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ORIGINAL ARTICLES

The Spread of Chemotherapeutic Agents at Work: Assessment Through Simulation

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ABSTRACT

An innovative simulation technique employing a saline-soluble fluorescent dye for evaluating the potential contamination by cancer chemotherapeutic agents of the work area and of personnel during normal mixing and administration procedures has been developed. The technique involves replication of routine mixing and administration procedures within a sampling frame laminated with a nonfluorescent surface. The user also wears protective clothing and gloves which are later examined for contamination by the fluorescent dye, as are the vials and syringe. Typical results are presented here. Observations made during technique development demonstrate that under many routine procedures the work surface, hands, and clothing, particularly the inner sleeves and chest covering, are contaminated by the dye. The usefulness of the technique and the implications of these data are discussed and practical suggestions for preventing similar exposure from cancer chemotherapeutic agents during actual use are given.

INTRODUCTION

The potential occupational exposure to cancer chemotherapeutic agents by medical personnel who mix and administer them has been under investigation for several years. The report of Falck et al. (1), which demonstrated elevated levels of mutagenic substances in the urine of nurses who routinely handle the drugs spurred much of this interest. Since then a few studies have shown that the drugs can become airborne during mixing and other manipulations (2) and minute traces of cyclophosphamide have been found in the urine of some oncology nurses (3). As a result, a number of guidelines have been issued by various agencies and professional groups in an effort to minimize the potential exposure (4).

It is believed that the major routes of occupational exposure to cancer chemotherapeutic drugs come from inhalation of the aerosolized drug or from absorption by direct skin contact. Aerosols of drugs can be generated by manipulations which include insertion and withdrawal of syringes from the vials containing the drug, the expelling of air from the syringe, and drug transfer

procedures. Skin contact can occur during the opening of the ampules, from spills and splatters, and also from contact with surfaces contaminated by the aerosols.

Despite this new awareness, and in some cases, anxiety about the potential problem, the true extent of exposure to the drugs among health care professionals is not known, nor have the major routes of entry of the drugs into the body been defined. Indeed, assessment of actual exposure is a technically difficult procedure for several reasons: (i) most users handle a variety of drugs during the workday; (ii) the quantity of materials mixed or administered during any single procedure is relatively small; and, (iii) generally the mixing and administration schedules vary greatly from day to day. These factors (e.g., small quantities and varying routines) make it difficult to apply typical air sampling and other industrial hygiene techniques routinely used to obtain precise and representative samples of workplace conditions. In these situations it becomes necessary to modify standard procedures.

In this paper we describe one approach developed for the evaluation of the potential spread of contamination by the drugs in work areas. The method employs a tracer substance used in a simulation technique, rather than a method entailing the direct measurement of airborne levels of drugs. It is designed to identify whether typical drug-handling techniques lead to the aerosolization of drugs or to spillage, with the consequent probable contamination of work surfaces, hands, arms, and clothing. This technique, which we call ChemoTest, was also developed to provide visualization of the potential sources of exposure to drugs to users and hence to help them to develop safer working procedures. Some typical results obtained during the development process are presented.

MATERIALS AND METHODS

The simulation method, ChemoTest, consists of the following. Drug mixing is monitored by use of a tracer dye which is visible under ultraviolet light. The dye was selected for its solubility in saline and because its molecular range is similar to a large number of the actual drugs. The dye is placed in a vial and the user is provided with two cardboard sampling frames, each 14 in.^{2} on the bottom surface and 14.5 inches in height, and laminated with a nonfluorescent surface material. Several sets of protective gloves and two sets of sleeve covers and aprons, all of which have been prescreened to insure the absence of fluorescent contaminants, and prelabeled plastic bags for storage are also provided. A blacklight detector is included for the on-site evaluation of the test.

A step by step set of instructions was developed with the assistance of the initial participants to guide the user through a procedure in which the dye is dissolved in saline, using the procedures and techniques that would normally be followed in an actual drug admixture. This mixing procedure is carried out in the "mixing" sampling frame (Fig. 1) while wearing the protective gloves, apron, and sleeve covers. After trials with different numbers of vials, it was determined that the mixing of three vials is adequate for visualizing aerosol dispersion and spread.

