

GAO

Report to the Chairman and Ranking
Minority Member, Human Resources and
Intergovernmental Relations
Subcommittee, House Committee on
Government Reform and Oversight

September 1995

CANCER DRUG RESEARCH

Contrary to Allegation, NIH Hydrazine Sulfate Studies Were Not Flawed



**Health, Education, and
Human Services Division**

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September 13, 1995

The Honorable Christopher Shays
Chairman
The Honorable Edolphus Towns
Ranking Minority Member
Human Resources and Intergovernmental
Relations Subcommittee
Committee on Government Reform and Oversight
House of Representatives

Cancer takes almost 500,000 lives annually and is the second leading cause of death in the United States. About 400,000 of the 1 million Americans who will develop cancer this year, however, will be cured.¹ Despite advances in treating cancer, some forms of cancer are often resistant to current therapies and have a very poor outcome. Based on the findings of an earlier study that suggested the drug hydrazine sulfate may improve survival for some patients with advanced cancer, the National Cancer Institute (NCI) sponsored three studies of hydrazine sulfate.

All three NCI-sponsored studies, however, failed to demonstrate any benefit from hydrazine sulfate. The developer of hydrazine sulfate therapy alleged in documents furnished to the Subcommittee that NCI compromised its studies on hydrazine sulfate. He asserted that the NCI-sponsored clinical trials² did not demonstrate any benefit for hydrazine sulfate because NCI's clinical investigators permitted the concurrent use of tranquilizers, barbiturates, and alcohol. He and other proponents of hydrazine sulfate therapy have interpreted animal studies and other data to suggest that hydrazine sulfate is incompatible with these agents. This allegation was echoed in the popular media.

This report responds to your request that we provide further information about the NCI-sponsored clinical trials of hydrazine sulfate. It provides background on the trials, including information on protocol design and data management procedures. It also discusses how NCI and the trials' investigators dealt with the issue of potential incompatibility with certain agents, the extent to which patients may have received these agents, and how this issue was reported.

¹Cured is defined as being free of any evidence of cancer for 5 years or more. These cured individuals will have the same life expectancy as others of the same age and sex who have never had cancer.

²Clinical drug trials involve testing a new drug in humans to determine whether it has therapeutic benefit.

To obtain information for this report, we reviewed NCI's policy guidance for conducting clinical trials of investigational agents. We also reviewed agency memorandums pertaining to protocol development for the hydrazine sulfate clinical trials and related correspondence. For each of the hydrazine sulfate clinical trials, we visited the research facilities and reviewed a sample of the research records documenting patient medications, including concurrent antiemetic (antinauseant and antivomiting) and barbiturate medications.³ We discussed the conduct of these trials with NCI officials and investigators, Food and Drug Administration (FDA) officials, and proponents of hydrazine sulfate therapy to obtain their perspectives on the issues involved. A more detailed description of our scope and methodology is in appendix I.

Results in Brief

In three large clinical trials, NCI found that hydrazine sulfate did not prolong survival for cancer patients. Nevertheless, controversy and confusion developed, in part, because some researchers have suggested that hydrazine sulfate is incompatible with tranquilizers, barbiturates, and alcohol. In testing hydrazine sulfate, NCI permitted study patients to use tranquilizing agents, barbiturates, and alcohol in one NCI-sponsored clinical trial. In the other two trials, NCI prohibited the use of barbiturates and alcohol, but patients were permitted to use tranquilizing agents as antiemetics to control nausea and vomiting. However, subsequent analyses of the use of concurrent medications found no evidence to invalidate NCI's conclusion that hydrazine sulfate is ineffective.

Nonetheless, there were lapses in record-keeping and reporting in these clinical trials. NCI did not require that complete and accurate research records be kept during one clinical trial documenting the use of tranquilizing agents, barbiturates, and alcohol by study patients. Also, NCI-sponsored investigators did not analyze this issue until recently, and the published results did not accurately describe the use of tranquilizing agents during one of these clinical trials.

FDA may have contributed to the confusion surrounding these trials of hydrazine sulfate with its more conservative position on how the drug should be administered to some patients. While accepting NCI's study designs and therapy plans, FDA apparently had concerns over possible incompatibility. About the same time these three trials were occurring, FDA approved more than 70 applications permitting the compassionate use of hydrazine sulfate. These approvals were accompanied by an FDA caution to

³Information was not available for us to document possible alcohol use by study patients.

physicians that their patients should avoid taking tranquilizers, barbiturates, or alcohol while taking hydrazine sulfate. Other FDA documents reflect this same concern.

Background

NCI, within the National Institutes of Health (NIH), Public Health Service, Department of Health and Human Services, is the world's largest sponsor of clinical trials in cancer treatment research. NCI spends about 20 percent of its research budget on clinical trials. Using its clinical trials network that includes cooperative groups,⁴ NCI funds therapeutic research that includes evaluating the safety and efficacy of investigational drugs in large multicenter clinical trials. NCI also sponsors therapeutic drug development through the submission of investigational new drug (IND) applications to FDA.

FDA is responsible for ensuring the safety of the public in matters related to clinical research with investigational drugs. FDA regulations define the terms under which clinical research may proceed. Through the INDS, FDA reviews the experimental rationale for conducting clinical drug trials, including results of animal toxicology studies, manufacturing data, purity and stability information, and an initial plan for clinical investigation. The responsibility for monitoring the trials rests with the sponsor.

