EPIDEMIOLOGY BULLETIN

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Editor: Carl W. Armstrong, M.D.

April, 1986

Volume 86, Number 4

Review of Guidelines for Safe Handling

Occupational Exposure to Antineoplastic Drugs

Therapeutic agents used to treat cancer are most commonly known as antineoplastic or cytotoxic drugs. At the present time, approximately 30 antineoplastic drugs are available commercially in the United States and another 70 are in some stage of clinical development. These drugs are administered to an estimated 200,000-400,000 patients annually (1). It has been estimated that a large hospital pharmacy may prepare more than one hundred injectable antineoplastic preparations during a week. In addition, these drugs are also administered in physicians' offices. Based on a survey, four specialties viz., internal medicine, general surgery, dermatology, and urology, utilize all forms of antineoplastic drugs to a great extent. Some specialists in internal medicine can be expected to administer an average of two parenteral antineoplastic drugs per week (2).

Antineoplastic drugs may be divided into several classes. These include alkylating agents, antimetabolites, antibiotics, mitotic inhibitors, and hormones (3). The major practical route of administering many antineoplastic drugs is via parenteral injection. Health care personnel such as pharmacists, nurses, physicians, and other hospital staff who are involved in the preparation, administration, and disposal of these drugs may be occupationally exposed to these agents. The potential routes of exposure to these drugs are primarily through inhalation of the aerosolized drug, absorption through the skin by contact, and ingestion through contact with contaminated food or cigarettes. Opportunity for exposure may occur at many points in the handling of these drugs. Aerosol generation may occur during any of the following manipulations: withdrawal of the needle from vials, use of syringes and needles or filter straws to transfer the drug, opening of ampules, expelling of air from syringes, or clipping of needles (2,4).

All of the cytotoxic or antineoplastic agents inhibit the growth of tumors by disrupting cell growth and killing actively growing cells. Even in therapeutic doses these agents produce toxic side effects due to their poor selectivity between target and normal cells. This picture of clinical toxicity has been well documented by the adverse effects noted in the treatment of patients (5). However, in recent years, there has been a considerable increase in concern over the potential occupational hazards associated with the handling of antineoplastic drugs. Several studies have appeared in the literature indicating that certain cytotoxic drugs have demonstrated mutagenic, carcinogenic and teratogenic effects (6-17). Albeit there is no conclusive evidence at the present time to suggest that repeated occupational exposures to small amounts of antineoplastic drugs over a long period of time have been causally related to carcinogenic or teratogenic effects, there is a growing concern for such potential effects in humans. A recent study has suggested associations between fetal loss among nurses and occupational exposure to antineoplastic

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drugs (18). Apart from their carcinogenic, teratogenic, and mutagenic potential, many antineoplastic drugs pose a more acute hazard due to their direct irritant effect on the skin, eyes, mucous membranes, and other tissues with which they may come into contact. Certain antineoplastic drugs may also produce allergenic responses upon contact with the skin (2,5). The occupational risk from handling an antineoplastic drug would depend upon its inherent toxicity, susceptibility of the individual to the drug's toxic effects, dietary habits, number of exposures, magnitude of exposure, and the type of exposure. Of these factors, only the number, magnitude, and the type of exposure can be controlled to any substantial degree (19).

In view of the potential occupational hazard to health care personnel handling antineoplastic drugs, various authorities and professional organizations have developed guidelines for the safe handling of these drugs. Included among these professional bodies are the National Institutes of Health (NIH) (20), American Society of Hospital Pharmacists (19), National Study Commission on Cytotoxic Exposure (21), the Society of Hospital Pharmacists of Australia (22), the Canadian Society of Hospital Pharmacists (23), Health and Welfare Canada (24), the Pharmaceutical Society, England (25), Mount Sinai Medical Center (26), and the Department of Industrial Relations, California (27). The recommended NIH guidelines have been reviewed by the Council on Scientific Affairs, American Medical Association (2) and accordingly, have been determined to be appropriate and most reasonable means of reducing the occupational exposure. Recently, the U.S. Occupational Safety and Health Administration (OSHA) (4) has also recommended controls and work practice techniques to limit exposure of workers to the antineoplastic drugs. The summary of guidelines recommended by various organizations and authorities is provided below and can be classified as: drug preparation, drug administration, accidental spills and exposure, waste disposal, and personnel policy.