The initial development of ChemoTest was carried out with the assistance of two oncologists, two pharmacists, and six oncology nurses, each of whom routinely mixes and administers cancer chemotherapeutic agents. A variety of working conditions were utilized in the testing, including both a horizontal and vertical laminar flow hood and open bench procedures.

ChemoTest was designed originally to be analyzed away from the worksite, with the user packaging the protective equipment and sampling frames and shipping them to the laboratory for evaluation. The on-site trials demonstrated, however, the utility to the user of visualization of aerosolization during the test and the test system was therefore modified to include a portable ultraviolet light. Thus after admixture, the protective clothing is scanned by the user under the ultraviolet light and then removed and placed in prelabeled plastic storage bags for a second closer inspection in the dark and then for shipment back to the author. Results of the on-site and darkened room analyses are recorded on precoded analysis sheets.

A second "administration" sampling frame is then set up in a location away from the admixing location, a new set of protective gear is put on and a simulation of the administration procedure carried out. In this phase the mixed dye from one of the vials is used and the user "administers" it into a bag of saline. Again the user is asked to replicate all usual drug withdrawal and administration techniques. No specific warnings against procedures such as removing air from the syringe by expelling into the air are given. The protective clothing is again examined and then removed and placed in designated storage bags for reinspection, recording of results and shipment.

After this simulation of mixing and administration, all the materials are removed and examined under the ultraviolet light in the darkened room. The ultraviolet examination will "visualize" drugs that have been aerosolized or splattered and have contaminated either the sampling frame or the protective clothing. After user examination of these materials, results are recorded and the