Early Studies of Hydrazine Sulfate Found Mixed and Inconclusive Results

Unexplained weight loss and physical deterioration of the body (cachexia) commonly accompany advanced cancer. Moreover, cachexia is associated with decreased survival. For example, data have shown that in patients with lung cancer, weight loss is associated with a 50-percent reduction in survival time.

Joseph Gold, M.D., director of the Syracuse Cancer Research Institute in New York, proposed a theory to explain why cachexia commonly accompanies advanced cancer. After extensive research, Dr. Gold proposed the use of hydrazine sulfate, a chemical that interrupts the abnormal sugar metabolism associated with weight loss, to arrest and reverse cancer cachexia.

⁴Clinical cooperative groups are composed of multiple institutions and investigators who collaborate to develop and implement treatment research in large numbers of patients. There are 11 cancer clinical cooperative groups, and all involve highly organized collaborations among geographically dispersed institutions with central data management offices and large statistical centers that support the administrative requirements of the research and perform data collection and analysis.

In 1973, Dr. Gold reported on results of animal tests indicating that hydrazine sulfate inhibited the growth of various rodent tumors and enhanced the antitumor action of some chemotherapeutic drugs. In 1975, Dr. Gold reported the results of hydrazine sulfate's use in cancer patients. Using reports from physicians whose advanced cancer patients were taking hydrazine sulfate, Dr. Gold noted several cases of tumor regression and subjective improvement in cancer patients treated with hydrazine sulfate. Additionally, Russian investigators have claimed some successes with hydrazine sulfate for more than 20 years.⁵ Although early clinical studies conducted in the United States found mixed results, later studies evaluating hydrazine sulfate as an anticachexia agent suggested that the drug benefited some cancer patients.

In the 1980s, studies at the Harbor-University of California Los Angeles (UCLA) Medical Center indicated that adding hydrazine sulfate to a standard chemotherapy regimen improved the nutritional status and survival time of some cancer patients. Of particular interest was a randomized clinical trial—involving 65 patients with advanced, inoperable non-small-cell lung cancer⁶—that compared chemotherapy and hydrazine sulfate with chemotherapy and placebo. Data from the study suggested that hydrazine sulfate may benefit some cancer patients. While overall survival differences between the two treatment groups were not significant, researchers found that hydrazine sulfate improved survival in a subset of study patients who began the trial in better overall condition. Given the inconclusiveness of the study, UCLA investigators believed that further trials of hydrazine sulfate were warranted to determine its effectiveness in improving survival.

NCI-Sponsored Trials Found Hydrazine Sulfate Ineffective

NCI sponsored three clinical trials that were designed to assess the effect of hydrazine sulfate on survival, weight gain, and quality of life. Two trials in patients with advanced lung cancer assessed the efficacy of hydrazine sulfate as an adjunct to chemotherapy. One of these trials, in patients with

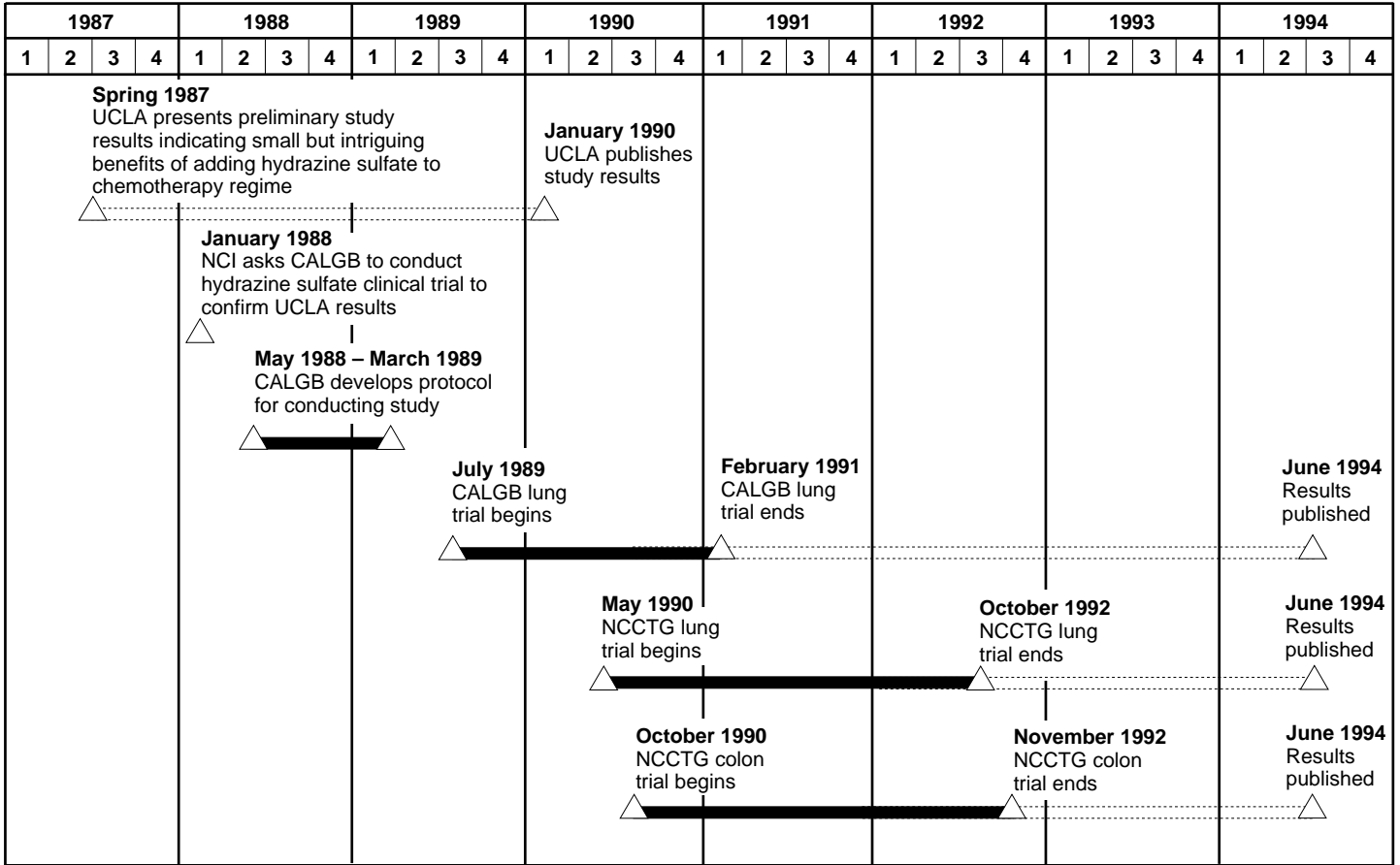
⁵The Russian studies, however, were not randomized or blind and have involved various types and stages of cancer. Randomized clinical studies are the “gold standard” for evaluating medical interventions. In a randomized study, each patient is randomly assigned to one of a number of treatments in order to ensure unbiased comparison of outcomes. Random assignment is the best method for ensuring that the patients in each group have equivalent prognoses. Because the groups should not differ on variables related to cancer survival, their outcomes can be directly compared, and any difference in survival can be attributed to the difference in treatment.

