ADRIAMYCIN EXPOSURE STUDY AMONG HOSPITAL PERSONNEL

R.L.Stephenson, C.I.H., Thomson Consumer Electronics Inc., Marion, IN.,
C.H.Rice, Ph.D., C.I.H., and J.Dimos, M.S., University of Cincinnati,
Department of Environmental Health, Kettering Labs, Cinti., OH.

ABSTRACT

Using antineoplastic drugs is one of the routine treatment regimes employed in combatting cancer. Nearly 250,000 cancer patients are treated annually with chemotherapeutic agents usually in either hospital outpatient or inpatient settings, however, some patients receive these drugs in physicians' offices or outpatient clinics.[1] The number and types of health care professionals who are potentially exposed to antineoplastic drugs includes but is not limited to 4,000 medical oncologists, 10,000 oncology nurses, 30,000 pharmacists, and even greater numbers of staff nurses and support personnel.[1,2]

A project was undertaken to utilize a visible light fluorescent method previously developed at the University of Cincinnati, to document areas of adriamycin contamination (skin and work surfaces). Specific aims of the study were to compare the degree of contamination among pharmacists or pharmacy technicians, intravenous (I.V.) therapy administration personnel, oncology nurses, patient care nurses, maintenance workers, and hospital laundry workers, and to describe the population at risk of dermal exposure to this antineoplastic agent and recommend measures to prevent exposure.

Sixty-four observations/monitoring sessions for adriamycin exposures in a hospital setting were conducted from June - August 1988, for dermal contact with adriamycin. No dermal exposures to adriamycin among the hospital staff monitored were found. In addition, no adriamycin contamination was documented on any work surfaces. There were however, several noteworthy findings. The ability to detect fluorescence of adriamycin (2 mg/ml to 0.002 mg/ml) applied to some of the disposable latex gloves, disposable gowns/smocks, toweling, front covers of the infusion pumps, and several other work surfaces typically found in the hospitals surveyed, varied according to the material/work surface and the concentration applied. Understanding of the sensitivity of the methods and potential interferences will greatly aid in the interpretation of positive results.

INTRODUCTION

Background

Antineoplastic drugs such as adriamycin, cyclophosphamide, methotrexate, mitomycin, dacarbazine, and cisplatin, are used in cancer treatment. Several of these drugs produce mutagenic, carcinogenic, and teratogenic effects in some cancer patients.[3,4,5] Clinical research has been concerned with patients and their health status following drug administration. Relatively little attention has been given to persons exposed to antineoplastic drugs occupationally, during preparation and administration of the drugs, or following treatment of the patient. However, there has been a growing number of studies in this area, some of which have shown mutagens or thioethers in the urine and sister chromatid exchanges among personnel regularly handling cytotoxic drugs.[6,7,8]

Some 25 antineoplastic drugs are commonly used in cancer therapy.[5] Thirty-two agents are commercially available for treatment, and another 80 are in clinical development.[1] Many of these modern antineoplastic drugs are highly toxic. Health care personnel who formulate, administer, and clean surfaces that have contacted these drugs may be at risk of developing a number of adverse effects, including cancer and fetal loss. The population presently estimated to be occupationally exposed to antineoplastic agents includes, but is not limited to, thousands of employees in the pharmaceutical manufacturing plants, 30,000 hospital pharmacists, 4000 medical oncologists, 10,000 oncology nurses, and even greater numbers of general staff nurses and support personnel in hospital laundry maintenance and housekeeping. Effects of chronic exposure to these drugs at very low dosages, as would be expected occupationally, cannot be predicted with presently available data. Only two studies have been published reporting any environmental sampling for antineoplastics in the hospital setting. Both of these papers reported airborne levels of antineoplastics, though neither study developed acceptable methods for generalized use in airborne exposure assessment.[9,10] In addition, no studies are available to confirm the effectiveness of engineering controls, protective apparel, or work practices, along with proper handling and disposal techniques for controlling the risk of contact with these drugs. Few if any reports have been published which examined drug contamination of hospital surfaces, staff clothing, or soiled bedclothes or methods to remove residual drugs.