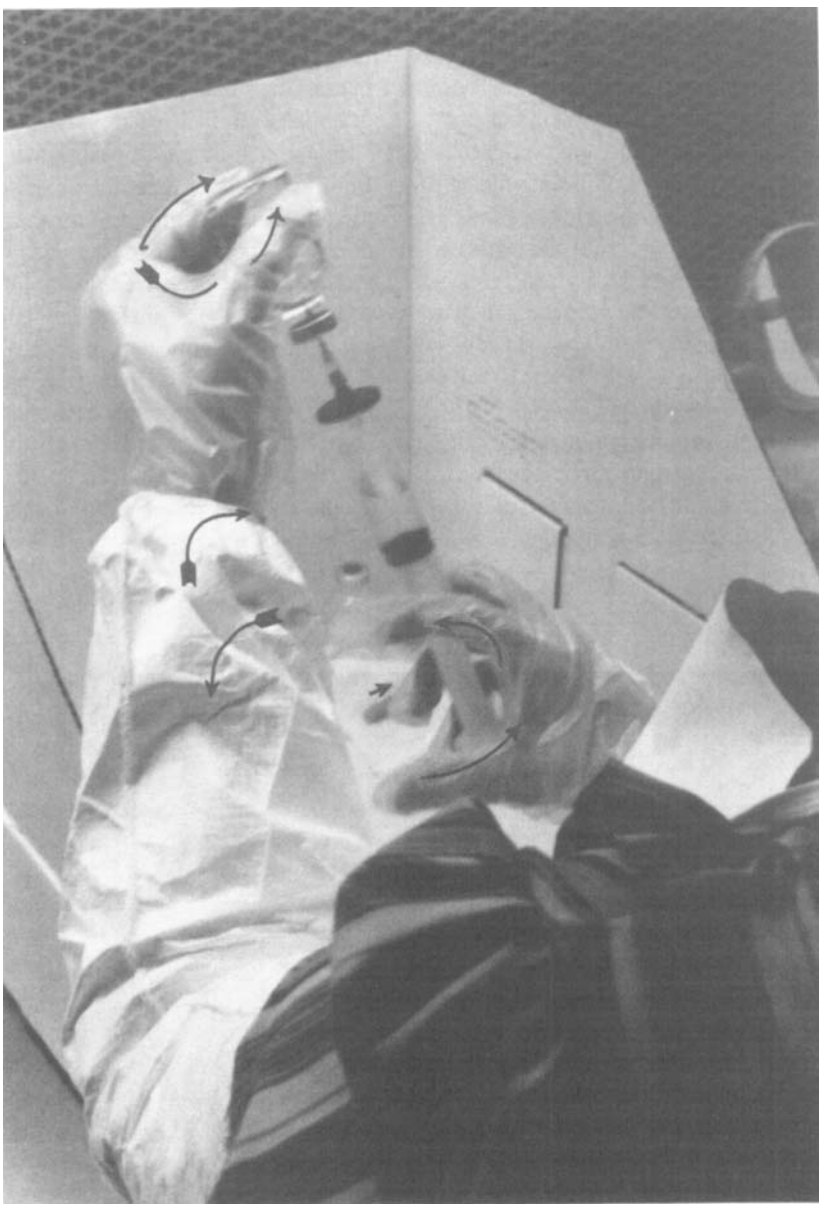

Figure 1. ChemoTest users dissolving fluorescent dye in sampling frame. Arrows indicate areas typically contaminated by the dye.

materials are packaged and returned to the author for more intensive evaluation and final report.

Discrepancies between the author's reading of the results and the users are discussed in a written report. Fluorescent spots and contaminated areas are highlighted with fluorescent marker and returned to the participant.

RESULTS

The results obtained during development of ChemoTe procedures demonstrate that the simulation technique c successfully be used to "visualize" the aerosolization tracer materials during admixing and administrati

maneuvers identical to those used during actual drug-handling techniques. The tests also show that the potential for spread to work surfaces, work area walls, and the hands and clothing, particularly the sleeves, is real.

Figure 1 shows the area of contamination most commonly observed on the gloves and sleeves of the participants in ChemoTest development and among the first test system users. The sleeves were typically contaminated with large "droplets" of dye, while the gloves showed a clear curved pattern, where contact with the vials or the syringe presumably occurred. Typically the protective aprons were "spattered" with the fluorescent dye material, particularly in the upper chest area. This occurred when tests were carried out both "open bench" and under a vertical laminar flow hood.

In Figures 2, 3, and 4 surface contamination of the workstation, the vials, and the syringe can be observed. These are typical findings. It should be noted that the contamination of the work surface station in Figure 2 is heaviest on the bottom, but also reached all three sides. Since contamination of the gloves, sleeves, and apron was also observed during this mixing procedure, it is logical to assume that the spray also went in the direction of the user. This surface contamination was observed after sequential "mixing" of three vials.

The contamination of equipment surfaces is shown in Figures 3 and 4, where droplets of dye can be seen on the end of the syringe and on the top and upper sides of the vial. This, again, is a typical pattern of spray. The gloves of the user were contaminated in areas corresponding to these surface contamination areas on the equipment. In only two instances to date, among more than 40 tests, was ChemoTest equipment analyzed in which no fluorescence attributable to the dye was observed. These tests were carried out by two pharmacists who placed an alcohol dampened pledglet around the needle and the top of the vial each time the needle was withdrawn.