⁶Non-small-cell lung cancer is commonly used as a catchall phrase to include all of the primary malignant lung cancers except small cell and accounts for approximately 70 to 80 percent of lung cancers. Almost all primary malignant cancers of the lung are one of four types: squamous cell carcinoma (cancer originating in the glandular, skin, or linings of internal organs), adenocarcinoma, large cell carcinoma, and small cell carcinoma.

advanced lung cancer, was conducted by the Cancer and Leukemia Group B (CALGB) and led by a principal investigator at the Scripps Clinic and Research Foundation in San Diego, California.⁷ The other trial in advanced lung cancer patients, was conducted by the North Central Cancer Treatment Group (NCCTG) and led by a principal investigator at the Mayo Clinic in Rochester, Minnesota. The third trial assessed the efficacy of hydrazine sulfate as the sole medical intervention in patients with advanced colon cancer. This trial was also conducted by NCCTG and led by the same principal investigator at the Mayo Clinic. Figure 1 shows highlights of activities surrounding NCCTG's and CALGB's clinical trials of hydrazine sulfate.

⁷We are using the term principal investigator to describe the role of the scientific coordinator (protocol chair) of a multicenter clinical trial. The principal investigator is responsible for developing and monitoring the study as well as analyzing, reporting, and publishing its results.

Figure 1: Time Line of the UCLA and NCI-Sponsored Clinical Trials of Hydrazine Sulfate



The NCI-sponsored clinical trials did not find the survival advantage observed in the earlier UCLA study. Results from the three clinical trials were published in June 1994.⁸ The data showed that hydrazine sulfate therapy does not result in any significant benefit. Specifically, in two trials involving over 500 patients with inoperable non-small-cell lung cancer, the

⁸Results of the three studies of hydrazine sulfate supported by NCI were published in the *Journal of Clinical Oncology*, Vol. 12 (June 1994), pp. 1113-29. The articles were "Cisplatin, Vinblastine, and Hydrazine Sulfate in Advanced, Non-Small-Cell Lung Cancer: A Randomized Placebo-Controlled, Double-Blind Phase III Study of the Cancer and Leukemia Group B," by Michael P. Kosty and others; "Randomized Placebo-Controlled Evaluation of Hydrazine Sulfate in Patients With Advanced Colorectal Cancer," by Charles L. Loprinzi and others; and "Placebo-Controlled Trial of Hydrazine Sulfate in Patients With Newly Diagnosed Non-Small-Cell Lung Cancer," by Charles L. Loprinzi and others.

addition of hydrazine sulfate to a standard chemotherapy regimen resulted in somewhat worse quality of life, no effect on weight gain or loss, and a suggestion of decreased survival when compared with placebo. In the trial evaluating the use of hydrazine sulfate as the sole therapeutic intervention in 127 patients with metastatic colon cancer, survival time for patients receiving hydrazine sulfate was decreased compared with patients given placebo.

Negative Trial Results Contested

Criticisms regarding the design of the three clinical trials arose in the media. Proponents of hydrazine sulfate therapy alleged that NCI compromised the trials by permitting study patients to ingest agents that they believe are incompatible with hydrazine sulfate. Some proponents believed that the concurrent use of tranquilizers, barbiturates, or alcohol with hydrazine sulfate would nullify the therapeutic effect of hydrazine sulfate and cause toxicity in patients. They based their beliefs on Russian and unpublished animal studies as well as some pharmacological data that they said suggested that hydrazine sulfate interacts with tranquilizing agents (particularly tranquilizing agents classified as benzodiazepines), barbiturates, and alcohol.⁹

NCI Concluded Concerns That Hydrazine Sulfate Was Incompatible With Some Agents Were Unfounded

