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# Minimizing Occupational Exposure to Antineoplastic Agents

**ABSTRACT**

The inherent toxicity of antineoplastic drugs used for the treatment of cancer makes them harmful to healthy cells as well as to cancer cells. Nurses who prepare and/or administer the agents potentially are exposed to the drugs and their negative effects. Knowledge about these drugs and the precautions aimed at reducing exposure are essential aspects of infusion nursing practice. This article briefly reviews the mechanisms of action of common antineoplastic drugs, the adverse outcomes associated with exposure, the potential for occupational exposure from preparation and administration, and recommended strategies for minimizing occupational exposure.

**Key words:** antineoplastic drug exposure, chemotherapy safe handling, hazardous drugs

Antineoplastic drugs, commonly referred to as chemotherapy, have been used for the treatment of cancer for more than 65 years. Since the approval of nitrogen mustard in 1949, the number of chemotherapy agents in common use has increased to more than 200. Infusion nurses are often responsible for preparing intravenous (IV) antineoplastic drugs, administering them, or both. Such routine activities may result in low-level exposure that is associated with adverse health outcomes. Although the risk-benefit ratio is positive for patients undergoing treatment with these drugs, most antineoplastic agents are hazardous to health care workers without any benefit.

The National Institute for Occupational Safety and Health (NIOSH) defines hazardous drugs (HDs) as those that meet at least 1 of the following criteria: carcinogenicity, genotoxicity, teratogenicity, reproductive toxicity, organ toxicity at low doses, and structure or toxicity similar to drugs known to be classified as hazardous.[1] The recently updated NIOSH list of HDs includes 184 drugs, more than half of which are antineoplastic agents. The remaining drugs are immunosuppressant, antiviral, hormonal, bioengineered, and miscellaneous agents.[2] This article will focus on HDs used in the treatment of cancer and will discuss how nurses are occupationally exposed, the potential adverse health effects of exposure, and recommended safe handling precautions to minimize exposure.

## EVIDENCE FOR ADVERSE OUTCOMES FROM OCCUPATIONAL HD EXPOSURE

Occupational HD exposure-related adverse outcomes have been documented in many studies since the late 1970s. Results are most often reported as the odds of developing a condition in individuals who are exposed to chemotherapy as compared with those who are not exposed. Although some of the studies included workers who were exposed before the regular use of safe handling precautions, they demonstrate the plausibility of such outcomes from occupational antineoplastic drug exposure.

Adverse health effects from occupational exposure to antineoplastic drugs are due to their inherent toxicity. Most of the drugs are cytotoxic when they reach a high-enough intracellular concentration. The usual mechanism of action is interference with cell division, either by disrupting deoxyribonucleic acid (DNA) synthesis, DNA replication, or mitosis. Table 1 lists the mechanisms of cytotoxicity for some common antineoplastic

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**TABLE 1**

## Antineoplastic Agents: Mechanisms of Action

| Drug Class | Mechanisms of Action | Examples |
|---|---|---|
| Alkylating agents | Break DNA helix strand; inhibit DNA replication | carboplatin (Paraplatin) |
| | | cisplatin (Platinol) |
| | | cyclophosphamide (Cytoxan) |
| Antimetabolites | Inhibit DNA synthesis | cytarabine (Cytosar-U) |
| | | 5-fluorouracil (Adrucil) |
| | | methotrexate |
| Antitumor antibiotics | DNA intercalation; DNA strand breaks | bleomycin (Blenoxane) |
| | | doxorubicin (Adriamycin) |
| | | mitomycin (Mutamycin) |
| Plant-derived agents | DNA strand breaks; inhibit cell division | etoposide (VePesid) |
| | | irinotecan (Camptosar) |
| | | paclitaxel (Taxol) |
| | | vincristine (Oncovin) |

*Abbreviation: DNA, deoxyribonucleic acid.*

drugs. A less-than-lethal concentration of the agents allows exposed cells to survive, but may still cause DNA damage. Such genetic damage, if not repaired, may predispose workers to future adverse health outcomes.[3]

