Hazardous Anticancer Drugs in Health Care

Environmental Exposure Assessment

THOMAS H. CONNOR

NIOSH MS C-23, Cincinnati, Ohio 45226, USA

ABSTRACT: Exposure of healthcare workers to anticancer drugs became problematic in the 1970s. Shortly thereafter, studies began documenting exposure of healthcare workers to these drugs. Investigations employing biological markers, such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and micronuclei, demonstrated associations between occupational exposures and elevated marker levels. Other analytical methods emerged to monitor workplaces where drugs were handled. These contemporary studies uncovered widespread contamination of drugs on work surfaces, trace amounts in air samples, and their presence in the urine of workers. Vials containing these drugs are often contaminated with the drug when they are shipped. Most workplace surfaces are contaminated with the drugs being prepared and used in that area. Other anticancer/hazardous drugs would most likely be used in these areas. The interior surfaces of biological safety cabinets and isolators, floors, countertops, carts, storage bins, waste containers, treatment areas, tabletops, chairs, linen, and other items are all potential sources of exposure to anticancer drugs. Patient body fluids contain the drugs and/or metabolites, often more biologically active than the parent compounds. An exposure assessment of areas where anticancer/hazardous drugs are handled must consider every potential source and route of exposure. Data from surface contamination and inhalation studies suggest that dermal exposure is the primary route of exposure. Assessment of exposure is the first step in providing a safe work environment for these workers. However, because of the many drugs to which they are exposed, any assessment can only be an estimation of the overall exposure.

KEYWORDS: antineoplastic drugs; occupational exposure; exposure assessment

Address for correspondence: Thomas H. Connor, Ph.D., NIOSH MS C-23, 4676 Columbia Parkway, Cincinnati, OH 45226. Voice: 513-533-8399; fax: 513-533-8138.
e-mail: tmc6@cdc.gov

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INTRODUCTION

According to the World Health Organization, more that 11 million new cases of cancer are diagnosed every year worldwide.[1] This number is expected to grow to 16 million by the year 2020. However, a diagnosis of cancer is not the dreaded death sentence that it used to be. Cancer patients are enjoying the benefits of the war on cancer. These benefits range from reduced side effects to improved and extended quality of life and in some cases, complete cures. A significant aspect of the treatment regimen for cancer patients is chemotherapy—treatment with drugs designed to kill cancer cells. Such drugs are often called anticancer drugs and have been in clinical use for decades. They are critical in the treatment of cancer and certain noncancer diseases.[2] An interesting historical note that was pivotal in ushering in the modern era of chemotherapy was the observation that exposure to mustard gas, used as a weapon in World War I, resulted in the hospitalization of veterans many years later with bone marrow toxicities. After World War II, the use of mustard gas analogs (nitrogen and sulfur mustards) led to remission in Hodgkin's disease. This initial success provided direction for today's status in which there are approximately 100 different anticancer drugs in use with many more under development. Chemotherapy has indeed opened many new avenues for today's cancer patient and provided hope for a disease that at one time had a very bad prognosis.

These drugs suppress cell proliferation and cause cell death, either directly by binding to DNA, RNA, or proteins in the cell or indirectly by inhibiting production of the same. Typically, these drugs cannot distinguish between normal and cancerous cells. As a purported consequence of this lack of selectivity, secondary malignancies were reported in patients who received anticancer drugs for other, usually solid, primary malignancies. The most commonly seen secondary malignancies were leukemia and bladder cancer reported after a latency period of 1–10 years.[3] While newer generation drugs, such as monoclonal antibodies may target sites other than genetic material and accordingly be more selective in their mechanism of action and as a result "safer," this is currently an exception and not the rule. The secondary malignancies, first observed in the 1970s, served notice of the potential problem. This problem is not just for cancer patients, but for workers in the pharmaceutical industry and members of the healthcare service team. The toxicity and hazards associated with the development of new drugs, the continued formulation of drugs currently employed as anticancer agents, and the preparation and administration of these drugs in the clinical setting all suggest this is an occupational concern. As the number of patients, the use of combinations of drugs, and higher doses of drugs increases, along with the development of more potent drugs, the potential for worker exposure to these hazardous drugs will also most likely continue to increase.