NCI rejected concerns that the concurrent use of hydrazine sulfate with tranquilizers, barbiturates, or alcohol would nullify the therapeutic effect of hydrazine sulfate. NCI concluded that there was no objective evidence or published studies of humans addressing interactions between hydrazine sulfate and these alleged incompatible agents to support the concerns. NCI concluded that, at most, Russian animal data suggested that large doses of alcohol or barbiturate medications consumed with hydrazine sulfate can increase the total overall toxicity. NCI also concluded that unpublished animal data did not support the hypothesis that the short-term use of tranquilizing agents with hydrazine sulfate would increase toxicity or prevent clinical benefit. These conclusions were based on the assessment of NCI scientists in consultation with CALGB and NCCTG researchers. In addition, NCI officials told us that because the UCLA study did not specifically prohibit patients from taking barbiturates and tranquilizers or

⁹Dr. Mikhail Gershanovich, one of Russia's leading cancer specialists and a professor at the Petrov Research Institute of Oncology, told us that he had no evidence of incompatibility between hydrazine sulfate and tranquilizers. He confirmed, however, that his studies with hydrazine sulfate have demonstrated an incompatibility with barbiturates and alcohol.

consuming alcohol, the NCI-sponsored confirmatory trials did not have to be any different in that regard.¹⁰

Nevertheless, in response to the issue of incompatibility, NCCTG investigators (at the Mayo Clinic) prohibited patients from taking barbiturates or consuming alcohol. Furthermore, patients were prohibited from taking tranquilizing agents, except for antiemetic purposes. The NCCTG principal investigator told us that he felt it would have been unethical to perform either of the Mayo clinical trials without allowing the use of antiemetic drugs, including drugs otherwise considered to be tranquilizers, by patients experiencing nausea or vomiting.

CALGB investigators, however, decided that it was more important to replicate the UCLA trial than attempt to address concerns of incompatibility by prohibiting the use of tranquilizers, barbiturates, and alcohol. Because the NCI-sponsored trials were designed to confirm the improved survival observed in the UCLA trial, CALGB investigators believed they should use essentially similar methods to those used in the earlier UCLA trial.

NCI-Sponsored Trials Included Some Use of Tranquilizing Agents

Published reports of the three trials did not disclose the extent of tranquilizer use among study patients. In examining research records, however, we found that patients in all three NCI-sponsored clinical trials of hydrazine sulfate were prescribed tranquilizers under varying conditions. In the NCCTG and CALGB clinical trials in non-small-cell lung cancer, virtually all patients received a variety of antiemetic drugs, particularly tranquilizing agents, for the short-term relief of chemotherapy-induced vomiting.

Our review of over 50 percent of CALGB's standard research forms revealed that patients with advanced lung cancer routinely received benzodiazepine and phenothiazine tranquilizing agents to relieve the nausea and vomiting associated with chemotherapy. Although CALGB investigators decided not to collect data on concurrent medications on their standardized research forms, some research associates voluntarily provided information on antiemetic usage. Data on the use of antiemetic medications for about half of the patients in our review were recorded on the research forms. Our analysis of research forms listing antiemetic medications revealed that

¹⁰Initially, there was some confusion surrounding whether these alleged incompatible agents, particularly tranquilizers, were permitted in the UCLA trial. Reports in the media were apparently inaccurate in suggesting that the UCLA researchers did not allow patients to take tranquilizers. Some of the confusion may have developed because in research documents describing protocols for other trials of hydrazine sulfate, UCLA researchers previously expressed concerns over potential incompatibility with hydrazine sulfate and alcohol, tranquilizers, and barbiturates. As noted on p. 10, however, the principal researcher said he did not have such concerns in the more recent UCLA trial.

88 percent of the patients received benzodiazepine and 71 percent received phenothiazine tranquilizing agents.^{11,12} Generally, it appeared that most patients were prescribed tranquilizing medications for short-term emetic relief. In several instances, however, patients were prescribed tranquilizing agents on an “as needed” continual basis. We also found one instance where a patient was prescribed a barbiturate.

At our request, NCTG and CALGB research associates reviewed research forms, medical records, or both for patients enrolled in their lung cancer trials to collect data on the concurrent use of antiemetic and barbiturate medications. Table 1 shows the number of patients receiving hydrazine sulfate and various antiemetic medications.

Table 1: Number of Patients Receiving Specific Antiemetic Medications Along With Hydrazine Sulfate in the Lung Cancer Clinical Trials

| Medication | CALGB trial (n=135) | NCCTG trial (n=116) |
|-----------------------|----------------------------|----------------------------|
| Benzodiazepines | 119 | 43 |
| Lorazepam | 113 | 43 |
| Other | 6 | 0 |
| Phenothiazines | 108 | 43 |
| Prochlorperazine | 98 | 37 |
| Other | 10 | 6 |
| Serotonin antagonists | 0 | 91 |
| Ondansetron | 0 | 90 |
| Other | 0 | 1 |

Investigators said it was necessary to prescribe antiemetic medications, including tranquilizing agents, to patients in all three clinical trials. In the two clinical trials involving patients with advanced lung cancer, patients received chemotherapy in addition to hydrazine sulfate or placebo. Because the chemotherapeutic regimen used to treat advanced lung cancer induces severe nausea and vomiting in almost all patients, NCTG and CALGB investigators did not deem it feasible or ethical to administer chemotherapy without the concurrent use of antiemetic drugs.

During the time when NCTG and CALGB were conducting their trials, the most effective antiemetic regimens available involved the use of tranquilizing agents. Accordingly, many study patients in both clinical

¹¹The primary benzodiazepine and phenothiazine drugs prescribed were lorazepam (Ativan) and prochlorperazine (Compazine), respectively.