Several studies have reported genotoxicity in nurses and pharmacy personnel following occupational exposure to antineoplastic drugs. As early as 1995, DNA strand breaks were found to be 50% higher in exposed nurses versus controls.[4] Yoshida and colleagues[5] used the Comet Assay, a general measure of DNA damage, to demonstrate a significantly greater DNA tail length (due to "unravelling" of genetic material) in nurses who routinely handled antineoplastic drugs as compared with nurses who did not handle the drugs. Chromosomal aberration analysis in peripheral blood lymphocytes showed significantly increased genetic damage in exposed versus unexposed nurses.[6] More recently, the specific chromosomal abnormalities associated with myelodysplastic syndrome and acute myelogenous leukemia were identified in nurses and pharmacists handling alkylating agents, and the occurrence of these abnormalities increased with the frequency of drug handling.[7]

Several chemotherapy agents are classified as chemical carcinogens by the International Agency for Research on Cancer.[8] Eleven individual antineoplastic drugs and 2 combination regimens are known human carcinogens; 8 are probable carcinogens, and 7 are possible carcinogens. See Table 2 for a list of antineoplastic agents with carcinogenic potential.

The occurrence of second malignant neoplasms in patients after antineoplastic drug treatment for a

**TABLE 2**

## Carcinogenic Potential of Antineoplastic Drugs[a]

| Known Carcinogens | Probable Carcinogens | Possible Carcinogens |
|---|---|---|
| Arsenic trioxide | Azacitidine | Amsacrine |
| Azathioprine | Carmustine | Bleomycin |
| Busulfan | Cisplatin | Dacarbazine |
| Chlorambucil | Doxorubicin | Daunorubicin |
| Cyclophosphamide | Lomustine | Mitomycin |
| Etoposide | Nitrogen mustard | Mitoxantrone |
| Melphalan | Procarbazine | Streptozocin |
| Semustine | Teniposide | |
| Tamoxifen | | |
| Thiotepa | | |
| Treosulfan | | |
| MOPP[b] | | |
| ECB[c] | | |

[a] *Data from the International Agency for Research on Cancer.*[8]
[b] *Combination regimen. MOPP = nitrogen mustard, vincristine, procarbazine, prednisone.*
[c] *Combination regimen. ECB = etoposide, cisplatin, bleomycin.*

  

**TABLE 3**

## Adverse Reproductive Outcomes Associated With Occupational Antineoplastic Drug Exposure

| Adverse Outcome | Occurrence[a] |
|---|---|
| Infertility | OR = 1.42 to 1.5 |
| Spontaneous abortion | 2- to 3.5-fold increased risk |
| Premature labor | OR = 2.98 |
| Premature birth | OR = 5.56 |
| Learning disabilities in offspring | OR = 2.56 |

*[a]Occurrence in exposed versus unexposed.*
*Abbreviation: OR, odds ratio.*
*Data from Martin,[11] Valanis et al,[12] and Lawson et al.[13]*

primary, unrelated cancer was recognized by the late 1970s. Research among health care workers has demonstrated similar results. Pharmacy technicians were found to have a 3.7-fold increase in the occurrence of non-Hodgkin's lymphoma.[9] Leukemia occurrence was increased 10-fold in nurses who worked with antineoplastic drugs.[10] A 3.27-fold overall increased occurrence of cancer in exposed nurses was reported by Martin.[11]

Adverse reproductive outcomes have occurred in workers exposed to antineoplastic drugs. In most of the studies, exposure was defined as handling. The unfavorable reproductive effects include infertility, spontaneous abortion, premature labor, preterm birth, and learning disabilities in offspring of exposed workers (Table 3).[11-13]

Reports of adverse health outcomes from occupational antineoplastic drug exposure, although important, do not convey the impact of those health effects on the individual nurses who are living with them. A small qualitative study in which nurses were asked to share personal stories about their HD exposure revealed that the nurses did not at first connect their health problems with the exposure. Once they suspected that their health changes were due to HD exposure, they had difficulty convincing others of the cause, since most discounted their concerns.[14] Knowing that health problems occurred as a result of their nursing practice was a source of distress.