Summary of Various Recommended Guidelines for The Safe Handling of Antineoplastic Drugs

Drug Preparation

1. All procedures involving preparation of antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet. Class II, Type A cabinets equipped with an exhaust canopy or Class II, Type B cabinets are preferred. Exhaust from the hood should be vented to the outside where feasible. OSHA recommends that where such cabinets are not currently available, a respirator with a high efficiency filter, preferably a Powered Air-Purifying Respirator, be used by personnel preparing the drugs.
2. The biological safety cabinet should be operated with the blower on, 24 hours a day, 7 days a week.
3. The biological safety cabinet should be certified by a qualified technician every six months or any time the cabinet is physically moved.
4. Work surface in the cabinet should be covered with plastic-backed paper to absorb spills and facilitate clean-up. The paper should be changed after each work shift or any overt spills.
5. The cabinet should be cleaned daily with 70% alcohol, and decontaminated weekly, or whenever spills occur.
6. Eating, drinking, smoking, chewing of gum, storing food, and applying cosmetics around or near the preparation area should be prohibited.
7. Personnel preparing the drugs should wear disposable surgical latex gloves. Polyvinyl chloride (PVC) gloves should not be worn since they are more permeable to a variety of drugs.
8. Double gloving is recommended for cleaning up spills.
9. Gloves should be routinely changed approximately every hour, or immediately if they are torn, punctured, or overtly contaminated.
10. A protective gown made of low permeability fabric with a closed front, long sleeves, and closed cuffs (elastic or knit) should be worn for all procedures.
11. All potentially contaminated garments must not be worn outside the work area.
12. Syringes and intravenous (I.V.) bottles should be labeled properly and include a warning for appropriate disposal.
13. All vials containing reconstituted drugs should be vented with a hydrophobic filter to reduce internal pressure. This will help to reduce the possibility of spraying and spillage when a needle is withdrawn from the vial septum.
14. A sterile alcohol-dampened cotton pledget should be used to wrap the needle and vial top during withdrawal from the vial septum. Similarly, when ejecting bubbles from the syringe, the tip of the needle should be covered with an alcohol-dampened cotton pledget.
15. The external surfaces of syringes and I.V. bottles should be wiped clean of drug.
16. Any material remaining in the top of an ampule should be tapped down before it is opened. A sterile gauze pad should be wrapped around the ampule neck before breaking the top to protect against cuts and to contain the aerosol produced.
17. Hands must be washed before and after gloving.
18. Contaminated needles and syringes should be disposed of intact to prevent aerosol generation by clipping needles. All contaminated bottles, vials, gloves, gowns, gauze, and other material should be placed in a plastic bag-lined box.

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Drug Administration

1. Disposable surgical latex gloves should be worn during all antineoplastic drug administration activities.
2. Protective outer garments, such as closed front surgical-type gowns with knit cuffs, should be worn.
3. Syringes and I.V. sets with Luer-lock fittings should be used whenever possible.
4. When bubbles are removed from syringes or I.V. tubing, a sterile alcohol-dampened cotton pledget should be carefully placed over the tips of needles, syringes, or I.V. tubing in order to collect any of the antineoplastic drug that may be inadvertently discharged.
5. Hands must be washed after administering the drug.
6. Contaminated needles, syringes, bottles, and other contaminated materials should be placed in a plastic bag-lined box for proper disposal.

Accidental Spills and Exposure

1. Overtly contaminated gloves or outer garments should be removed and replaced immediately after an exposure.
2. Hands should be washed after removing gloves.
3. In case of skin contact with the antineoplastic drug, the affected area should be washed thoroughly with soap and water. For eye exposure, affected eye should be flushed with copious amounts of water.
4. All personnel involved in the clean-up of a spill should wear protective clothing. All clothes and other material used in the process should be treated or disposed of properly.
5. Double gloving should be used in the cleaning up of spills.

Waste Disposal

1. All contaminated materials should be placed in a leakproof, puncture resistant container appropriately labeled as hazardous waste.
2. Antineoplastic drug waste should be transported according to the institutional procedures for contaminated materials.
3. Housekeeping personnel should wear gowns and surgical latex gloves when handling contaminated containers and cleaning the spills.

Personnel Policy

1. All personnel working with antineoplastic drugs must receive special training on handling procedures, proper use of equipment and materials, spill clean up procedures, and medical policies.
2. Access to the drug preparation area should be limited to only necessary authorized personnel.
3. A policy should be established for personnel who are pregnant or breast-feeding, and those who are actively trying to conceive a child.