Antineoplastic drugs include alkylating agents, antimetabolites, antimitotic agents, antibiotics and other drugs. The main therapeutic purpose is to destroy cancer cells by blocking various biochemical pathways. The specific site of action varies, depending on the particular class of agent. The general mechanism of action is either through direct interaction with DNA or inhibition of nucleic acid synthesis.[11] Many of these drugs have been shown to be carcinogenic, mutagenic and teratogenic in experimental systems, and therapeutic doses of antineoplastic drugs have been associated with the

development of secondary tumors in patients receiving chemotherapy. Aside from their actions on tumor cells, antineoplastic agents can interfere with normal body cells resulting in damage and, in some cases, cell death.[11]

Surgery, radiation, and chemotherapy are three types of medical treatment commonly employed to combat cancer. Chemotherapeutic agents such as adriamycin, are used because of their cytotoxicity. Adriamycin is one of the most widely used of all the anticancer agents. It is frequently used to treat tumors characteristic of leukemias, lymphomas, Hodgkins disease, and carcinomas of the breast, ovaries, bladder, stomach, lung, thyroid, and bronchus. Most of the antineoplastic agents currently in use today are supplied as powders in vials or as liquid solutions requiring reconstitution or dilution prior to administration by intravenous or parenteral injection. Often pharmacists wearing gloves and protective smocks handle these drugs in biological safety cabinets. The concentration is usually 2 mg/ml adriamycin hydrochloride in sterile saline solution and the volume is adjusted for each patient using additional sterile saline for dilution. The recommended dosage schedule (adriamycin) for adult patients is 60-75 milligrams per square meter (mg/m^2) of body surface as a single I.V. infusion. The drugs are administered in various schedules, such as once every three weeks, or on three successive days every four weeks, until a total dose of 550 mg/m^2 (adriamycin) has been given.[12] The exact regimen depends on the drugs used, type of cancer and the health status and responsiveness of the patient. Patients may receive drug therapy in a variety of settings; hospital inpatient, hospital outpatient, in the physician's office or in the home.

A variety of personnel are potentially exposed to the antineoplastic drugs including nurses, doctors, and pharmacists who prepare and administer the drugs, and maintenance and housekeeping staff, who repair, clean, and/or dispose of equipment following administration of the drugs or work in the rooms or offices where the drugs were administered. Adriamycin, like most other drugs, is often not fully utilized by the patient (the dose administered is not fully absorbed: some of the drug is excreted as is and some is excreted in metabolized forms). Therefore, vomitus and excreta may contain the drug and/or its metabolites. Housekeeping and custodial staff may be exposed during routine operations. Patient care personnel must handle bed linens contaminated with vomitus and excreta which may contain drugs. Unprotected laundry workers may unknowingly transfer drugs from the linens to their hands. In general, contaminated waste, bedlinens, vomitus and excreta may be handled by a number of persons involved in either treatment, patient care or facility maintenance and the extent to which the personnel contaminate their skin as a result of contact with drugs, waste or soiled linens has not been documented. Other ways that the antineoplastic drugs can be released into the work environment include contaminated packaging (broken vials damaged during shipping), powders and liquid sprays (aerosols) released during preparation, administration and routine cleanup operations, spills or leakage from syringes, I.V. bags, residual contamination on used syringes, gloves, linens, vials, I.V. bags, and tubing. Although volatilization is not a property of the currently available cytotoxic agents, aerosolization of the drugs can occur during preparation and administration. Routes of entry into the body

are through skin absorption (dermal), inhalation of aerosolized drug, accidental self-innoculation and ingestion. Ingestion can occur during mouth-breathing, smoking, eating, drinking, or other hand-to-mouth contamination. Direct skin contact and inhalation of aerosolized drug are often the greatest sources of exposure.

