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Exposure to hazardous drugs in Healthcare: An issue that will not go away

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The *Journal of Oncology Pharmacy Practice* (JOPP) was first published in June 1995 as the official journal of the International Society of Oncology Pharmacy Practitioners (ISOPP). In a supplement to that issue, as part of a review of the ISOPP IV symposium presentations, an article by Professor Graham Sewell was included titled 'Pharmaceutical issues: preparation and handling'.[1] This article raised concerns about various aspects of quality and safety associated with cytotoxic drug reconstitution. It discussed the use of cytotoxic safety cabinets versus isolators, the use of early 'closed systems' and even the possible future use of robotics. In the 15 years since that first publication, interest in the handling of hazardous drugs used to treat cancer patients has not waned. At the recent ISOPP XII symposium held in Prague in May 2010, ten presentations and seven submitted abstracts on the topic of safe handling were included. From the highly technical use of robotics and the use of specialized closed systems to the basic use of personal protective equipment (PPE) in under-resourced countries, this subject remains highly topical.

One reason for the interest in this topic is the inability to quantify the occupational risk of handling anti-cancer drugs. It is well recognized that patients treated with therapeutic doses of these drugs may develop second cancers years later. However, the risk associated with long-term very low level exposure to these agents is not currently measurable. A basic tenet of employment is the provision of a safe workplace. It may be impossible to remove all risk but it is imperative that risk is minimized. Large pharmaceutical companies manufacturing anti-cancer drugs do so in totally enclosed environments with workers wearing full respirator suits reminiscent of movies of outbreaks of a deadly virus. But it is financially completely beyond individual hospitals, institutions and clinics to supply such protective equipment. The smaller the preparation facility, the less viable it is to introduce expensive protective measures.

Many pharmaceutical companies have improved the presentation of their anti-cancer drug products in several ways. The drugs are generally presented, when stability allows, in liquid form – this means less manipulation is required to prepare a dose. The drugs are generally packaged in plastic containers – this means less chance of vial breakage. When compatibility problems arise and do not permit plastic packaging, and glass containers are required, these are generally protected in some way to avoid breakage and leakage e.g., an 'overcoat' of plastic is placed over the vial. These improvements in packaging are applauded. However, it is known that external chemical contamination of drug vials arriving from the manufacturer is a problem. Manufacturers must accept responsibility for ensuring that only clean product leaves their facilities. It is discouraging when every safeguard is taken to protect staff preparing anti-cancer drugs, to find that a major source of contamination is the outside of the drug vials themselves.

Before we place all the responsibility onto the manufacturers, we must first ensure that we are doing everything possible ourselves to reduce the contamination of the environment and ourselves and we still have quite a long way to go.

The paper by Shin-ichi Sugiura et al. 'Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide' in this issue of *The Journal* describes a pilot study performed in 2006 looking at cytotoxic drug environmental contamination in two similar hospital departments.

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The difference being that one department utilized a biological safety cabinet for the preparation of cytotoxic drugs by pharmacists using PPE and the other did not. Using a well-validated method where surface wipe and urine samples were analyzed using the Sessink method, surface contamination was found in both departments (highlighting the inadequacy of a biological safety cabinet to contain contamination). However, urine contamination was found only in staff medical doctors preparing drugs without wearing appropriate PPE (not even gloves) or nurses caring for patients, again without wearing gloves. All the pharmacists tested who wore PPE and followed safe handling guidelines were clear of measurable contamination. The conclusion being that all personnel who prepare cytotoxic drugs should follow safe handling guidelines and wear appropriate PPE. Risk from exposure to cytotoxic drugs does not depend on the profession of the person doing the preparation. The best way to ensure these two requirements are followed is to centralize preparation.

