Cancer Chemother. Pharmacol. 3, 121–124 (1979)

Cancer Chemotherapy and Pharmacology

Clinical Study of Hydrazine Sulfate in Advanced Cancer Patients

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Summary. *Twenty-five patients with a variety of solid tumors were treated with hydrazine sulfate. Hydrazine was given orally in the form of 60 mg capsules from one to four times daily. No patient had a 50% reduction of tumor size. Subjective benefit was seen in three patients but it was of brief duration.*

Introduction

Hydrazine sulfate has been tested as an antitumor agent in animals [2, 4, 5] and in man [1, 8–10, 12, 14]. These trials were based on Gold's [2, 7] proposal that the separate pathways of glycolysis in cancer cells and gluconeogenesis in normal cells constituted a systemic metabolic circuit capable of draining significant amounts of energy from the body. He postulated that this mechanism was responsible for cancer cachexia, and he further suggested that interruption of gluconeogenesis at the phosphoenolpyruvate carboxykinase (PEP CK) reaction could result in a measurable anticachexia or anticancer effect.

There were reports of patient response from Gold [8]. Ochoa et al. [10], Lerner and Regelson [9], and others [14] have reported negative results. However, Russian investigators have recently supported Gold's observations in both laboratory models [13] and clinical trials [1, 12].

Our group was the first to enter into an FDA approved clinical trial of hydrazine sulfate. In addition to looking for antineoplastic activity, we evaluated each patient for changes in weight and for improvement in mood. We have decided to report our negative results at this time because the positive results reported by Gershanovich [1], Seits [12], and Shapot [13] have again raised the question of possible antitumor activity of this agent.

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Materials and Methods

Following FDA and insitutional approval, hydrazine sulfate was obtained from the Calbiochem Company (San Diego, California, 92112) in 60 mg capsules. Analysis of hydrazine sulfate has revealed no mislabeling and has shown that the chemical activity of hydrazine sulfate was unchanged after 3 years.

Hydrazine sulfate was given as a 60 mg capsule three times a day. The full dose was introduced over a 4 day period so that on days 1 and 2 the patient received one capsule and on days 3 and 4 the patient took one capsule twice a day. Patients who had no side effects after 4 weeks of treatment had their dose increased to 60 mg qid. The capsules were taken with milk or honey prior to meals.

Dose reduction was allowed for hypoglycemia, peripheral neurophathy, or central nervous system symptoms. The appearance of any of these problems caused dose reduction to one capsule per day. If the problem persisted the patient was to be taken off study.

Only patients with recurrent advanced cancer not curable by surgical resection or radiotherapy were entered into the study. Patients who had either measurable or evaluable disease were included, provided survival was estimated at greater than 1 month.

Most patients either had tumors for which no standard chemotherapy was available or were refractory to standard agents. The patients with ovarian carcinoma and breast carcinoma had not received prior treatment with adriamycin.

Study parameters obtained included weight, tumor measurement, CBC/platelet count, SGOT, LDH, bilirubin, alkaline phosphatase, BUN, creatinine, albumin, total protein, and calcium, recorded prior to study and at weekly intervals.

Results

Twenty-five patients were treated with hydrazine sulfate as a single agent. Age of patients, sex, tumor type, prior treatment, length of time on study, total dose of hydrazine, response, and reason for stopping the drug are shown in Table 1.

Two patients (JM and EC) noted slight subjective improvement consisting of transiently increased appetite. Their tumor types were adenocarcinoma of the lung and pleural mesothelioma. One of these two patients gained 2 lb, while the other lost weight. Among the re-

