Effects of Some Tranquilizers on a Mammary Adenocarcinoma in Mice*

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Reserpine was reported recently to inhibit the growth of localized leukemic tumors in mice and to prolong their survival time (2, 3). Both reserpine and chlorpromazine were shown to inhibit the growth of Sarcoma 37 in mice (1). The purpose of this communication is to report the effects of these drugs and of related compounds on recently isolated transplants of a mammary adenocarcinoma in mice.

MATERIALS AND METHODS

An adenocarcinoma arising spontaneously in a Z(C3H) breeding female mouse was transplanted by trocar into ZBC mice and later retransplanted into other ZBC mice for succeeding generations. Only young female mice were used. The present work includes experiments with the second to the fourth generations of the same tumor.

Tumors were measured in two perpendicular directions with calipers to obtain their length and breadth. In most experiments, mice were divided into treatment and control groups when tumors measured approximately 1.5 × 1.8 mm. (10–14 days), care being taken to balance any variations in tumor sizes between the different groups. Usually, each group consisted of ten mice, five being housed to a cage. Therapy was administered either by mixing powdered drug (finely ground with mortar and pestle) with ground diet (Purina Fox Chow) given ad libitum or by daily intraperitoneal injections (six injections per week). For injection purposes, reserpine was dissolved in Vehicle C (Ciba) and other drugs in saline in sufficient concentration for the desired dose to be contained in 0.1 ml/20-gm mouse. Therapy was continued for 14 days. At autopsy, on the 15th day, tumors were dissected out and weighed on a Roller-Smith precision balance. Control mice were fed Purina Fox Chow kibbles and did not receive saline injections. Vehicle C was found to have no effect on tumor growth.

In two experiments therapy was started 3 days after transplantation of tumors and continued for 28 days. Twenty to 30 mice per group were used. In another experiment mice were treated for the usual 14 days, at which time the tumors were removed and transplanted into untreated recipient mice.

Tests for significance were made whenever the average treated tumor weight was inhibited by 25 per cent or more with five or more mice surviving.

RESULTS AND DISCUSSION

Results of most experiments are summarized in Table 1. Resperine was administered in drug-diet concentrations of 0.0005–0.001 per cent and by daily intraperitoneal injections of 0.05—0.8 mg/kg. In only one experiment, 0.001 per cent drug-diet for 14 days, was a significant decrease in tumor weight found. This showed significance at the 3 per cent level. Associated with this inhibition there was a decrease in body weight of 2.5 gm., which, in an experiment on restricted food intake,[1] caused significant inhibition in tumor growth. However, greater losses in body weight have been recorded frequently without any marked tumor inhibition. The same drug-diet concentration (0.001 per cent) given for 28 days was without effect. Daily intraperitoneal injections, even in toxic doses, were also without significant effect on tumor growth.

Chlorpromazine, by drug-diet administration or by daily intraperitoneal injections in close to toxic doses, showed no significant inhibition of tumor growth. Two closely related drugs, promazine and promethazine which, like chlorpromazine, are phenothiazine derivatives and are tranquilizers, also failed to induce tumor inhibition.

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To test for a possible effect on the transplantability of tumors, reserpine and chlorpromazine were given by drug-diet administration to donor mice for 14 days, at which time treated tumors were transplanted into untreated recipient mice, usually five mice receiving trocar pieces from one donor tumor. Results are shown in Table 2. A slight delay in the appearance of palpable tumors and a slight decrease in their growth up to 4 weeks were noted. It is doubtful whether any significance can be attached to this small difference. Mice were checked only once a week for tumor palpability and size. Also, this difference might be a reflection of the health of donor mice

TABLE 1

EFFECTS OF RESERPINE, CHLORPROMAZINE, PROMAZINE, AND PROMETHAZINE ON A MAMMARY ADENOCARCINOMA IN MICE

Drug	Dose, as DD conc.* or mg/kg I.P.	No. days therapy	No. mice surviving	Change body wt., treated/control (gm.)	Tumor wt., per cent change	No. deaths/ no. treated
Reserpine	.001%	14	26	−2.5/+1.3	− 64.6†	2/28
	.001%	28	42	−0.7/+3.2	− 6.5	8/50
	.00075%	14	10	+0.7/+3.1	− 7.3	0/10
	.0005%	14	10	−0.1/+1.6	− 15.8	0/10
	.8 mg/kg	7–13				10/10
	.4 mg/kg	14	10	−4.0/+1.4	− 31.2	15/25
	.2 mg/kg	14	25	−1.0/+1.5	+ 72.3	0/25
	.1 mg/kg	14	10	−0.7/+1.7	+ 35.2	0/10
	.05 mg/kg	14	10	+1.0/+1.7	+ 22.5	0/10
Vehicle C	.1 ml/20 gm	14	9	+1.4/+2.0	+ 16.0	0/9
Chlorpromazine	.3%	14	4	−3.6/+1.6	− 61.0	6/10
	.2%	14	15	0/+1.4	− 28.4	4/19
	.2%	28	18	+2.8/+6.4	− 56.6	1/19
	50 mg/kg	2–14				10/10
	25 mg/kg	14	25	−1.1/+1.8	− 27.2	5/30
	25 mg/kg	28	28	+1.6/+1.0	+ 35.0	2/30
Promazine	100 mg/kg	2–4				10/10
	50 mg/kg	14	7	−2.1/+1.4	+ 32.3	13/20
	25 mg/kg	14	10	−0.4/+1.7	+156.2	0/10
Promethazine	100 mg/kg	3–11				10/10
	75 mg/kg	14	5	−1.9/+1.7	+ 7.9	15/20
	50 mg/kg	14	10	0/+1.1	− 24.4	0/10

* DD means drug-diet concentration.