Following on from the pilot study described above, a larger multicenter study was undertaken. The paper by Shin-ichi Sugiura et al. 'Multicenter study for environmental and biological monitoring of occupational exposure to cyclophosphamide in Japan' highlights one of the major confounders of the safe handling of cytotoxic issues i.e., the attitude of some professionals to the risk of harm from cytotoxic drug exposure. Cyclophosphamide was detected in 90 urine samples out of the 276 examined, representing 23 of the 41 healthcare professionals tested. Exposure was deemed to be both percutaneous and *via* inhalation. One hospital with a high degree of environmental contamination had little measurable urinary cyclophosphamide, this being attributed, by the authors, to the wearing of PPE such as gloves. Thus, the inverse can be assumed, i.e., in other hospitals where urinary contamination was high, the use of basic protective equipment such as gloves was minimal or nonexistent. This cavalier attitude can be said, in part, to be due to ignorance of the individual to the risk but can also be said to be due to the long latency period between the exposure and outcome and the current inability to precisely measure either exposure or risk. It is in situations such as this that people must be protected from themselves. Since, oncology healthcare workers cannot wear simple 'exposure monitors' such as radiation workers do, it is necessary to have strict guidelines in place that will reduce both initial contamination of the environment and possible exposure – both percutaneous and *via* inhalation. Oncology pharmacists are in the perfect position to mandate the use of such guidelines within their institutions but they need the financial backing of their institutions to ensure that the guidelines can be fully implemented.

A third paper from Japan by Yoshida et al. 'Association between occupational exposure levels of antineoplastic drugs and work environment in five hospitals in Japan' compared five hospitals where the cytotoxic drug preparation was all done by pharmacists using appropriate PPE within biological safety cabinets. The major contaminant was 5-fluorouracil (5-FU) and this is easily explained, since in Japan 5-FU is only available in ampoules. The process of breaking ampoules and then withdrawing drug from these ampoules (with or without filtering the contents to remove glass fragments) and the subsequent disposal of the open contaminated glass ampoules leads to a far greater opportunity for contamination compared to drug supplied in vials. Pharmacy purchasing officers in Japan should be demanding 5-FU supplied in vials since these are readily available in other countries. The use of glass ampoules of 5-FU can be considered a health and safety violation. In addition to environmental contamination, this article also looked at personnel contamination by examining 24-h urine collections in 17 pharmacists. Three pharmacists were found to have measurable levels of drug in the urine. This worrying result highlights the need for people planning pregnancy (both males and females) to be excluded from preparing cytotoxic drugs to prevent foetal damage.

It would have been extremely interesting to compare the biological contamination seen in the three Japanese studies with contamination from the study mentioned next, where 22 hospitals from the United States were studied. Unfortunately, the American study did not include any biological monitoring.

In this issue of *The Journal*, we find the largest ever published study on the efficacy of a closed-system drug transfer device (CSDTD) used in the preparation of hazardous drugs. This multicenter study conducted over a period of 5 years is authored by four of the most widely recognized workers in the field of hazardous drug environmental contamination. As Sessink et al themselves point out, this is not the first paper of this kind to be published, but what sets this paper aside is the scale of the work and the inclusion of strong statistical analyses. All of the previously published work involving a CSDTD has been conducted in only one to three institutions and the results have been largely descriptive in nature. The sample sizes of wiped sites have been small as have the number of urine samples available if a biomonitoring component has been included in the study. The methodologies used in these studies have been varied making it difficult to compare the results with each other. This study, in contrast, has been conducted at 22 sites across the United States using a uniform sampling procedure and testing for the same drugs at the same sites.

Sessink et al. collected 114 surface wipe samples from 22 hospital pharmacy departments during the study period. Samples were collected following the preparation using a traditional needle and syringe technique and again following the preparation using a commercially available CSDTD. Samples were tested for the presence of cyclophosphamide, ifosfamide, and 5-FU.

The results of this study very clearly demonstrate the efficacy of a CSDTD in reducing environmental contamination when compared to standard preparation techniques. Contamination was still detected following the use of the CSDTD but the percentage of samples testing positive for cyclophosphamide, ifosfamide, and 5-FU was reduced by 10%, 9%, and 13%, respectively. However, the statistically significant reduction in levels of contamination is striking, with median values for cyclophosphamide, ifosfamide, and 5-FU being reduced by 95%, 90%, and 65%, respectively. This provides very clear evidence that the use of a CSDTD results in reduced operator exposure to hazardous drugs.