Adriamycin

Adriamycin, also known as doxorubicin, is a red crystalline solid that is soluble in water, aqueous alcohols and methanol. This cytotoxic antibiotic is isolated from cultures of Streptomyces peucetius. It is produced by three companies; one in Japan, one in Italy and by one domestic manufacturer. Spectrofluorometric methods have been used for identification and estimation of the drug in biological fluids and tissues.[12]

By knowing the excitation and emission wavelengths characteristic of a compound, one can use the fluorescence phenomenon to identify and quantitate such compounds. One of the physical characteristics of adriamycin is that it fluoresces when activated by certain wavelengths of visible and short wave ultraviolet light. In prior research studies conducted by Rice, Van Raalte, and Dimos et. al.[13] at the University of Cincinnati, a spectrophotometer was used to characterize the absorption spectrum of adriamycin hydrochloride in saline solution with lactose, as it is constituted for patient administration. They found that absorption in the visible range took place, with a peak at 470nm. Using a spectrofluorometer they examined the excitation/emission spectrum for adriamycin hydrochloride in saline solution and found a maximum intensity occurring at 580 nm. The examination of fluorescence excitation/emission was confined to the visible region since ultraviolet illumination was not considered as an option for the project.

EVALUATION METHODS

To insure the easy availability of the equipment used for this project, only readily accessible materials were considered for the various components shown in Figure I. A Kodak model AF-1 Ektagraphic slide projector was used as a light source to stimulate fluorescence; the optical system of the projector was equipped with a condensing lens and an infrared filter. The projector was equipped with a 300 watt tungsten-halogen projection lamp and a glass filter (BG-12 4084 Filter) which selectively passed short wave (blue) visible light was placed into the slide projection compartment. A 35mm single lens reflex camera with a Vivitar 55mm 1:2.8 macrolens and a Kodak Wratten number 21 gelatin filter (75mm x 75mm) was used to photograph the fluorescent emission from adriamycin. The Wratten filter absorbed the stimulating blue light emitted by the light source, allowing only the orange-red fluorescent glow of the adriamycin to be photographed. Sunglasses were worn during visual observations to filter out the interfering light emitted by the stimulating light source; ultraviolet and blue filtering sunglasses manufactured by Sun Tiger (Pasadena, CA) block transmission of light below 550 nm and were used in this research. To insure constant intensity and maximize sensitivity, attempts were made to maintain the background light levels at a minimum. All photographs were taken with the stimulating light source (projector) and camera held at 20-25cm from the fluorescent materials, and the angle between the light source and camera held to less than 45 degrees. With background light levels under 10 lux, using Ektachrome 160 tungsten film, exposure times between 1/4 and 1 second, and a maximum aperture setting of 2.8, the presence of adriamycin fluorescence on test materials was demonstrated with concentrations ranging from 2.0 to 0.002 mg/ml placed on various materials including but not limited to stainless steel, benchtop absorbent padding, a cotton lab coat cloth and latex glove material. These materials were felt to be typical of the types of materials on which antineoplastics might spill or leak in the clinical setting. Orange-red fluorescence was observed on all test materials at all concentrations except for the most dilute which was not observed to fluoresce on stainless steel or latex. Monitoring was conducted on the worksurfaces, protective clothing and exposed skin both prior to and after handling adriamycin itself or materials possibly contaminated with adriamycin.

RESULTS

Sixty-four separate monitoring sessions for adriamycin exposures in hospital environments were conducted from June - August 1988, for dermal contact with adriamycin. The various jobs monitored for adriamycin exposure included full-time pharmacists, pharmacy interns, technicians, physician assistants, nurses, laundry workers and maintenance workers. The areas and work surfaces monitored for adriamycin contamination included chemotherapy preparation areas, outpatient departments, filters in biological safety cabinets and HVAC systems, hospital laundry areas, and chemotherapy infusion equipment. No dermal exposures to adriamycin among the hospital staff monitored were found. Many of the pharmacists monitored were double gloved and wore protective smocks when they mixed adriamycin. Furthermore, all the hospital personnel surveyed followed good work practices when handling antineoplastic drugs. In addition, no adriamycin contamination was documented on any work surfaces. There were however, several noteworthy findings.

