provided a striking demonstration that food deprivation did not contribute to the capacity of canavanine to inhibit rat colon tumor growth. The food intake and weight loss of the 10-g/day group were almost identical to the canavanine, 3.0-g/kg treatment group making it an ideal comparison of the effects of restricted caloric intake to the effects of canavanine treatment on the colon tumor. Rats receiving 10 g of food/day exhibited a 14% reduction in body weight and consumed an average of 9.6 g of food/day. Rats that received canavanine, 3.0 g/kg/day suffered a 17% decrease in body weight and consumed 8.2 g of food/day; however, the T/C% values differed dramatically between the two groups. The T/C% values for the 10-g/day group and the canavanine treatment group were 193 and -17%, respectively. This indicated that rats receiving similar amounts of food and losing the same percentage of body weight as canavanine-treated animals experienced no reduction in tumor growth as compared to controls; therefore, restricted caloric intake cannot be responsible for the inhibitory effect of canavanine on the rat colon tumor.

The 5-g/day experimental group demonstrated that even when the rats ate less food (4.6 g/day) and lost more weight (25%) than the canavanine-treated animals, the growth of the tumor was not adversely affected.

DISCUSSION

Our studies represent the first evaluation of the effect of L-
canavanine on a solid tumor and demonstrate the ability of this natural product to produce significant growth inhibition of solid, colon tumors in rats. Substantial cumulative toxicity results in death to 2 of 5 rats in the 3.0-g/kg-for-9-days treatment group; however, canavanine toxicity is virtually eliminated when administered for 5 days at a 2.0-g/kg dose level while still producing a significant T/C value of 23%. Toxicity is reduced significantly when 3.0 g/kg is administered for 5 instead of 9 days, although the 19% body weight loss is still undesirable.

A need exists for additional study of appropriate dose levels and schedules to achieve maximum tumor inhibition while minimizing canavanine toxicity in the rat. The reason for the cumulative toxicity of canavanine also deserves detailed scrutiny, since reduction of toxicity would enhance the efficacy of this drug. The rate of tumor growth returns to control values 2 to 3 days after cessation of canavanine treatments and the animals begin to recover from their initial weight loss. These findings suggest that it may be possible to dose less frequently, since the tumors are depressed 2 to 3 days after canavanine treatments are discontinued. It may, for example, be possible to administer canavanine every second or third day and thereby minimize its cumulative toxicity or enhance its efficacy by extending the dosing schedule duration; alternatively, smaller but more frequently administered doses may be better tolerated by the animals while enhancing the efficacy of canavanine.

The observation that tumor growth inhibition was associated with body weight loss led us to determine the contribution of caloric deprivation to the efficacy of canavanine. Our results demonstrate convincingly that reduced caloric intake is not responsible for the antitumor action of canavanine and that this higher plant nonprotein amino acid has significant potential as an antitumor drug.

The biochemical bases for the antitumor effects of canavanine are unknown currently. Based upon the biochemical mode of action of canavanine, several hypotheses can be developed. Inhibition of tumor growth can result from canavanine incorporation into tumor proteins, causing the production of aber-

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**Fig. 1.** Tumor growth in male Fischer rats following canavanine, 2.0 (●) or 3.0 (○) g/kg daily for 5- (A) or daily for 9 days (B). Controls received a 0.9% NaCl solution (△). Tumor volumes, determined daily by caliper measurement, were estimated by $V = L \times w^2/2$. Treatments were initiated when tumors reached a size of 500 to 1000 mm$^3$. Rats were sacrificed 2 days after the last canavanine injection. The SE (bars) was omitted if it fell within the area occupied by the data point. $n = 5 \pm SE$.

**Fig. 2.** Tumor growth in male Fischer rats following canavanine, 2.0 (●) and 3.0 (○) g/kg daily for 5 consecutive days. Controls received a 0.9% NaCl solution (△). Rats were sacrificed 6 days after the last canavanine injection. See Fig. 1 for further experimental details. The SE (bars) was omitted if it fell within the area occupied by the data point. $n = 5 \pm SE$. 

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Table 2  Effect of caloric restriction on rat colon tumor growth

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial tumor wt (mg)</th>
<th>Final excised tumor wt (mg)</th>
<th>T/C (%)</th>
<th>Food eaten* (g/day)</th>
<th>Body wt net change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>673 ± 119*</td>
<td>1290 ± 220</td>
<td>21.8 ± 0.50</td>
<td>+9 ± 1</td>
<td></td>
</tr>
<tr>
<td>10 g/day</td>
<td>642 ± 44</td>
<td>1830 ± 220</td>
<td>9.6 ± 0.14</td>
<td>−14 ± 2</td>
<td></td>
</tr>
<tr>
<td>5 g/day</td>
<td>593 ± 37</td>
<td>1470 ± 200</td>
<td>4.6 ± 0.09</td>
<td>−25 ± 1</td>
<td></td>
</tr>
<tr>
<td>Canavanine</td>
<td>616 ± 80</td>
<td>510 ± 80</td>
<td>−17</td>
<td>8.2 ± 0.60</td>
<td>−17 ± 2</td>
</tr>
</tbody>
</table>

* Determined by caliper measurements and the formula

\[
\text{Vol} = \frac{1}{2} \times w^3
\]

\[
\text{T/C} = \frac{\text{Final tumor wt} - \text{initial tumor wt of treated tumors}}{\text{Tumors wt} - \text{initial tumor wt of control tumors}} \times 100.
\]

* Food eaten was less than the amount provided since food was lost from the cage.

* Mean ± SE.

The antitumor effects of canavanine may involve mechanisms that have been described for canavanine toxicity; that is, the production of aberrant canavanyl proteins, canavanine-free proteins are degraded inadvertently.

The antitumor effects of canavanine may involve mechanisms that have been described for canavanine toxicity; that is, the production of aberrant canavanyl proteins, canavanine-free proteins are degraded inadvertently.

Rat colorectal tumors are a major cause of cancer-related death, and canavanine as an antitumor agent. Further studies on the mechanism of action and toxicity of canavanine are planned to determine the potential therapeutic value of this drug. Along with developing dosing regimens to minimize toxicity, we are currently examining the effects of canavanine on human colon tumors xenografted in athymic nude mice to determine if the antitumor activity of canavanine extends to human tumors. We have also undertaken studies to compare the efficacy of canavanine to such standard therapeutic agents as 5-fluorouracil.

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