These guidelines are intended to provide information for the protection of health care personnel participating in the clinical process of cancer chemotherapy. They appear to be prudent and if followed, should provide reasonable means to reduce the occupational exposure to antineoplastic drugs. However, these recommendations represent only basic safety procedures and may require supplementation by each institution, depending upon the facilities, local conditions, and practices.

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Heparin Sodium Contamination with *Pseudomonas putida*

On three occasions, from December 1985 to January 1986, *Pseudomonas putida* was isolated from routine surveillance cultures of bone marrow harvested from three donors at a single hospital in Minnesota. Cultures of all materials added to bone marrow at the time of collection were performed by the hospital. Eight of 70 unopened 5-ml glass ampules of a single lot (#84339) of heparin sodium without preservatives (manufactured for O'Neal, Jones & Feldman Pharmaceuticals, St. Louis, Missouri, by Torigian Laboratories, Queens Village, New York) were culture-positive for *P. putida*. Heparin was added to the marrow as an anticoagulant during the collection procedure. The hospital received lot #84339 in April 1985, but it was not used until November 1985.

Two of the three contaminated marrow specimens had been administered to recipients before the culture results were known. Neither recipient had blood cultures positive for *P. putida* or clinical signs of bacteremia, although antibiotic therapy was begun for both patients approximately 24 hrs after transplantation.

Investigation of *P. putida* bloodstream infections involving three other patients from two additional hospitals are ongoing. One patient, a 31-year-old female, developed *P. putida* bacteremia in July 1985, 7 days after receiving an allogeneic bone-marrow transplant. Harvested bone marrow had been mixed with heparin sodium without preservatives. The other two patients were neonates in a single hospital during July and August 1985. Their blood cultures were drawn through umbilical artery catheters and grew organisms identified as either *P. putida* or *P. fluorescens*. The catheters had been flushed with heparin sodium without preservatives. The lot numbers of heparin used on these three patients were not recorded, although the source of the product was the same as that for the Minnesota hospital.

Editorial Note: P. putida is a glucose nonfermenting gram-negative rod that has only rarely been associated with clinical infection. *P. putida* has many biochemical characteristics similar to *P. flourescens* (*1*). Heparin sodium without preservatives may be selected for use in clinical situations in which preservatives might have undesirable effects, such as for maintaining patency of intravenous catheters in neonates or anticoagulation of bone marrow harvested for transplantation.

After receiving the report of apparent *P. putida* contamination of heparin ampules from the hospital in Minnesota, the U.S. Food and Drug Administration (FDA) notified the product's distributor. The distributor voluntarily contacted purchasers of lot #84339, indicating that ampules of this lot should not be used until further notice. CDC, FDA, the distributor, and the manufacturer are performing cultures to detect potential contamination of other heparin ampules.

Hospitals that have identified patients with *P. putida* bloodstream infections in the past year are requested to report their findings through local and state health departments to CDC's Hospital Infections Program, telephone (404) 329-3406.

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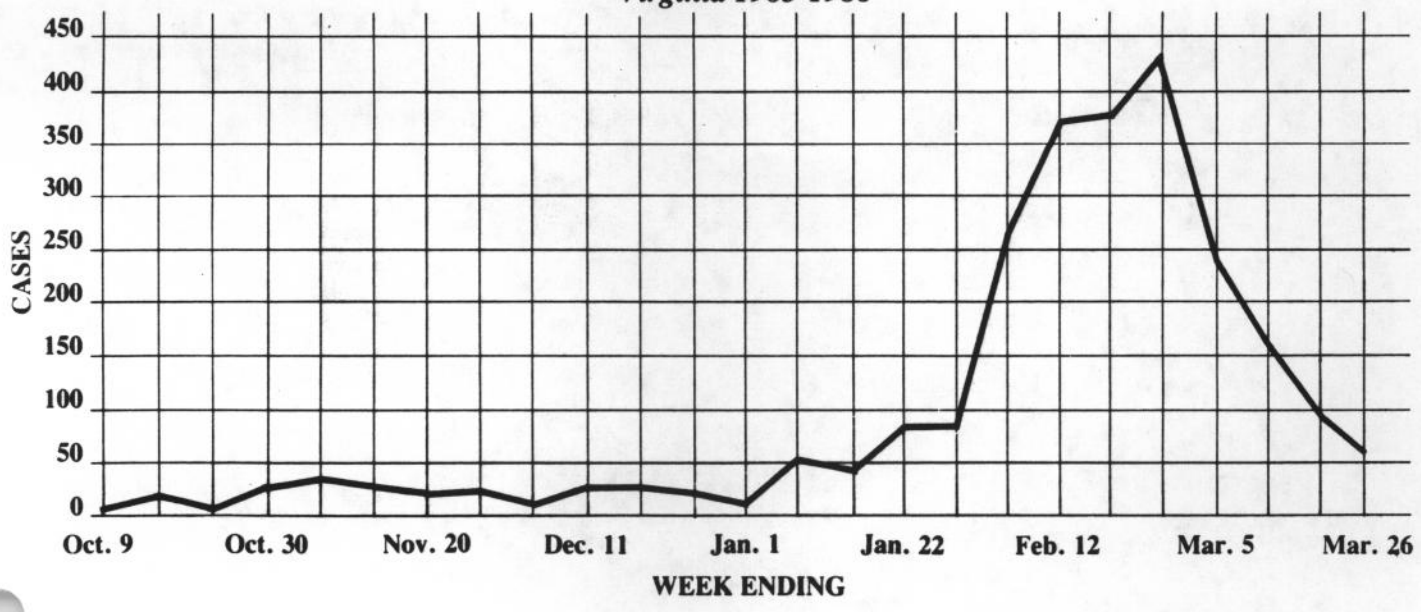
Reprinted from MMWR 1986; 35:123-4.