¹²Our results closely paralleled the results obtained in a comprehensive subsequent review done by CALGB and presented in table 1.

trials were prescribed phenothiazines and benzodiazepines.¹³ Although patients in NCCTG's colon cancer trial were not undergoing chemotherapy, some patients with advanced colon cancer experience nausea and vomiting associated with their disease. NCCTG and CALGB investigators told us that they would not deny standard medical care to control nausea and vomiting in patients who were dying from cancer.

Also, patients enrolled in the UCLA clinical trial reportedly received tranquilizing agents while taking hydrazine sulfate. Medical records for 40 study patients treated at Harbor-UCLA Medical Center indicated that 22 patients received hydrazine sulfate and chemotherapy.¹⁴ In addition, these patients received tranquilizing agents to control their chemotherapy-induced vomiting. Specifically, patients who received hydrazine sulfate also received a total of 16 doses of benzodiazepines and 20 doses of phenothiazines. Other possible uses of tranquilizing agents and barbiturates outside of chemotherapy treatment as well as possible alcohol use are not known.

Retrospective Analyses Found No Evidence of Adverse Effects From the Use of Allegedly Incompatible Drugs

Analyses of data from NCI-sponsored clinical trials found no evidence of adverse effects on survival associated with hydrazine sulfate and the use of tranquilizing agents as antiemetics and barbiturates. Researchers at the Mayo and Scripps clinics retrospectively analyzed clinical trial data in an attempt to address the issue of incompatibility raised by hydrazine sulfate proponents. Their analyses suggested that the concurrent use of hydrazine sulfate with tranquilizing agents or barbiturates did not adversely affect the survival of lung cancer patients enrolled in the hydrazine sulfate trials. Also, their post-trial analyses did not change the conclusions originally drawn from the clinical trials: There was no benefit for patients who received hydrazine sulfate compared with those who received placebo.

Because patients who entered later in NCCTG's lung cancer trial did not receive benzodiazepine tranquilizing agents as antiemetics, NCCTG investigators were able to retrospectively compare the clinical outcomes of patients who received benzodiazepines with those of patients who did

¹³In the late 1980s, tranquilizing agents were used extensively in oncology to treat chemotherapy-induced vomiting. In addition to sedation, phenothiazines and benzodiazepines have some antinauseant and antiemetic effects. Furthermore, benzodiazepines were useful additions to antiemetic regimens because they relieve anxiety about nausea or vomiting surrounding chemotherapy treatment.

¹⁴Because data on concurrent medications were not collected on standard research forms, we asked the principal investigator to review the medical records for study patients maintained at Harbor-UCLA Medical Center. We did not attempt to verify these data.

not.¹⁵ The data showed no statistically significant differences in survival time between patients who received hydrazine sulfate and a benzodiazepine tranquilizer as an antiemetic and patients who received hydrazine sulfate and new non-benzodiazepine antiemetics. Furthermore, analyses showed no statistically significant differences in terms of time to disease progression for patients who received hydrazine sulfate and a benzodiazepine tranquilizer compared with those who did not.

CALGB researchers also looked retrospectively at this incompatibility issue. Beginning in January 1995, CALGB conducted a retrospective review of primary medical records and documented the medications that were used by patients enrolled in its clinical trial of hydrazine sulfate. On June 5, 1995, we received the results of CALGB's examination of the effect of benzodiazepines, barbiturates, or phenothiazines on patient survival. The data showed no statistically significant differences in survival between patients who received hydrazine sulfate and barbiturates or benzodiazepines or phenothiazines and patients who received hydrazine sulfate but none of these allegedly incompatible agents. Furthermore, the data also showed no statistically significant differences in survival between patients who received hydrazine sulfate and barbiturates or benzodiazepines or phenothiazines and patients who received placebo and any of these agents.

FDA Handled the Issue of Possible Incompatibility Somewhat Differently From NCI

FDA handled the issue of possible incompatibility differently in approving the use of hydrazine sulfate by individual physicians than it did in approving NCI's sponsored clinical trials. FDA recommended that NCI-sponsored investigators monitor study patients to detect possible interactions between hydrazine sulfate and possible incompatible agents. However, while NCI was conducting its clinical trials, FDA was cautioning other physicians to avoid possible incompatible agents when administering hydrazine sulfate.

In reviewing NCI's IND applications to conduct clinical trials of hydrazine sulfate, FDA raised safety concerns to NCI regarding hydrazine sulfate's interactions with other drugs, including tranquilizing agents. In his review of NCI's IND, the FDA medical officer stated, "The following drugs are interdicted, due to known interactions: ethanol [alcohol], barbiturates, and

¹⁵Patients entered later in NCCTG's clinical trial were treated with new antiemetic agents, primarily ondansetron (Zofran). Ondansetron was the first of a whole new class of antiemetics—serotonin receptor antagonists—to become widely available for the prevention of nausea and vomiting associated with emetic chemotherapy. The development of serotonin receptor antagonists represented a vast improvement in controlling vomiting. For example, ondansetron works well even against chemotherapy regimens most notorious for causing severe vomiting in most people.

tranquilizers.” This was followed by a recommendation that NCI outline all precautions to be taken by study investigators “to fully explore the neurotoxic potential of hydrazine.” NCI complied.