## EVIDENCE FOR OCCUPATIONAL HD EXPOSURE

Patients receiving antineoplastic therapy generally receive treatment with therapeutic doses of a few drugs over several months. In contrast, health care workers, such as pharmacists or nurses who handle antineoplastic drugs, are potentially exposed to low doses, but to multiple drugs, and the exposure occurs over many years. For health care workers, there is no benefit from the antineoplastic drug exposure; there is only the potential for harm.

The most likely route of occupational exposure to drugs is absorption through skin or mucous membranes.[1] Such exposure can occur from direct contact with the drugs from leaks, drips, or spills during drug preparation and administration. Indirect contact with drug residue on contaminated workplace surfaces is now thought to be the most common source of exposure.[1]

Injection is another route of drug exposure and may occur as a result of injury involving contaminated sharps or broken vials, ampoules, or glass IV bottles. Ingestion of a drug can occur when food or beverages are contaminated with drugs or from hand-to-mouth transfer of drug residue from contaminated surfaces. Inhalation is also a potential source of exposure that occurs when drug vapors or aerosols are released during drug preparation or administration.

Ample evidence of health care worker exposure to antineoplastic drugs has been reported. Approximately 15 studies have been published since 1992 in which antineoplastic drug residue has been found on external vial surfaces. This occurs because of contamination during vial filling and when vials are inadequately washed before packaging the drugs for shipment.[15] Because of external vial contamination, there is the potential for worker exposure when handling the vials and from the transfer of drug residue to other surfaces.

Antineoplastic drug residue has been recovered from wipe sampling of workplace surfaces in more than 100 studies since 1994. Although not every sample exhibited detectable levels of drugs, every study has shown that surface contamination is common in areas where antineoplastic drugs are stored, prepared, administered, or discarded. For example, 2 studies published 10 years apart found that 75% of surfaces sampled in pharmacies were contaminated with drugs above the

limit of detection, and that 43% to 65% of samples from drug administration areas were positive for drug residue.[16,17]

More than 60 studies have documented antineoplastic drugs or their metabolites in the urine of nurses or pharmacy staff. Some studies recovered measureable amounts of drugs from the urine of individuals who did not report handling them, which suggests that the exposure occurred as a result of contaminated workplace surfaces.[18,19]

These findings from the literature have implications for infusion nursing practice. It is clear that routine medication handling can result in HD exposure. Guidelines exist for safe handling precautions that reduce occupational exposure to antineoplastic agents.[1,20-22] Infusion nurses must know about recommended precautions and must be able to identify drugs that are hazardous so that appropriate precautions can be practiced. Any worker who fails to handle antineoplastic agents carefully puts themself and others at risk for exposure.

## APPROACHES TO REDUCING HD EXPOSURE

The Occupational Safety and Health Administration first recommended safe handling guidelines for antineoplastic agents in 1986.[20] The guidelines for protecting health care workers from HD exposure are based on the hierarchy of controls commonly used for other types of workplace hazards.[23] The hierarchy recommends always using the highest level of protection available to minimize worker exposure. The highest level of protection, elimination of a hazard, is not always feasible. The next level of protection involves using engineering controls, such as machines or equipment that contains a hazard. That is followed by administrative controls and work practices aimed at minimizing worker harm. The lowest level of protection is personal protective equipment (PPE), which is the use of barriers to protect employees. A discussion of the hierarchy of controls for reducing antineoplastic drug exposure follows.

### Engineering Controls

The primary engineering controls used with antineoplastic drugs are biologic safety cabinets (BSCs) or compounding aseptic containment isolators (CACIs). These are ventilation controls that protect workers from the aerosols generated during drug preparation. Workers perform drug manipulations, such as reconstitution and withdrawing drugs from vials, inside the enclosed cabinets. These devices do not prevent the generation of contamination, but contain the aerosols to prevent inhalation exposure. Closed system transfer devices (CSTDs) are supplemental engineering controls. They are devices that prevent the transfer of environmental contaminants into a system and the escape of drugs from the system.[1] CSTDs have components that attach to vials to prevent leaks during drug preparation, and adapters for syringes, IV bags, and tubing to prevent leaks during drug administration. New standards from the U.S. Pharmacopeial (USP) Convention will require CSTDs for injectable antineoplastic agents in July 2018.[24]

### Administrative Controls

Administrative controls are programmatic plans and activities that reduce worker exposure to antineoplastic agents. Having written policies and procedures describing how HDs should be handled is essential to a comprehensive program. Procedures should outline the techniques for safely preparing and administering the drugs, for disposing of HD waste, and for handling the contaminated excreta of treated patients. Another administrative control is an updated list of all HDs used in a facility. This enables pharmacy personnel to identify and label the agents to communicate the need for special handling.