Influenza Surveillance
Virginia 1985-1986



Reports of influenza-like illness peaked for the week ending February 26 and subsequently subsided in March. Influenza type B was repeatedly isolated by several laboratories, suggesting that this virus type was in large part responsible for the outbreak.

Cases of selected notifiable diseases, Virginia, for the period March 1 through March 31, 1986

Disease	State					Regions				
	This Month	Last Month	Total to Date 1986	Total to Date 1985	Mean 5 Year To Date	This Month N.W.	This Month N.	This Month S.W.	This Month C.	This Month E.
Measles	0	0	0	7	5	0	0	0	0	0
Mumps	4	1	9	11	18	0	2	1	0	1
Pertussis	3	4	9	2	6	0	0	3	0	0
Rubella	0	0	0	0	1	0	0	0	0	0
Meningitis—Aseptic	4	15	37	60	33	0	0	2	0	2
*Bacterial	35	21	78	86	75	3	5	8	1	18
Hepatitis A (Infectious)	26	10	40	59	44	15	2	4	1	4
B (Serum)	63	30	117	143	126	4	13	16	15	15
Non-A, Non-B	8	8	18	26	22	2	1	1	1	3
Salmonellosis	92	65	224	293	235	8	21	16	22	25
Shigellosis	4	4	13	17	70	2	1	0	0	1
Campylobacter Infections	23	26	76	111	69	5	7	1	1	9
Tuberculosis	43	24	79	69	107	4	10	3	12	14
Syphilis (Primary & Secondary)	45	28	127	86	138	4	5	13	5	18
Gonorrhea	1662	1492	4433	4571	4815	—	—	—	—	—
Rocky Mountain Spotted Fever	1	0	1	0	0	1	0	0	0	0
Rabies in Animals	35	9	50	45	82	19	7	3	6	0
Meningococcal Infections	29	6	37	23	23	15	2	3	3	6
Influenza	1153	1696	2863	791	1418	63	10	702	118	260
Toxic Shock Syndrome	3	1	6	0	1	0	1	2	0	0
Reyes Syndrome	0	0	0	1	3	0	0	0	0	0
Legionellosis	0	0	3	5	4	0	0	0	0	0
Kawasaki's Disease	3	2	7	13	8	0	0	2	0	1
Other: Acquired Immunodeficiency Syndrome	9	24	54	15	—	1	3	1	1	3

Counties Reporting Animal Rabies: Caroline 1 raccoon; Fauquier 4 raccoons, 1 skunk; King George 1 fox, 1 horse; Rockingham 1 raccoon; Shenandoah 1 grey fox, 3 raccoons, 1 skunk; Warren 1 lamb, 3 raccoons, 1 sheep; Fairfax 1 fox, 3 raccoons; Loudoun 2 raccoons, 1 skunk; Alleghany 1 bobcat, 1 raccoon; Russell 1 skunk; Hanover 6 raccoons

Occupational Illnesses: Pneumoconioses 30; Asbestosis 8; Silicosis 4; Dermatisis 3; Hearing loss 3; Carpal tunnel syndrome 3; Chemical poisoning 1; Respiratory disorder 1.

*other than meningococcal

Published Monthly by the
VIRGINIA HEALTH DEPARTMENT
Division of Epidemiology
109 Governor Street
Richmond, Virginia 23219