FDA took a more conservative view of the use of possible incompatible agents with hydrazine sulfate under its compassionate use program. Before completion of NCI’s sponsored clinical trials, FDA approved more than 70 applications permitting the compassionate use of hydrazine sulfate. Because of publicity given to hydrazine sulfate, FDA received many requests from individual physicians for approval to use hydrazine sulfate on a case-by-case “compassionate” basis on the chance that patients with no other available effective therapy might benefit.¹⁶

A central nervous system depressant effect associated with hydrazine sulfate consistently prompted FDA to caution patients regarding the use of hydrazine sulfate with any potential sedative agent.¹⁷ In its approvals, FDA staff requested that physicians caution their patients to avoid tranquilizers, barbiturates, and alcohol while taking hydrazine sulfate. FDA officials told us that the reason for this instruction was that these physicians were not trained clinical investigators and, under the circumstances, would be less likely to recognize adverse reactions from interactions between hydrazine sulfate and possible incompatible agents.

NCI Did Not Ensure Collection of Data on the Use of Alleged Incompatible Agents

NCI contributed to the subsequent controversy surrounding these trials by not requiring better data collection and analysis of this issue. Although NCI officials were aware of the concerns surrounding the use of allegedly incompatible agents with hydrazine sulfate, they did not believe it was necessary to maintain research records during its trial regarding concurrent medications and possible alcohol use.¹⁸ NCI and CALGB documents, however, stated that all data, including concurrent medications taken by study patients, would be recorded on standardized research forms.

¹⁶In the case of a serious disease, a drug that is not approved for marketing but is under clinical investigation may be made available for a serious or immediately life-threatening disease in patients for whom no comparable or satisfactory alternative drug or other therapy is available.

¹⁷FDA may also have been influenced by positions taken by other researchers in trials of hydrazine sulfate. In earlier INDs submitted to FDA, a few researchers had developed study protocols or therapy plans that said patients should not receive alcohol, barbiturates, or tranquilizers.

¹⁸As stated above, data on the actual antiemetics as well as any concurrent medications used by patients in CALGB’s clinical trial were available from patients’ primary medical records.

The Chairman of CALGB told us that the cooperative group decided before starting the trial that they would not require such data to be recorded on standardized research forms because the evaluation of concurrent medications with hydrazine sulfate was not a study objective. Even after the trial began, however, the CALGB principal investigator and an NCI official assured proponents of hydrazine sulfate that CALGB would collect and analyze data on antiemetic medications to determine the possible effects of benzodiazepines and phenothiazines on patients taking hydrazine sulfate. A statement submitted by NCI staff to media representatives pointed to the purpose for this:

“[A]ll concurrent medications were well documented in the Cancer and Leukemia Group B (CALGB) study (a routine component of clinical trials data collection) so that any differences in study outcomes could be reviewed from the perspective of these potential ‘incompatibles’.”

Despite these assurances, CALGB did not uniformly collect data on the use of concurrent medications, including tranquilizing agents and barbiturates, and possible alcohol use. Furthermore, in a published article describing the results of the clinical trial, CALGB investigators incorrectly reported that data on the use of concurrent medications were recorded on standardized research forms. CALGB investigators should have accurately reported their data collection efforts. In addition, NCI should have ensured that CALGB investigators prospectively collected data on concurrent medications and alcohol use on research forms to permit investigators to analyze trial data to determine the possible effects of these agents on patients taking hydrazine sulfate.

CALGB’s Published Trial Results Did Not Accurately Describe Tranquilizer Use

A paper presenting the final results of the CALGB clinical trial did not clearly describe the use of tranquilizing agents by study patients. Authored by the principal investigator for the trial, this scientific paper did not accurately reflect the widespread use of tranquilizing agents in the CALGB lung cancer trial.

In the published paper, the investigator wrote that “no patients received barbiturates and virtually no patients received phenothiazine-type tranquilizers, with the exception of prochlorperazine . . . , which was used as a short-term antiemetic.” Data from the medical records, however, showed that phenothiazines, including prochlorperazine, were prescribed to 80 percent of study patients. In addition, over 88 percent of study patients were prescribed benzodiazepines. Medical records also showed

that approximately 5 percent of study patients were treated with barbiturates. The principal investigator told us that he used data submitted by some research associates to form his “impressions” of concurrent medication usage. Because CALGB did not routinely collect data on concurrent medications, however, the data used to support his impressions are not an accurate and complete reflection of information contained in the medical records.

In a letter to us dated February 27, 1995, the Chairman of the CALGB cooperative group said the principal investigator would prepare a letter to the Journal of Clinical Oncology correcting his statement regarding study patients’ use of barbiturates. The Chairman told us, however, that he believed the description of tranquilizer use was accurate. He based his assessment on, first, the fact that most medical records did not indicate that phenothiazines were prescribed for long-term use as tranquilizers. Second, the tranquilizing agents, phenothiazines and benzodiazepines, were interchangeable in the investigator’s description of their use as short-term antiemetics. Accordingly, he concluded that the principal investigator was justified in stating that “virtually no patients received phenothiazine-type tranquilizers.” We disagree with the Chairman in this regard. We believe the investigator erred in not reporting the widespread use of benzodiazepine tranquilizing agents.

In June 1995, the Journal of Clinical Oncology published a letter to the editor from CALGB correcting and clarifying CALGB’s published results.¹⁹ The letter corrected information on the use of barbiturates during CALGB’s clinical trial. The letter also clarified that in addition to the use of a phenothiazine tranquilizing agent as an antiemetic, many patients received a benzodiazepine antiemetic.