The ability to detect fluorescence of adriamycin (2 mg/ml to 0.002 mg/ml) applied to some of the disposable gloves, disposable gowns/smocks, toweling, front covers of the infusion pumps, and several other work surfaces typically found in the hospitals surveyed, varied according to the material/work surface and the concentration applied. For example, the ability to detect fluorescence on some types of latex gloves and especially orange-red colored gloves, and on stainless steel, was reduced with the more dilute concentrations of adriamycin. Allowing the eyes time for dark adaptation may play a role in increasing one's ability to detect fainter fluorescence over smaller areas. The increased illuminance of background light levels in the survey area which were more than the optimum range of 10 to 35 lux, provides for an additional interference problem. The excitation BG-12 4084 filter mounted on the projector was chosen due to its availability and because it has a transmission peak at 400nm; it passes relatively little of the fluorescence stimulating energy of 480 nm wavelength. While the filter was adequate, fluorescence intensity would likely increase with the use of a filter with peak transmission at 480nm. Lastly, some difficulties arose in conducting the field evaluation using the bulky equipment. No doubt, miniaturization of the detection system would provide greater acceptance for its use throughout the health care environment.

CONCLUSIONS

This research demonstrates that a unique fluorescent detection system can be used to reduce present uncertainties involved in occupational exposure to antineoplastic drugs. Fluorescence detection provides a simple means of measuring the contacted area. This method is quite useful in assessing the adequacy of cleanup after the drug has been spilled. The method is sensitive, minimal equipment is required, and very little training is needed to enable personnel to monitor their own work areas and skin. For less than $100.00, along with a slide projector, any work area can be monitored for adriamycin contamination on a continuing basis by visual observations. Further research is needed to define the limit of detection of visible light stimulated fluorescence detection of adriamycin and optimize the method for use in the field. The use of visible light to stimulate fluorescence may have broader applications in industrial hygiene and dermal exposure and surface contamination studies. Stimulating light sources equipped with several interchangeable filters could allow for rapid detection of a number of compounds.

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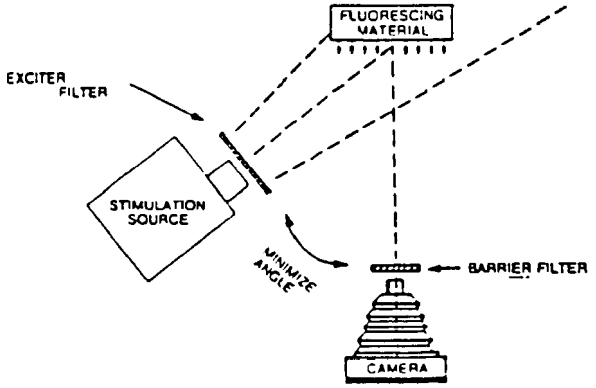

Figure I. Schematic of fluorescence detection equipment.

DISCUSSION

PHIL GREENBAUM: I wondered if you had checked to see if any studies had been done as far as birth defects related to this drug?

RICH STEPHENSON: Perhaps there's some literature that has been published on that. I can't recall them off the top of my head, though.

JUDD POSNER: It seems to me that this red drug had a capacity for being determined with probably the simplest of the spectrophotometers that involve the eye, and how much more sensitive in general was the UV than just looking around for red spots?

RICH STEPHENSON: We didn't use the UV detector because of the hazards associated with the UV light. We went with something that posed less of a hazard, the visible light source.

JUDD POSNER: How much more sensitive was the visible light measurement than the eye could see? I mean, do you have some idea about what kind of increase in sensitivity that gave you?

RICH STEPHENSON: That wasn't part of my thesis. It perhaps would be an interesting topic for additional work.

HARRY SALEM: You stated that there was no dermal contamination, yet I observed from your slide the pharmacist was wearing double gloves and short sleeves. Was the potential dermal contamination tested on the bare arms or under the gloves or protective clothing?

RICH STEPHENSON: Before the pharmacist or intern mixed or applied the drug, we looked at the hands and the arms, and any exposed skin surface. And definitely before they donned any gloves. And then we looked at it afterwards. In prior studies done by Rice and VanRaulty, they did find some contamination. But I think just knowing that we were present in the hospital environment and telling the participants what we were looking for and why we were there, there was a learning curve that happened right on the spot. So they took extreme caution to follow good work practices and not spill any on their hands or clothing.

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