† "*t*" value is .03. Other inhibitions of over 25 per cent have "*t*" values over .05.

TABLE 2

EFFECTS OF RESERPINE AND CHLORPROMAZINE ON THE TRANSPLANTABILITY OF TUMORS

Reserpine, 0.001 per cent DD, and chlorpromazine, 0.2 per cent DD, were given to donor mice for 2 weeks, at which time tumors were transplanted by trocar to untreated recipient mice.

		Donor mice		
	No.	Size of tumor in mm.*		Change in body wt.
Treatment	mice	Start	2 wk.	(gm.)
Reserpine	10	1.6×1.8	5.4×5.7	−2.1
Chlorpromazine	10	1.5×1.8	4.4×5.3	−0.8
Controls	10	1.5×1.8	4.2×5.6	+1.8

				Recipient mice†		
				Size of tumor in mm.		
Donor mice	No. donors	No. recipients	Tumor palpable. (wk.)	4 wk.	8 wk.	10 wk.
Reserpine	10	46	2.3	3.3×4.1 (46)	8.5×11.7 (45)	9.9×16.2 (45)
Chlorpromazine	10	42	2.9	3.1×3.9 (42)	9.4×12.8 (42)	11.8×16.0 (38)
Controls	10	48	1.8	4.2×5.8 (48)	9.2×11.0 (46)	12.2×16.2 (45)

* Size represents the average diameter of tumors taken in two perpendicular directions, giving length and breadth.

† Tumors failed to become established in three of 49 reserpine recipients, in six of 48 chlorpromazine recipients, and in two of 50 control recipients. These mice are excluded from the calculations. Numbers in parentheses represent number of mice alive.

rather than evidence of any specific antitumor effect, since treated donor mice had lost weight, whereas control donor mice had gained weight.

These experiments seem to demonstrate the lack of any specific inhibitory action of reserpine, chlorpromazine, promazine, and promethazine on recent isolates of a mammary adenocarcinoma in mice. The difference between these results and the beneficial effects reported for reserpine and chlorpromazine in leukemia and on Sarcoma 37 (1–3) may be owing to a more specific action of these drugs on the latter types of tumors or possibly to the difference in methods of administration. Goldin *et al.* (2) gave single doses of 10–40 mg/kg of reserpine. The higher and more effective doses caused deep depression, with failure to eat or drink for a week or more in both leukemic and nonleukemic mice. However, Goldin *et al.* reported that similar restriction in food and water intake alone did not decrease growth of local leukemic tumors nor increase survival time and that overcoming the resperine depression with *d*-amphetamine did not alter the antileukemic effect of reserpine. Single doses of 50 mg/kg of reserpine were given by Belkin *et al.* (1). This induced deep tranquilization and death of 56 per cent of mice within 6 days. Chlorpromazine was used by the latter authors in doses of 25 and 50 mg/kg, followed by a second dose of 25 mg/kg 2 days later. Deep tranquilization developed, with a mortality of 70–80 per cent within 5 days.

In the experiments reported in this paper drugs were administered for 2 weeks or more. A drug-diet concentration of 0.001 per cent reserpine usually produced no specific evidence of sedation but occasionally caused loss of appetite, cold skin, and mild to moderate depression. Higher concentrations were found to lead to severe weight loss. Daily doses of 0.2 mg/kg of reserpine intraperitoneally did not produce sedation; twice this amount was definitely toxic, as evidenced by humped back, cold skin, sluggishness, loss of body weight, and a 60 per cent mortality at 2 weeks; but, when picked up, mice did not appear tranquil. With chlorpromizane, 0.2 per cent drug-diet administration led to no evidence of depression; daily doses of 25 mg/kg intraperitoneally caused unconsciousness for a few hours after each injection, but 25 of 30 mice survived this dose for 2 weeks in one experiment and 28 of 30 mice survived it for 4 weeks in another experiment (Table 1), giving a much lower mortality rate than that found by Belkin *et al.* (1). Daily doses of 25 mg/kg of promazine and 50 mg/kg of promethazine caused sluggishness lasting an hour or 2 after each injection, but unconsciousness did not occur.

SUMMARY

Reserpine, chlorpromazine, promazine, and promethazine lacked significant inhibitory action on the growth of recently isolated transplants of a spontaneous mammary adenocarcinoma in mice.

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