Education and training are essential administrative controls. Workers should receive education and training specific to their job responsibilities. Worker competency must be validated before assuming responsibility for handling. Education and training should include the following:

- The hazardous nature of antineoplastic drugs and the potential health risks
- The location and availability of the HD list
- The location and availability of safety data sheets (SDSs) for the HDs
- The location of policies and procedures that outline safe handling
- All measures the employee should take to protect him- or herself from exposure
- Proper use of safety equipment such as BSCs, CACIs, and CSTDs
- Proper donning and doffing of PPE
- Proper drug disposal
- HD spill management and cleanup
- Work practices that minimize worker exposure and environmental contamination

Organizational policies should address the process for employees to follow when they want to request alternative duty that does not include HD handling. Alternative duty must be made available on request to health care workers who are actively trying to conceive (males and females) or who are pregnant or breast feeding. During orientation to HD handling, employers must provide information about the potential risks to a fetus or newborn infant from HD exposure. USP *Chapter 800*[24] will require employees of childbearing capability to acknowledge the risks of exposure. Employees should notify their supervisor of their

request in a timely manner so that temporary protective reassignment can be made.[25]

Medical surveillance is another administrative control for minimizing the adverse effects of chemotherapy exposure.[26] Employers must have a process in place to manage acute chemotherapy exposure, as well as a plan for monitoring the health of workers who are responsible for HD handling. The recommendations include baseline health monitoring of employees before assuming HD handling responsibilities and periodic health appraisal.

### Work Practice Controls

Work practice controls are procedures and practices aimed at minimizing worker exposure and environmental contamination with antineoplastic drugs. Examining workflow step by step will reveal the opportunities for exposure. Some recommended practices include identifying HDs with a distinctive label; transporting HDs in sealed, leak-proof containers; and inspecting containers for leaks. Activities associated with exposure, such as spiking and unspiking IV containers and priming IV tubing, should not be performed at the drug administration site. A safer practice is to spike and prime before the HDs are added to the IV bag. In addition, used IV equipment should be discarded intact. Nurses should avoid touching unnecessary items with contaminated gloves as well as wearing PPE outside drug handling areas to prevent the transfer of contamination. Finally, staff should wash hands with soap and water after removing PPE that was used to handle chemotherapy.

### Personal Protective Equipment

PPE is recommended for all handling activities involving HDs. PPE includes gloves and gowns for most activities, plus face and respiratory protection for some handling tasks.[27] Gloves should be powder free and tested with HDs. The American Society for Testing and Materials has a standard for chemotherapy gloves.[28] Gloves meeting the standard prevent the permeation of 9 selected agents from various categories for a minimum of 30 minutes. Several gloves made of different materials are available. Test results may be printed on the outer glove box, or are available from the glove manufacturer.[29] Recommended glove wear time is 30 minutes. Two pairs of gloves should be worn, with the inner glove cuff under the gown cuff and the outer glove cuff over the gown cuff. After completion of handling activities, gloves should be doffed 1 at a time and carefully turned inside out to prevent the transfer of contamination from the outer gloves to hands and other surfaces.

Gowns that are tested with HDs should be worn for all handling activities except the administration of intact, unit-dose oral forms of chemotherapy. Gowns should be disposable, with back closure and cuffs. Gowns coated with polyethylene or vinyl provide the best protection. Gowns are intended for single use, which means they should be discarded when removed.