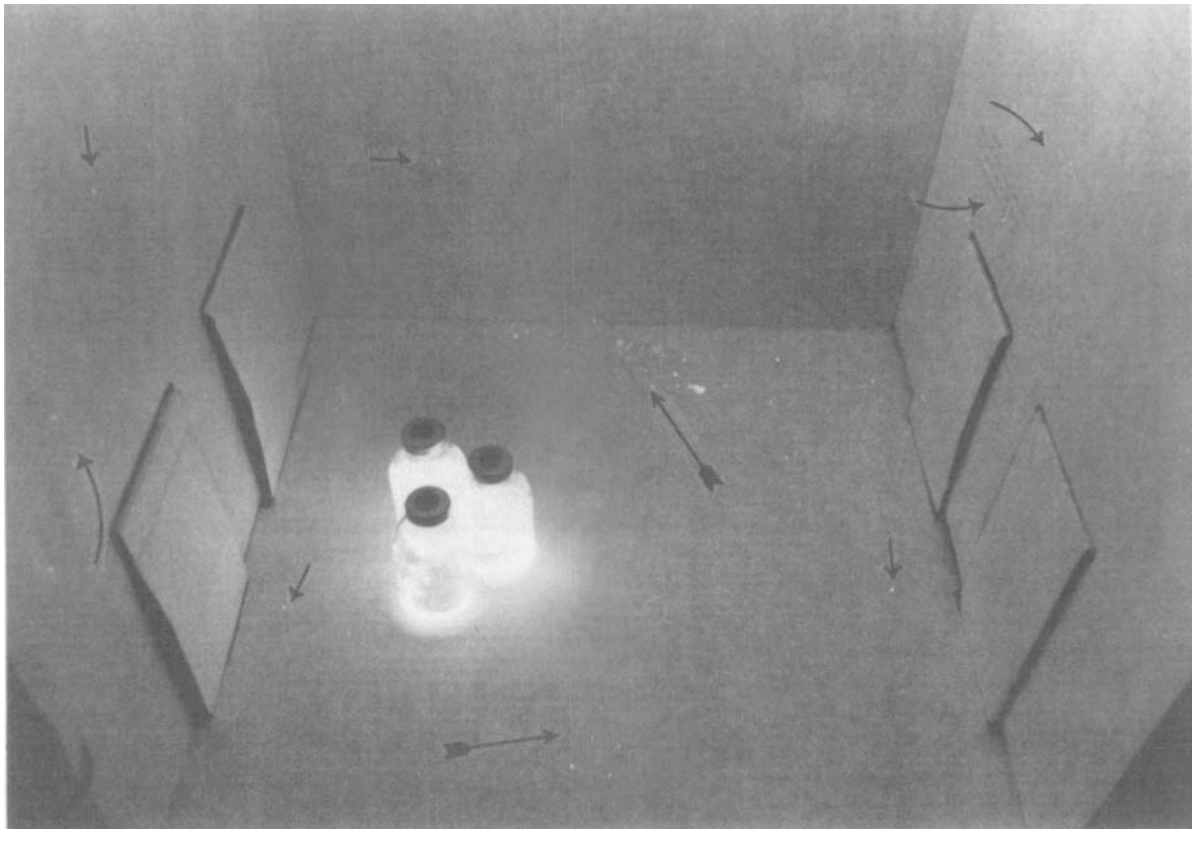

Figure 2. Work station observed under ultraviolet light after three vials containing dye were mixed with saline. Arrows indicate areas where fluorescence can be seen.