0344-5704/79/0003/0121/$ 01.00

Table 1. Patient characteristics

Patient	Age/Race/ Sex	Tumor	M or E[a]	Length of time on study days	Total dose of hydrazine mg	Response	Reason to stop drug
ER	54 W M	Hypernephroma	M pulmonary	29	4980	None	Weight loss
DH	50 W M	Colon	E ascities	20	3360	None	Progression
ISG	69 W F	Breast	M skin	10	1560	None	Dizziness
COK	66 W F	Breast	M skin	47[b]	5280	Physical exam. showed some increase in lung aeration	Progression
MJ	65 W F	Ovary	E ascites	34	5880	None	Progression
MAS	54 W F	Melanoma	M skin	19	3240	None	Progression
RG	83 W F	Squamous-cell query primary	M nodes	11	1740	None	Died
GP	57 W M	Melanoma	M skin	19	3180	See case history	Progression
WB	59 W M	Lymphoma	E	1	60	None	Died
CH	52 B M	Adenocarcinoma probably pancreas	M nodule	7	900	None	Progression
AF	49 W F	Breast	M skin	4	360	None	Patient and family wanted no further treatment
JFM	66 W M	Alveolar cell carcinoma of lung	E pleural effusion	29	4980	None	See case history
ED	61 W F	Oat cell	E	14	2280	Lost to	Follow-up
LW	68 W F	Adenocarcinoma of lung	E	7	900	None	Died
EC	50 W M	Adenocarcinoma of lung	M	16	2640	See case history	Progression
MN	59 W F	Breast	M skin	4	240	None	Dysphagia
RB	31 B M	Colon	E liver, Brain	6	720	None	Died
JM	66 W M	Mesothelioma	E pleura	7	900	See results	Progression
MH	27 W F	Carcinoma of rectum	E liver	7	900	None	Died
CW	50 B M	Linitis plastica stomach	M liver	7	900	None	Dysphagia
MFH	56 B F	Ovary	M	9	1380	None	Died
JAT	14 B F	Hepatoma	M liver	11	1740	None	Died
AC	48 W F	Ovary	M nodes	16	2640	None	Patient request
CW	54 W M	Multiple myeloma	E	20	–	None	Unknown
CG	55 W F	Squamous-cell carcinoma esophagus	E	Dose not increased at 4 weeks; 42 days	5320	None	Died

[a] M, measurable; E, evaluable
[b] Started at 30 mg tid because of weight loss

Table 2. Toxicity

Toxic effect	Dizziness	Hypoglycemic	Flushing after alcohol ingestion
No. of patients	1	1	1

maining 23, one patient's weight remained stable and all other patients lost weight or had weight gain attributable to ascites, edema, or pleural effusion.

No patient achieved objective tumor regression by the conventionally defined 50% decrease of measurable tumor. One patient with malignant melanoma showed slight measurable regression (less than 50%) of subcutaneous nodules for a 2 week period. There was no change in his liver disease. This 57-year-old white male had axillary and liver metastasis. He had had previous treatment with dacarbazine and methyl-CCNU, carmustine, tilorone, and vincristine. Hydrazine sulfate was started 3 weeks after the last dose of chemotherapy. He survived $1\frac{1}{2}$ months after the start of the hydrazine study. Another patient with evaluable chest-wall disease from breast cancer and a pleural effusion had an improvement in the aeration of her lung for 3 weeks.

One patient with cancer of the breast experienced dizziness while on hydrazine sulfate. The drug was stopped for 3 days, with clearing of the dizziness. When hydrazine was resumed, dizziness recurred. One patient (JFM) with alveolar cell carcinoma of the lung developed hypoglycemia (glucose 68 and 38 mg%) during treatment. This same patient noted flushing after alcohol ingestion. Liver function tests, CBC, and BUN were obtained at frequent intervals. No evidence of hydrazine toxicity was seen in these laboratory values (see Table 2).

Discussion

No significant responses were seen in the hydrazine sulfate treated patients.

The median length of time on study was only 2 weeks. Even in this short time, progressive disease was the most common reason for removing the patient from study.

Clinical study of hydrazine sulfate was restricted to a total daily dose of 180 mg or 240 mg, which comes to approximately 2.5 mg/kg/day, divided into three, or at most four, doses. These levels were recommended by Gold [8], and escalation of the dose was restricted because of anxiety about the theoretical liver toxicity or hypoglycemic action of the drug.

