Potential Health Hazards With Antineoplastic Drugs

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INTRODUCTION

The basic objective of all cancer chemotherapy is the preferential destruction of cancer cells, with sparing of normal cells as much as possible (Dreizen, Bodey & Rodriquez, 1975). Even in therapeutic dose, cytotoxic drugs produce toxic side effects due to poor selectivity between target cells and normal cells. Most all of the chemotherapeutic agents that are given today for treating cancer kill or impair susceptible cells by blocking a drug-sensitive biochemical or metabolic pathway (Knowles & Virden, 1980).

Chemotherapeutic agents described in this paper are the antineoplastic drugs, i.e., steroids, immunostimulants, and cytotoxic agents. These substances are used widely; about 30 are available commercially, and another 70 are in some stage of clinical development. It is estimated that these agents are given to 200,000-400,000 patients annually (DeVita, 1982:153).

As the use of chemotherapeutic agents increases in hospitals, in outpatient departments and in homes, more people come into contact with them. Not only are nurses, pharmacists, and physicians increasing their risk for potential long-term exposure, but so are the patients and their families.

Antineoplastic drugs have proven carcinogenic and mutagenic in bacteria or animals and have been implicated in causing tumors in humans. It is possible that workers exposed to these drugs by handling and administering them are at risk.

Should there be concern about what is being done to prevent the potential risk of developing a malignancy among those in frequent contact with these drugs? During the past decade there have been dramatic improvements in the survival of patients with cancer due to increased knowledge about the natural history of certain cancers and aggressive treatment with radiotherapy and chemotherapy. Concurrently, there has been increased exposure to these potential hazards to health care workers by handling chemotherapeutic agents; agents which appear to be carcinogens themselves.

The acute patient side effects of intensive therapies are relatively well known. But the delayed consequences of treatment with antineoplastic agents have only been documented in the last decade and continue to be defined and studied. One delayed consequence associated with cancer therapy is a second malignant neoplasm (Brody, Schottenfeld, & Redi, 1977; Krikonian, Burke, Rosenberg, & Kaplan, 1979). Prolonged use of antineoplastic agents also has been associated with an increase in the incidence of acute leukemia and second malignant tumors (Kapadia, Krause, Ellis, Pan, & Wald, 1980).

OCCUPATIONAL HANDLING OF ANTINEOPLASTIC SUBSTANCES

Epidemiological studies of hazards to nurses and pharmacists who prepare and administer cytotoxic drugs have been few in number with limited data. In most institutions a few nurses and/or pharmacists have been chronically exposed to cytotoxic drugs. Due to the small numbers of subjects in studies conducted, the statistical significance relating chemotherapeutic agents as directly or indirectly associated with occupational exposure precludes definitive conclusions.

If antineoplastic agents were a primary or contributing cause of cancer in people who are occupationally exposed, then one might expect an increased incidence of cancer in workers in the pharmaceutical companies that make such drugs. So far there have been no reports of an increase in their cancer rates (Reich, 1981). These "negative" reports result from the latency period required for neoplastic development and upon how carefully the workers are monitored. Also, workers in the production of anticancer drugs presumably are better protected than hospital workers.

Routes of exposure to antineoplastic agents are primarily through inhalation of the aerosolized drug product, ingestion, and direct skin contact (Reich, 1981; Zimmerman, Larsen, Barkely, & Gallelli, 1981). These agents have direct irritational effect on the skin, eyes, and mucous membranes. Handling antineoplastic agents without attention to skin protection can lead to local toxic and/or allergic reactions. Irritation to skin or mucous membranes by antineoplastic agent handlers is apparently rare; there

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is only one report in the literature of a nurse developing an irritant reaction after accidentally spilling cyclophosphamide solution on her hands (Knowles & Virden, 1980).

Neal, Wadden, and Chiou (1983) studied the effects of four antineoplastic agents by ambient air sampling. They found that personnel handling these drugs were subject to systemic absorption of the agents by inhalation. One of the ways they noted these drugs were being released into the environment was during the drug preparation.

Zimmerman et al. (1981) suggest excreta from patients receiving antineoplastic agents, such as methotrexate, may contain high concentrations of the drug and nurses should be informed of this potential source of exposure. Patient excreta has only recently been considered a potential exposure hazard for antineoplastic agents. Venitt, Crofton-Sleigh, Hunt, Briggs, and Speechley (1984) found that certain chemotherapy agents were excreted by patients unchanged. Therefore, they concluded contact with urine from patients undergoing intensive chemotherapy may be hazardous.