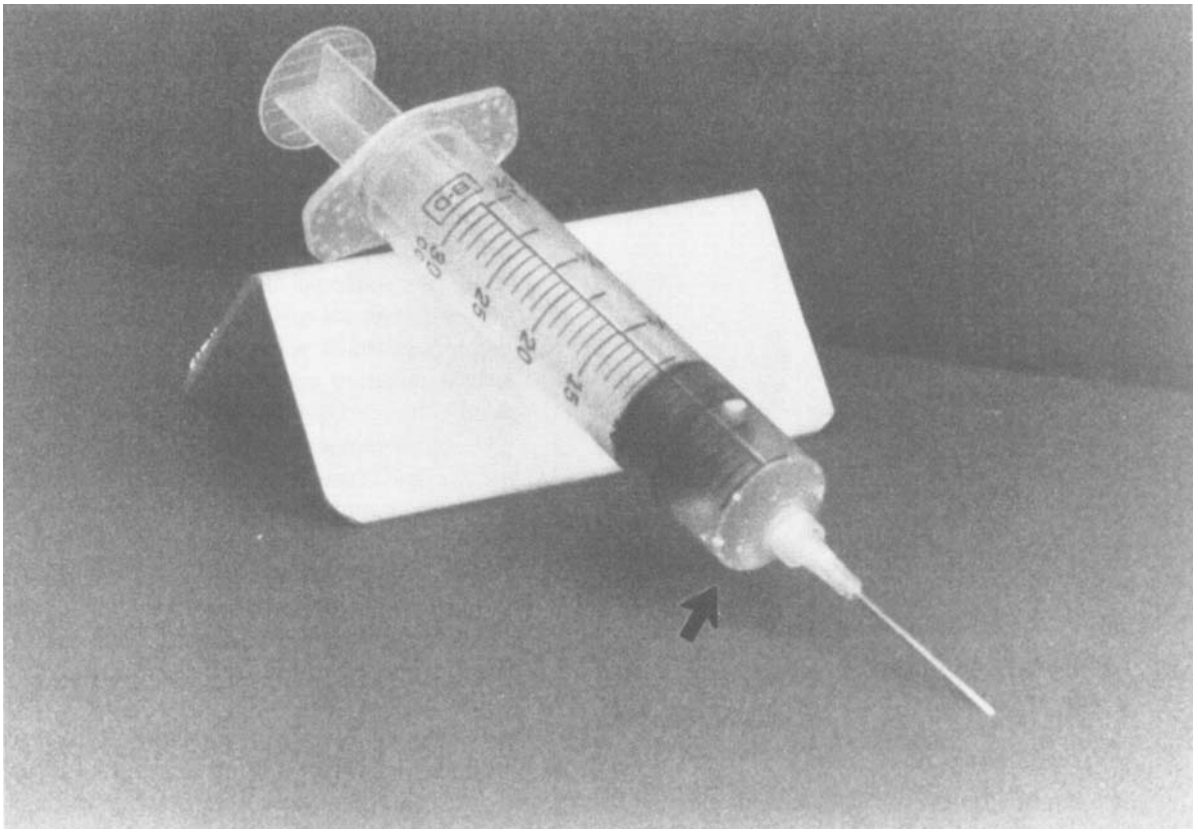

Figure 3. Contamination of exterior of syringe by fluorescent dye after mixing procedure.

DISCUSSION

The question of inadvertent exposure of health care personnel to cancer chemotherapeutic agents is, of course, a timely and important issue. As discussed above, the technical difficulties in the industrial hygiene assessment of exposure have hampered the ability to define fully the extent of exposure, if any, to these drugs. The data presented here show that the tracer system described can be useful in further elucidating those techniques which can lead to exposure, and those which can successfully prevent it. Further, the results obtained during the development of the test and from initial users "visually" demonstrate some potential areas in which the agents can be spread during routine work.

The first results obtained from participants in the ChemoTest monitoring system demonstrate a possibility that a large percentage of people who mix and administer cancer chemotherapeutic agents use techniques with the potential for spreading the agent onto work surfaces, clothing, and most probably with the potential for aerosolization and consequent inhalation. The techniques used for the dye mixing and administration procedures showed extensive contamination to the protective gloves in all but two of the users.

It is important to note that these data are not reflective of actual drug contamination but rather of contamination attributable to the simulation technique. There is also no data presented here which measures whether absorption of these dyes (which are nontoxic) occurred. There is little reason, however, to believe that mixing and administering techniques which were used in the simulation technique produced a different result from that which would be obtained from a procedure entailing actual drugs.

The next logical step in the use of the simulation technique is to use the tracer substance in the systematic series of simulated situations which cover the range of operations and environments usually encountered during drug mixing and administration. For example, the use of needle clippers can and should be monitored in this way.