Conclusions

In three large, randomized, placebo-controlled clinical trials sponsored by NCI, hydrazine sulfate was ineffective in extending the survival time for certain cancer patients. The developer of hydrazine sulfate therapy has suggested that the trials were compromised because investigators permitted some study patients to take agents that are possibly incompatible with hydrazine sulfate. We confirmed that all three trials permitted some use of tranquilizing agents to varying degrees and one trial permitted the use of barbiturates and alcohol. Specifically, many patients received short-term dosages of tranquilizers for antiemetic purposes. Retrospective analyses, however, found no evidence that the use of

¹⁹Vol. 13 (June 1995), pp. 1529-30.

allegedly incompatible agents adversely affected NCI's clinical trial results. Although our work did not support the allegation that the studies were flawed, NCI should have made sure that complete and accurate records were kept during CALGB's clinical trial regarding concurrent medications and possible alcohol use. Furthermore, this issue should have been analyzed on a more timely basis in the NCCTG and CALGB clinical trials, and the published results of CALGB's trial should have been accurate with regard to tranquilizer use.

Agency Comments

In commenting on a draft of this report, the Public Health Service agreed with the report's main conclusion that there is no evidence to support the allegation that the three trials sponsored by NCI were flawed. In addition, retrospective analyses suggested that the use of tranquilizers as antiemetic agents, barbiturates, or alcohol by patients receiving hydrazine sulfate did not produce greater toxicities or interfere with hydrazine sulfate's alleged benefits. (See app. II for a copy of the Public Health Service's comments.)

The Public Health Service did not agree, however, that either NCI or the clinical investigators were remiss for not ensuring that concurrent medications were recorded on research forms. NCI and CALGB documents provided that data on concurrent medications would be recorded on research forms. As noted previously, NCI staff wrote to media representatives that all concurrent medications were well documented as a routine part of the trial's data collection so that any differences in outcomes could be analyzed in terms of the allegedly incompatible agents.

Although CALGB informed NCI that the use of concurrent medications would be captured on the patient research forms in accordance with the research plan, CALGB investigators did not uniformly record this information on the forms as originally intended. Under the terms of the cooperative agreement that provided funding for CALGB's clinical trial, it was the responsibility of CALGB to record such data. NCI officials told us that the agency has specific expectations with respect to cooperative group performance and it is the grantee's responsibility to successfully accomplish these. We believe, however, that NCI, as the funding agency, has the oversight responsibility for ensuring that their expectations are met. Furthermore, CALGB should have complied more completely with its proposed plan for data recording.

The Public Health Service also does not believe that NCCTG and CALGB clinical investigators should be criticized for not having analyzed data on

concurrent medications promptly. The issue of incompatibility was consistently part of the public controversy surrounding the NCI-sponsored clinical trials of hydrazine sulfate. Therefore, we believe that NCI was remiss as were NCCTG and CALGB investigators for not settling the controversy by promptly analyzing data on the impact of specific medications on the effects of hydrazine sulfate.

The Public Health Service agreed that the initial published article describing the findings of CALGB's study was not accurate with respect to the use of tranquilizing agents as antiemetics and barbiturates. NCI criticized this lapse and ensured that a letter from the CALGB investigator was published that provided more complete and accurate information.

The Public Health Service also provided technical comments which have been incorporated where appropriate, in our report.

We are sending copies of this report to the Secretary of Health and Human Services and the Director of NCI; the Commissioner of Food and Drugs; and interested congressional committees. Copies will also be made available to others upon request.

Please call me at (202) 512-7119 if you or your staff have any questions. Other major contributors to this report include Barry D. Tice, Assistant Director, (202) 512-4552, and Gloria E. Taylor.



Mark V. Nadel
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Contents

| | | |
|---|---|----|
| Letter | | 1 |
| Appendix I Scope and Methodology | | 20 |
| Appendix II Comments From the Public Health Service | | 21 |
| Table | Table 1: Number of Patients Receiving Specific Antiemetic Medications Along With Hydrazine Sulfate in the Lung Cancer Clinical Trials | 9 |
| Figure | Figure 1: Time Line of the UCLA and NCI-Sponsored Clinical Trials of Hydrazine Sulfate | 6 |

Abbreviations

| | |
|-------|--------------------------------------|
| CALGB | Cancer and Leukemia Group B |
| FDA | Food and Drug Administration |
| IND | investigational new drug |
| NCCTG | North Central Cancer Treatment Group |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| UCLA | University of California Los Angeles |

Scope and Methodology

To obtain information for this report, we reviewed NCI's policy guidance for conducting clinical trials of investigational agents, agency memorandums documenting protocol development for the hydrazine sulfate clinical trials, and related correspondence. We also discussed the conduct of these trials with NCI officials, cooperative group representatives and investigators, FDA officials, officials in the Office of Research Integrity, and proponents of hydrazine sulfate to obtain their perspectives on the issues involved. We performed an extensive literature search on hydrazine sulfate as well as topics related to cancer research, the conduct of clinical trials, approaches to chemotherapy treatment, and drugs to control chemotherapy-induced vomiting. In addition, we discussed the issue of incompatibility with a leading Russian researcher and viewed several hours of a taped interview with senior Russian oncologists. We also discussed the interpretation of animal data with experts in pharmacology.

In our examination of the extent to which barbiturates and tranquilizers were used during the clinical trials, we reviewed research records maintained by the data management and statistical centers for each cooperative group. For the CALGB clinical trial, we visited the cooperative group's Data Management Center located at Duke University. We randomly selected research records for 137 of 291 study patients for review. For the NCCTG clinical trial, we visited the Data Management Center for the cooperative group at the Mayo Clinic. Before our arrival, NCCTG research associates had compiled a list of antiemetic medications administered to each study patient. We randomly selected 15 percent of 116 study patients' research records to verify the accuracy of NCCTG's data collection efforts.