This dosage is far below the toxic doses used in animal toxicology in preclinical studies. In these studies, 12 rhesus monkeys received daily doses of hydrazine ranging from 5–20 mg/kg, given in 4–20 injections. All animals lost weight during the administration of hydrazine. In monkeys, serum glutamic oxalacetic transaminase and bilirubin rose with doses of 20 mg/kg. At these high levels, loss of appetite, vomiting, lethargy and severe weakness were seen, with evidence of liver, muscle, and kidney changes [11].

In our study, the upper limit of clinical toxicity was not determined and we limited our dosage to a maximum of 240 mg/day (between 2 and 3 mg/kg/day). The majority of patients received only 180 mg/day.

Despite the absence of clinical response in our patients, it is important to indicate the logical theoretical considerations that led to clinical testing of hydrazine sulfate. These were based on the concept that tumors have a preferential glycolytic capacity for energy metabolism. Hydrazine is an inhibitor of PEP CK, so by blocking this step one might interfere with gluconeogenesis; this in turn would block an alternative source of glucose for the tumor and thus prevent the wasting of protein resources, which is responsible for cachexia [7, 3].

Gold has reported that hydrazine sulfate has antitumor activity against Walker 256 intramuscular carcinoma in rats [4]. He further reports hydrazine sulfate to be active against B-16 melanoma and Murphy-Sturm lymphosarcoma [5]. Although hydrazine sulfate by itself did not show a significant degree of activity in L1210 leukemia, in combination with Cytoxan, mitomycin-C or bleomycin the antitumor effects seen were reported to be greater than with the single drug [5].

The details of several clinical trials with hydrazine sulfate have been published. The first study, which began almost simultaneously with ours, was conducted by Ochoa et al. [10] at Memorial Sloan-Kettering, and involved 32 patients. No evidence of antitumor effect was reported. In contrast to our experience, 50% of the Memorial patients had peripheral neuropathy, with paresthesias being the most common side effect. It is of interest that we saw no paresthesias in our study, although dosage and patient selection appeared to be similar.

Our toxic findings were minimal, and similar to those described in other reports, including that by Gershanovich et al. [1] where paresthesias were not a significant problem, occurring in only 3 of 102 patients. In that study, nausea and vomiting were seen in 14 of 102 patients. Occasional (11 of 102) patients showed CNS effects (dizziness, hallucinations, general excitement, and insomnia), most of which occurred after 2 weeks of drug therapy.

Positive results have been reported by Gold [8], Seits et al. [12], and Gershanovich et al. [1]. Gold's review was based on studies reported to Calbiochem, where 84 of 158 cases were evaluable. Fourteen of 84

cases showed objective response, and 59 of the 84 reported subjective improvement while on hydrazine sulfate. Of the subjective response group, 42% were receiving no concurrent chemotherapy, while 50% of objective responders had no other treatment. In Gold's summary of this experience, responses included stabilization of disease and survival greater than expected. Certainly this is not what we have seen, but it is similar to what Seits et al. [12] and Gershanovich et al. [1] have indicated.

Gershanovich et al. [1] reported on 18 evaluable lung cancer patients, stabilization or regression being recorded in eight. They reported subjective improvement (appetite, activity) in 55%, with objective regression (greater than 50% reduction of tumor mass) in only 3%. In addition, mobilization of ascites and pleural effusion was observed in another 3%. The drug dose used in this study was quite comparable to ours. Their patients received 60 mg on days 1–3, 60 mg bid on days 4–7, and 60 mg tid thereafter. This study seems to support a role for hydrazine sulfate in stabilization of tumor growth.

In contrast to Gershanovich's and Gold's reports [1, 8], the subjective alteration in our patients was not impressive. We saw no significant effect on appetite, activity, or weight loss.

In conclusion, we feel that hydrazine sulfate as given in this study is an inactive compound.

Acknowledgements: We wish to thank William Banks, Ph.D., for performing the hydrazine sulfate assay, and Mario Kupermic, M.D., Susan Mellette, M.D., and Paul Richter, M.D., for patient referrals.

This work was supported by NIH Grant CA-10572.

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Received December 27, 1978/Accepted May 3, 1979