The awareness of continued contamination in the workplace is not confined to the United States. Australia has long been proud of its high standards in the safe handling of cytotoxic drugs, but recent work there has highlighted environmental contamination of a similar magnitude to that reported in other parts of the world. Two studies have demonstrated widespread contamination with cyclophosphamide, gemcitabine, and 5-FU in both pharmacy and nursing areas.[2,3] A third study from Melbourne suggests again that the use of a CSDTD may reduce further environmental contamination when used in conjunction with existing measures.[4]

So what? Does this further reduction in environmental contamination and potential operator exposure really matter? Isn't it enough to continue working in a cleanroom gowned in PPE without the added expense of a CSDTD?

Since the late 1970s, studies have reported adverse health effects related to exposure to hazardous drugs. Based on these epidemiological studies, it is extremely difficult to quantify the risk to healthcare workers handling these agents on a regular basis and it is assumed that the degree of risk is directly proportional to the level of exposure. More recently, various measures have been employed to better define the risk to healthcare workers. Studies have shown excesses in non-specific measures of genetic outcomes such as sister chromatid exchanges (SCE), micronuclei (MN), DNA damage (Comet) and total chromosomal aberrations. At the ISOPP XII meeting in Prague in May of 2010, McDiarmid presented results from the multicenter Health Care Worker Study.[5] In this study, workers exposed to hazardous drugs were tested for damage to chromosomes 5, 7, and 11, the key chromosomal lesions associated with myelodysplastic syndrome and acute myeloblastic leukaemia. What McDiarmid found, is that workers routinely handling alkylating agents appear to have a statistically significantly higher risk of the occurrence of such a chromosomal aberration compared to a nonexposed population. This is yet another study demonstrating a potential health risk to healthcare workers exposed to hazardous drugs.

So, yes it matters.

All of the occupational safety measures we have in place around the world today are aimed at reducing this level of exposure as much as possible. There is currently no known safe level of exposure to these drugs. Even if permissible exposure limits were set for these agents, interpretation would be extremely difficult in the hospital pharmacy setting where workers may be exposed to 40 or more different drugs in the course of a normal working week. All possible means should be employed to prevent exposure and Sessink and his colleagues here demonstrate that the use of a CSDTD helps in further reduction of surface contamination and so operator exposure to hazardous drugs.

The use of a needle and syringe is no longer the safest way for us to be handling these agents. NIOSH, ISOPP, and ASHP all advocate consideration of using a CSDTD to prepare hazardous drugs.[6–8] This important study should send a clear message to hospital managers and administrators that additional funding must be made available to enhance the safety of staff working with these agents.

When testing the efficacy of a CSDTD, one of the confounding factors is contamination arising from a source outside of the primary drug/device assembly. This is evident in the study by Sessink et al. in this issue of *The Journal* where the use of a CSDTD was unable to reduce environmental hazardous drug contamination to undetectable levels. The investigators postulate that the most likely source is contamination on the outside of commercially supplied drug vials. This has been previously well documented. When CSDTDs are tested in an operating pharmacy, there is also the issue of background existing contamination to consider.

Here, Zock and his colleagues report on the testing of two CSDTDs in an experimental laboratory setting. They reconstituted cyclophosphamide and transferred this to intravenous bags in a biological safety cabinet that had never before been used with cyclophosphamide. Prior to the study, no cyclophosphamide could be detected on any surface. Any surface contamination detected either had to come from the outer surface of the drug vials or from the reconstitution and transfer process.

In this study, both the CSDTDs performed well although some cyclophosphamide was detected on the workbench and gloves following the study. Once again, it is postulated that this may have come from the exterior of the drug vials, some of which tested positive for cyclophosphamide at the beginning of the study. It is also suggested that the incorrect use of one of the CSDTD may have resulted in some contamination.