We conducted our work from July 1994 to April 1995 in accordance with generally accepted government auditing standards.

Comments From the Public Health Service



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rockville MD 20857

JUL 12 1995

Mr. Mark V. Nadel
Associate Director, National and Public Health Issues
Health, Education and Human Services Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Nadel:

The Public Health Service has reviewed the General Accounting Office's draft report entitled Cancer Drug Research: New Analyses Refute Allegation that Hydrazine Sulfate Studies Were Flawed. Our comments on the draft report are attached.

We appreciate the opportunity to review the draft report before it is finalized.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Anthony L. Itteilag".

Anthony L. Itteilag
Deputy Assistant Secretary for Health
(Management and Budget)

Attachment

Appendix II
Comments From the Public Health Service

PUBLIC HEALTH SERVICE COMMENTS ON
THE GENERAL ACCOUNTING OFFICE DRAFT REPORT
"CANCER DRUG RESEARCH: NEW ANALYSES REFUTE ALLEGATION
THAT HYDRAZINE SULFATE STUDIES WERE FLAWED"

The Public Health Service (PHS) has reviewed the General Accounting Office (GAO) draft report and has the following comments.

GENERAL COMMENTS

We agree with the report's main conclusion that the comparable results of all three trials sponsored by the National Cancer Institute (NCI) showed that the use of antiemetic agents, barbiturates, or alcohol by patients receiving hydrazine sulfate did not produce greater toxicities or interfere with hydrazine sulfate's alleged benefits. We do not agree, however, that either the clinical investigators or the NCI were remiss with regard to recording or analyzing information about the use of concomitant medications.

The advocates for hydrazine sulfate, who are outside the general medical and scientific community, cite animal studies (many not published in scientific journals) and observations not based on controlled clinical trials as the basis for their allegations that certain antiemetics, barbiturates, and alcohol are incompatible with hydrazine sulfate. Upon careful scientific review by NCI and extramural scientists, the information provided by the proponents (which was not based on scientifically sound research) was found to be inconclusive. Therefore, it was judged unnecessary to prohibit the use of these substances during the trials. The research plan provided that data on the concomitant use of allegedly incompatible agents would be recorded, but the data were to be analyzed only if unexpected toxicities occurred.

The GAO draft report criticizes NCI for not ensuring that concomitant medications were recorded on the research forms and that these data were analyzed promptly. Under the terms of the cooperative agreements which provided funding for these trials, it was the responsibility of the North Central Cancer Treatment Group (NCCTG) and the Cancer and Leukemia Group B (CALGB) to record the use of concomitant medications in accordance with the research plan. In addition, the form on which concomitant medications were to be recorded was to be determined by the research centers.

Since no unexpected toxicities were observed during the trials, we do not believe that NCCTG and CALGB should be criticized for not having done such analyses sooner. The data were clearly available, either on the patient research forms or on the patient medical records, as demonstrated by the fact that the analysis of the effects of concomitant use of the

Appendix II
Comments From the Public Health Service

supposedly incompatible agents on the alleged effectiveness of hydrazine sulfate has been done.

In addition, although FDA's actions with regard to the NCI and the "compassionate use" Investigational New Drug (IND) applications were not identical, we do not agree that they were inconsistent. Before allowing the "compassionate use" INDs to proceed, the FDA Medical Officers charged with reviewing the applications assured that each requesting physician had a basic knowledge about the drug, how to administer it, the side effects to expect (including potential neurotoxicity from certain drug interactions), what patient monitoring would be required, and specific endpoints within a defined period of time. A letter permitting the "compassionate use" IND was sent to each of the requesters who satisfied the above criteria. These criteria stated the conditions under which the drug should be used; including the advice that the patients be cautioned to avoid when possible the use of antiemetics, barbiturates, or alcohol while taking hydrazine sulfate. The reason for this instruction was that these physicians were not trained clinical investigators and, under the circumstances, would be less likely than trained clinical investigators to recognize adverse reactions resulting from drug interactions.

The advice to NCI and the physicians giving hydrazine sulfate for "compassionate use" was different because their knowledge bases were different. The NCI was already aware of the potential interaction issues, which, although published, were not widely known in the United States. It was the judgement of the FDA Medical Officers involved that under the conditions of "compassionate use," the most conservative approach should be taken to protect the patients. In regard to the "compassionate use" INDs, where the conditions of benefit-to-risk were not well defined, the reports of a potential for drug interactions were considered enough to warrant the advice that the drugs in question be avoided whenever possible. While the advice given to NCI and the physicians giving the product for "compassionate use" was somewhat different, it was not inconsistent.

We also note that the GAO draft report repeatedly refers to agents given to control chemotherapy-induced nausea and vomiting as tranquilizers. We believe that this could be misleading to report readers who may assume that the use of these agents was optional. Good medical care requires the use of antiemetics in conjunction with chemotherapy containing cisplatin, such as the regimens used in the hydrazine sulfate trials. Benzodiazepenes and phenothiazines were the most effective antiemetics available at the time these studies were

Appendix II
Comments From the Public Health Service

initiated, and are typically given for short periods of time. These drugs are also prescribed as tranquilizers, but generally for extended periods. We suggest that, in order to accurately convey the purpose for which these drugs were used, the report either name them or describe them as antiemetics throughout.

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