In terms of occupational exposure, a hazardous drug is defined as an agent that presents a danger to healthcare personnel due to its inherent toxicity. These

drugs are identified based on one or more of the following characteristics: carcinogenicity; teratogenicity or other developmental toxicity; reproductive toxicity; organ toxicity at low doses; genotoxicity; or structure and toxicity profiles that mimic existing hazardous drugs.[4–6] Hazardous drugs include anticancer and cytotoxic agents, some hormonal agents, immunosuppressants, antiviral medications, monoclonal antibodies, and several other miscellaneous drugs. A list of drugs that require special handling should be posted in every facility where hazardous drug preparation and/or administration take place.

BIOLOGICAL EVIDENCE OF EXPOSURE

Falck and co-workers[7] reported that nurses who worked in environments where anticancer drugs were prepared and administered had higher levels of mutagenic substances in their urine when compared to nonexposed workers. This study suggested that nursing personnel were being occupationally exposed to anticancer drugs, many of which are mutagenic. The results of this study was confirmed in many other efforts examining urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and other end points in pharmacists and nurses who handle anticancer drugs.[8–10]

In addition to various acute toxic effects resulting from exposure to anticancer drugs,[6] a review of 14 studies described an association between exposure to antineoplastic drugs and adverse reproductive effects, nine of which showed some positive association.[11] The most common reproductive effects found in these studies were increased fetal loss,[12,13] congenital malformations,[14] low birth weight and congenital abnormalities,[15] and infertility.[16]

SOURCES FOR WORKPLACE EXPOSURES

Many of the toxicological end points reported above are nonspecific and only serve as indirect measures of exposure. Such studies only imply causality and do not necessarily validate events in the exposure–disease continuum. Consequently, more direct methods of determining exposure have been developed. These methods include environmental air and surface sampling techniques to assess workplace contamination and analysis of the urine to determine the presence of parent drugs and/or metabolites of hazardous drugs handled by healthcare workers. All workers who come in contact with anticancer and other hazardous drugs have the potential to be exposed to them. These workers include: pharmacy and nursing personnel, physicians, operating room personnel, environmental services workers, workers in research laboratories and animal care facilities, veterinary care workers, shipping and receiving personnel, and waste disposal personnel. Exposure to anticancer drugs in the workplace may result from one or more of the common routes of exposure.

Dermal and inhalation routes are the likely routes of exposure to anticancer drugs in healthcare facilities. Therefore, surface wipe sampling and sampling for airborne drugs have been employed to determine workplace contamination with anticancer drugs. This methodology is similar to methods used in other occupational settings to determine the level and extent of contamination of the workplace and to establish safe working levels for other hazardous substances.

Surface Wipe Sampling: The method employed for determining chemical contamination in the healthcare facility has been the measurement of a number of marker anticancer drugs using wipe samples.[17] Sampling and analytical procedures have been developed for some of the more commonly used anticancer drugs that have been employed as markers of overall surface contamination. The more common drugs sampled include: cyclophosphamide, ifosfamide, 5-fluorouracil, methotrexate, paclitaxel, doxorubicin, and platinum-containing drugs.[17]

Since the early 1990s, studies by a number of researchers have examined environmental contamination of areas where anticancer drugs are prepared and administered in healthcare facilities.[18–31] Using wipe samples, all investigators measured detectable levels of one or more anticancer drugs in various locations, such as surfaces in biological safety cabinets (BSCs), floors, countertops, storage areas, tables and chairs in patient treatment areas, and locations adjacent to drug-handling areas. All of the studies reported some level of contamination with at least one drug, and several reported contamination with all the drugs for which assays were performed.

Several studies have documented that the outer surfaces of anticancer drug vials are often contaminated with the drug contained in the vial.[19,32–38] Various methods have been used to measure the amount of drug on the outer surface of the vials. These include wipe sampling, rinsing, and total emersion of the vials using a suitable solvent. However, because of the nature of the surfaces being sampled, it is difficult to determine the recovery efficiencies with drug vials, which likely results in underreporting of contamination. Once the samples are collected, analytical methods similar to those that have been used for surface wipe sampling have been applied for determination of the external contamination levels.