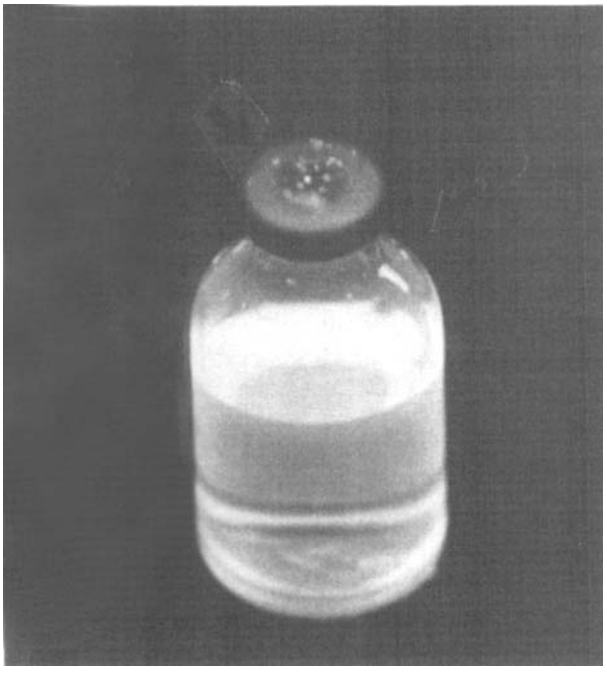

Figure 4. Typical areas of contamination on exterior of vial containing dissolved fluorescent dye.

Other techniques, such as injection of air into the vial prior to removal of the liquid should also be assessed. Such research is currently underway.

Despite the fact that this systematic investigation of working conditions and techniques is not yet complete nor reported here, based on the available data, it appears likely that the handling of cancer chemotherapeutic agents is a task which can expose the practitioner to the drugs unless appropriate precautions are taken.

Although no studies of potential long-range effects attributable to such exposures have been carried out as yet, it would seem that the most prudent course of action would be to eliminate all unnecessary exposures. Indeed, the results obtained here demonstrate the need on the part of many practitioners for active intervention with techniques and equipment designed to eliminate such exposure to the drugs. Some of these techniques and practices have already been formulated by several agencies such as the National Institutes of Health, NIH (5) and the American Society of Hospital Pharmacists (6).

From our results it would appear that the following precautions are minimally essential:

1. Protective clothing which includes covering of the sleeves, front, and protective gloves must be worn, although one must recognize the limitation in protection associated with such equipment, such as permeability of the gloves to the agents (7). Also, given the extent of potential spread observed here, either disposable protective equipment or laundering facilities which segregate the contaminated clothing would appear warranted.
2. Work surfaces must be thoroughly and regularly swabbed to preclude inadvertent contamination through body contact by both drug handlers and other health care staff, including the maintenance staff, as well as inadvertent contamination of other equipment.
3. Techniques which reduce the pressure in the vials, such as puncture with a second needle, as recommended by the NIH, should be used.
4. An alcohol-dampened pledglet should be securely placed around the needle and vial each time the needle is inserted or withdrawn and the user must at the same time exert care to avoid puncture wounds.
5. All swabs, clothing, and other equipment used should be handled as if they were contaminated with a chemical carcinogen and disposed of according to methods prescribed for such chemicals (8).

It is also important to note that although the research described in this paper was not designed to evaluate specific working techniques, or the efficacy of equipment such as laminar flow hoods for reducing exposure, most of the participants in the ChemoTest trial, in fact, carried out the mixing procedures under a vertical laminar flow hood. Therefore, even if air contamination is reduced by the hood, it appears that there remains the probability that work surface contamination and body contact can still occur unless adequate precautions are taken.

Finally, these data do not address another important potential source of contamination: contact with patient excreta and vomitus, which can be expected to be heavily contaminated both with cancer chemotherapeutic agents and with their metabolites. Many metabolites retain the toxic properties of the drug, or in many instances, may even have enhanced toxic properties. Appropriate disposal methods and segregation of patient wastes are needed (9).

It should also be noted that private hospitals, and in some states "public" hospitals as well as physicians who employ others to carry out tasks involving such potential exposure, may be already legally required, under the Occupational Safety and Health Act, to provide a workplace free from generally recognized hazards. Although no legal tests have yet been made in the specific case of cancer chemotherapeutic agents, it is an area

already under investigation by the federal government (10). It can be conjectured that all employers will soon be required to treat these drugs as "carcinogens" within the meaning of the law.

ACKNOWLEDGMENT

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