Falck, Grohn, Sorsa, Vanio, Heinonen, and Holsti (1979) looked for mutagenic activity in the urine of patients on chemotherapy and of nurses who handled and administered these drugs. They found that the urine of the study group did exhibit a higher level of mutagenicity than did the urine of the control group. It was also noted that mutagenicity decreased almost to zero after a duty-free weekend.

A study of the chromosomes of two groups of nurses evaluated the possible occupational health hazard of handling cytotoxic agents. A group of nurses handling cytotoxic agents showed significantly more chromosome gaps and a slight increase in sister chromatid exchange than did a control group of nurses who did not handle cytotoxic agents (Waksvik, Klepp, & Brogger, 1981). A chromatid gap in itself may not represent serious chromosome damage, but an increase in the frequency of such chromosome gaps does indicate exposure to mutagenic agents (Brogger, 1974).

Norppa, Scorsa, Vanio, Grohn, Holsti, and Nordman (1980) found an increased frequency of sister chromatid exchanges in the blood lymphocytes of nurses handling cytostatic drugs. They showed nurses working on oncology units had a higher frequency of sister chromatid exchanges than other hospital nurses.

Crudi (1980) noted that certain "side effects" were experienced by a group of intravenous therapy nurses who mixed and administered antineoplastic agents. These "side effects," light headedness, dizziness, nausea, headache, skin and mucous membrane irritation, and allergic reactions, only occurred while mixing the drugs in a small unventilated area. These "side effects" could have been attributable to exposure while mixing these agents in the poorly ventilated area.

Pharmacists who prepared antineoplastic drugs for a 33-bed oncology unit complained of light headedness, dizziness, and facial flushing while preparing certain admixtures. However, when a glove box was installed within which they would mix the drugs, no further incidents were reported (Ladik, Stoehr, & Maurer, 1980).

Contradictory results to the above were reported by Wilson and Solimando (1981) who observed no complaints of the types of "side effects" reported by Falck, et al. 1979, Ladik, et al. 1980, or Crudi, 1980. Wilson and Solimando (1981) studied pharmacists who prepared and administered antineoplastic chemotherapeutic agents to outpatients and to patients in the hospital medical and surgical oncology units, the pediatric hematology/oncology units, and the gynecology/oncology units. These pharmacists shared responsibility with the house staff for the administration of the chemotherapeutic agents to patients. Between September 1975 and January 1981, nine persons worked within this group. Throughout that time, there were no complaints of any "side effects." However, neither symptomatology of "side effects" was gathered nor was urine mutagenicity noted in the study group. A horizontal laminar flow hood was in use by these pharmacists. This study, therefore, did not address the potential hazard to those who handled and/or administered cytotoxic agents without protective devices but suggests the possible effectiveness of a horizontal laminar flow hood.

Staino, Gallelli, Adamson, and Thorgeursson (1981) studied hospital pharmacists who reconstituted and admixed antineoplastic agents for intravenous administration. Eight subjects participated in their study and all the drugs were handled in a ventricular laminar flow hood or a horizontal laminar flow hood. No matter which hood was used, no mutagenic activity was detected in the urine of these subjects.

Other researchers examined pharmacists in whom mutagenicity was detected in the urine of all personnel during the study time period when antineoplastic agents were prepared in a horizontal laminar flow hood, without pharmacists wearing gloves and/or masks. When these admixtures were prepared in the vertical flow biological safety cabinet by personnel wearing gloves, no urine mutagenicity was detected (Anderson, Puckett, Dara, Nguyen, Theiss, & Matney, 1982).

The liver plays a prominent role in the metabolic activation and degradation of many of these antineoplastic agents. Thus, the occurrence of clinical liver disturbances among patients receiving antineoplastic agents has become a problem (Vainio, 1982). Simultaneously, increasing emphasis is being placed on the possible hepatic effects of long-term, low-grade occupational exposure of hospital workers to cytotoxic drugs. Sotaniemi, Sutinen, Arranto, Sutinen, Sotaniemi, Lehtola, and Pelkonen (1983) found three head nurses employed consecutively developed liver injury after three years of handling cytostatic drugs. After identification of these three cases, ten nurses from two oncology units were studied. None had any observable liver damage symptoms, and all conventional laboratory tests for liver function were negative. These ten nurses' exposure to cytotoxic agents had been smaller than the head nurses. One can hypothesize that the intensity and duration of exposure to cytotoxic agents may play a role in the development of liver diseases.