Studies of surface contamination with anticancer drugs typically employ a collection matrix (e.g., tissue or filter paper wipes) and a solvent system proven to aid recovery of the drugs being studied.[17] Specific strategies have been developed for collecting wipe samples for other chemicals in various industries[39,40] and similar methods have been applied to the sampling of cytotoxic drugs. If a sampling program is established for a healthcare facility, a sampling scheme should be developed which incorporates the areas of interest based on published studies. Such a program would require the appropriate analytical techniques necessary to identify and quantify the drugs that are being measured. Several analytical methods have been employed by researchers and are available in the

published literature.[17] These include high-performance liquid chromatography with ultraviolet detection (HPLC-UV), gas chromatography coupled with mass spectrometry or tandem mass spectrometry (GC-MS or GC-MS/MS) or high-performance liquid chromatography-tandem mass spectroscopy (LC-MS/MS). With the use of GC-MS (or GC-MS/MS) for drugs, such as cyclophosphamide and ifosfamide, derivatization is required prior to analysis.[18] Platinum-containing compounds can be analyzed using either voltammetry[29,41] or inductively coupled plasma mass spectrometry (ICP-MS).[22,42]

Measurement of Airborne Anticancer Agents: Several studies have measured airborne concentrations of antineoplastic drugs in healthcare settings.[18,20,28,41,43–48] In most cases, the percentage of air samples containing measurable airborne concentrations of anticancer drugs was low, and the actual concentrations of the drugs, when present, were also low. Most studies have employed glass fiber or paper filters to capture airborne particulates. These results may be attributed to the inefficiency of sampling and analytical techniques used in the past.[48] A solid sorbent material may be more efficient at collecting particulate forms of anticancer drugs. Both particulate and gaseous phases of one antineoplastic drug, cyclophosphamide, have been reported in two studies.[28,48]

Workplace exposure levels have been established for toxic chemicals in many occupational settings. However, no exposure levels have been established for airborne concentrations of anticancer drugs. There are, however, some exposure limits for soluble platinum salts and inorganic arsenic, which would include some of the anticancer drugs, such as platinum-containing compounds and arsenic trioxide.[6,49] Some pharmaceutical manufacturers have developed occupational exposure limits (OELs) that are used to set exposure limits in manufacturing facilities.[50]

While sources of exposure of healthcare providers to anticancer drugs include inhalation, dermal or possibly oral, a major route of exposure is inhalation via droplets, particulates, and vapors. Many procedures can result in aerosol generation (i.e., drug injection into an intravenous [i.v.] line, cleaning of air from the syringe or infusion line, and leakage at the tubing, syringe, i.v. spike, or stopcock connection, clipping used needles and crushing used syringes.[51,52] Drug particles can become airborne after drying of contaminated areas. Vaporization of antineoplastic agents has been recorded with various drugs, such as BCNU, ifosfamide, thiotepa, and cyclophosphamide.[28,53]

Ingestion: Inadvertent ingestion is another problematic issue. When food or beverages are prepared, stored, or consumed in work areas, they may become contaminated with airborne particles of cytotoxic drugs or by dermal contact. Hand-to-mouth exposure is a most likely route since most surfaces in areas where anticancer drugs are handled have demonstrated contamination. Because surface contamination has been reported outside of areas where anticancer drugs are handled,[24] exposure may result in adjacent areas where food or beverages are present.

SIMULATED EXPOSURE STUDIES

The use of fluorescent markers has been employed in some situations to simulate environmental contamination with anticancer drugs. Kromhout and co-workers[51] developed a semiquantitative fluorescent method to evaluate environmental contamination and Spivey and Connor[52] employed a fluorescent marker to demonstrate sources of environmental contamination during simulated drug preparation and administration. Prepared test kits that use a fluorescent marker are available to evaluate worker skills and training during drug preparation and administration.[54]

CONCLUSIONS

As the need for more anticancer drugs increases in the future, the potential for healthcare workers to be exposed to higher levels of more potent drugs becomes apparent. Past and current evidence indicates that workplace settings where anticancer drugs are prepared and administered to patients are contaminated with the drugs that have been used as markers of contamination. Since, the number of drugs that are typically assayed for is a small percentage of the known hazardous drugs, it is easy to speculate that contamination of the workplace with hazardous drugs is an ubiquitous event. Recent studies have documented the presence of these same marker drugs in the urine of healthcare workers, indicating systemic exposure to them. All this evidence highlights the critical need to reduce the risk of exposure to hazardous drugs to workers in the healthcare environment.

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