Certain chemotherapy handling tasks that are likely to result in splashing require face and eye protection. Whenever HD aerosols may be present, a respirator is also recommended. SDSs list appropriate respiratory protection for specific HDs. While a fit-tested N-95 face piece may protect against inhalation exposure for some drugs, a powered air purifying respirator may be necessary for cleaning up spills. A surgical mask does not provide respiratory protection.

### Handling Contaminated Equipment and Excretions

Any equipment used in the preparation or administration of chemotherapy is considered contaminated. All contaminated disposable IV equipment, PPE, protective drapes, and other items should be handled by people wearing PPE and discarded in designated chemotherapy waste containers. Contaminated sharps should be discarded in a puncture-proof container. After disposing of used equipment, staff should remove and discard the outer glove, then the gown, and then the inner glove. This procedure leaves hands protected throughout disposal. Separate HD-contaminated items from blood and body fluid-contaminated items. Using appropriately labeled containers alerts personnel responsible for transporting the waste to wear appropriate protective gear, since gowns and gloves providing protection from chemical waste and potentially infectious (eg, red bag) waste differ. Requirements for disposal of HD waste once it leaves a clinical facility vary based on regulations in each state.

The body fluids and excreta of patients who have received antineoplastic agents are considered contaminated for at least 48 hours. This is a suggested time frame for using safe handling precautions; excretion times vary for individual drugs.[21] Health care workers should wear PPE for handling excretions or when handling linens contaminated with drugs or bodily fluids. Staff who are responsible for handling urinals, bedpans, and emesis basins should have access to PPE and be alerted to the need to protect themselves when handling contaminated excreta. Health care facilities should have separate toilet facilities for staff and patients. Patients should be taught to dispose of their excreta in a way to protect family members from exposure.

## BARRIERS TO HD PRECAUTION USE

Knowledge about the potential adverse outcomes from occupational antineoplastic exposure coupled with the documentation of ongoing exposure opportunities

- Policies and procedures exist. Compliance is expected.
- Education and training in safe practices is provided.
- Equipment and supplies necessary for safety are available.
- Safe behavior is reinforced and feedback provided to workers.
- Management supports safety programs.

**Figure 1** Indicators of a positive safety climate in health care facilities.

should be motivation enough for the universal adoption of safe handling precautions. Unfortunately, there is ample evidence to the contrary.[30,31] Nurses' education and training is necessary but not sufficient to ensure safe practice related to HD handling. Recent research indicates that characteristics of the practice setting are important in promoting health care worker safety.[31-33]

Many barriers exist that interfere with HD precaution use. Pender defines a barrier as the "unavailability, inconvenience, expense, difficulty, or time consuming nature of a particular action."[34(p53)] Types of barriers include practical barriers, such as the lack of or unacceptable nature of protective equipment; psychosocial barriers, such as worker or peer attitudes; environmental barriers, such as the safety climate in the organization; and situational barriers, such as time constraints, work pace, and work load.

Safety culture refers to the prevailing principles, norms, values, beliefs, and assumptions related to safety in an organization. Safety climate is how workers experience the culture, including their perceptions about the commitment of the organization to safety, which can be described as positive, neutral, or negative. Safety culture and safety climate are important because they affect workers' use of protective behaviors.[35-37] Some characteristics of a positive safety climate in health care organizations are listed in Figure 1.

Safety when handling antineoplastic drugs is a joint responsibility of employers, health care organizations, and employees, nurses, and other health care workers.[1,38] Employers should design a comprehensive program for safe handling with multidisciplinary participation. A comprehensive program includes policies and procedures, education and training, provision of safety equipment and PPE, and efforts to address workplace barriers that influence safety. In turn, employees have the responsibility to participate in education and training, recognize sources of exposure, and use safety equipment and PPE.

## SUMMARY AND CONCLUSIONS

This article provided a summary of the evidence for adverse outcomes from occupational exposure to antineoplastic drugs. Data were provided indicating that infusion nurses are potentially exposed to HDs in their practice. Finally, current recommendations for reducing occupational HD exposure were presented. The safety of infusion nurses and other health care workers is as important as patient safety. Nurses should not have to risk their own health when caring for patients. A careful evaluation of one's workplace and work practices related to antineoplastic drug handling is the first step in making the practice setting safe for patients and staff.

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