These studies seem to be limited to a potential risk from the mixing and handling of antineoplastic agents. The body

of literature suggests that when no precautions are taken, there is an increased risk of mutagenicity in urine concentrates, whereas when precautions are taken the risks decrease. Although precautions seem to eliminate observable urine concentrate mutagenicity or complaints of side effects by using present technology, there is insufficient evidence to determine the long-term effects of handling antineoplastic agents. On the other hand, there is no documentation to support that the handling or mixing of antineoplastic agents causes cancer.

KNOWLEDGE BASE OF NURSES

About 85% of patients with cancer are now receiving antineoplastic agents for treatment (Engelking & Steele, 1984). Consequently, the role of the nurse caring for cancer patients is changing. Preparing, administering, monitoring patient responses, and educating the patient and family about their drug regimens with chemotherapeutic agents are increasingly being done by the general nursing staff (Engelking & Steele, 1984). Family members exposed to cancer patients in treatment with chemotherapeutic agents may be at increased risk, too. This shift therefore requires the nurse to be knowledgeable about chemotherapeutic agents.

How knowledgeable a nurse is about the potential risk in handling and administering chemotherapeutic agents depends on the nurse's work environment and/or exposure to materials or information on potential risk. Some agencies employing nurses provide inservice education and have policies and procedures for handling antineoplastic agents. Some other agencies offer little or no information to nurses. Often nurses need to seek out information and implement procedures for themselves.

Information for the safe handling of chemotherapeutic agents is available in literature (Jeffrey, 1983; Anderson, et al., 1981; Zimmerman, et al., 1981). Despite this, nursing literature gives minimal attention to the possible hazards of handling chemotherapeutic agents and the need for protection when administering such agents (Gross, Johnson, & Bertino, 1981). Research could be conducted to determine nurses' perceptions of risk in handling and administering these agents as well as what safety precautions if any are being used.

OCCUPATIONAL HEALTH NURSE'S ROLE

The role of the occupational health nurse in a hospital setting where large amounts of antineoplastic agents are being administered and handled is one of major importance. The nurse in this role must act as a catalyst in the goal to decrease the risk of potential hazards associated with antineoplastic agents. In order to attain this goal, the occupational health nurse needs: a) management commitment, b) to establish procedures for handling antineoplastic agents, c) a health surveillance program, d) an educational/inservice program, and e) appropriate documentation.

Management commitment must come from the very top of the organization for it to be successful. This commitment must be sincere, genuine, and serious. It must be talked about often and the managers in the organization need to be informed as to the effectiveness of their safety and health program.

The establishment of procedures for handling antineoplastic agents are recommended to provide information for safe practices in the clinical process of chemotherapy. Many articles by government agencies and private organizations have published guidelines on handling known or suspected carcinogens (Harrison, 1981; Jeffrey, et al., 1983; Zimmerman, et al., 1981; Anderson, et al., 1981).

Although more research is needed regarding the most effective surveillance program, Harrison (1981) recommends preassignment examinations with a complete blood count, including differential, to provide a baseline. He also recommends a periodic physical examination, at least once a year, and more often as necessary. This examination is designed to detect any changes from the baseline, and to note changes in areas specifically vulnerable to chemical exposure such as the skin and mucosal membranes.

An effective educational/inservice program can only be achieved after the above has been completed. All nurses and other persons involved with the administration and handling of antineoplastic agents, and those in management roles, need to be informed about potential hazards associated with chemotherapeutic drugs. Since symptomatology is not well defined with respect to hazards associated with antineoplastic agents and the latency period involved with the development of cancers, it is the responsibility of the occupational health nurse to stay current with the literature and with recommendations to answer questions employees and an employer may have regarding the need for protection.

Occupational health nurses can make significant contributions to employee health and safety through appropriate documentation. The significance of good and accurate record keeping cannot be emphasized enough. Employee health records are a good source of data from which both analytical and descriptive studies can be performed (Brown, 1981).

CONCLUSION

A larger number of patients, now more than ever before, receive antineoplastic agents for treatment of cancer. Therefore more health professionals, mostly nurses, are administering and handling chemotherapeutic drugs and are at risk to the potential hazards associated with these agents.

The occupational health nurse is in an excellent position to contribute to the nursing literature on the potential hazards of handling chemotherapeutic agents and the need for personnel protection when administering such agents. The occupational health nurse in working with other health professionals who are administering and handling antineoplastic agents can be a catalyst for change. The occupational health nurse can initiate programs, open up communications, and advise management about the need for health

protection. Through educational/inservice programs, health surveillance programs and accurate record keeping, the occupational health nurse can improve the health and safety of those employees at risk.

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