One previous report has compared the same two CSDTD in a head-to-head fashion. In this evaluation, the authors concluded that there was no difference between the two systems in their efficacy at controlling surface contamination.[9]

If, in fact, the different closed systems currently available are equally effective, then the choice comes down to cost and ease of use. The purchaser must ensure that the system is capable of containing the hazardous drug throughout all handling steps from reconstitution to administration. Each system is different in terms of the mechanisms whereby the hazardous drug is contained during manipulations, and each system has its own unique characteristics to which the operator must become accustomed. Previous workers have published information on managing vials with over or under-pressure, and on managing viscous liquids when using one of the CSDTDs available.[10] As Zock et al. demonstrate, the system must be used correctly in order to be totally effective.

The studies by Sessink and Zock suggest that drug manufacturers need to do more to ensure the delivery to pharmacy departments of contamination free products. This is noted in the ISOPP Standards of Practice. ISOPP would like drug manufacturers to guarantee that 100% of all batches are washed and to provide written documentation (preferably from an independent laboratory) about the levels of contamination present on vials and other primary packaging of cytotoxic drugs.

As previously mentioned, when purchasing and implementing a CSDTD, variables such as efficacy, cost, and ease of use must be considered. In this issue of *The Journal,* Hama et al. examine another variable that could potentially influence the choice of closed system used. In this article, investigators document the volumes retained in three different chemotherapy preparation devices after use. Two different CSDTDs and a chemotherapy spike are tested. The issue being addressed is the error rate resulting from delivery of inaccurate volumes.

All the devices tested well, with extremely small residual volumes detected in each system. The two closed systems seemed to perform slightly better than the vented minispike although residual volumes appear very low for each device. The authors conclude that under normal conditions the residual volumes are so low that this should not result in any significant dosing error. However, if dosage volumes themselves are very small then perhaps the potential for a residual volume related dosing error should be considered. The various devices performed differently when aqueous or viscous liquids were handled, but again residual volumes were low in all cases.

This interesting study shows that there are no major concerns over dose measurement accuracy if using a CSDTD to prepare chemotherapy. This should reassure any pharmacists considering the use of such a device to reduce surface contamination and operator exposure to hazardous drugs.

The paper from Forges et al. 'Comparative parallel assessment of a transfer device in reducing 5-fluorouracil environmental contamination inside positive air pressure isolators' evaluated a novel drug transfer device for its applicability in the preparation of one anti-cancer drug, 5-FU. The device was the Spike Swan® by Codan, which consists of a needle-free transfer device with a 0.2-μm hydrophobic filter and an autolock valve. In a side-by-side evaluation, the drug transfer device was compared to the standard technique using needles, aeration needles, and swabs. The effectiveness of the device was evaluated by collecting surface wipe samples inside the isolator over a period of several days and analysing the samples for 5-FU, which was a high volume drug for this facility. The Spike Swan® was not designed for use with anticancer drugs and is much simpler in design that the CSDTDs currently on the market. There appeared to be little difference in the amount of contamination by 5-FU although only a small number of samples was employed in this study.

Based on the limited number of samples, the authors concluded that the device does not significantly reduce environmental contamination and may even increase it. They suggested that the device might be useful for preparation of anti-cancer drugs in small pharmacies, where the pharmacies are not accustomed to handling these drugs. However, there does not appear to be evidence to support this recommendation.

The inclusion of monoclonal antibodies into the oncologist's armamentarium has only added to the safe handling confusion.

In Halsen and Krämer's article, 'Assessing the risk to health care staff from long-term exposure to anticancer drugs-the case for monoclonal antibodies' the authors have undertaken a difficult task in attempting to assess the risk posed by monoclonal antibodies to health care personnel. Unlike the majority of anticancer drugs, the monoclonal antibodies are large molecular weight proteins. Typically, they are not evaluated for carcinogenicity or mutagenicity as are other anti-cancer drugs during the developmental stage.

Additionally, there are no reported acute toxicities for the monoclonal antibodies.

The authors screened a number of sources in order to evaluate the potential carcinogenic, mutagenic, and reproductive (CMR) effects of these monoclonal antibodies. They stress the heterogeneous nature of the group of monoclonal antibodies and recommend that a general risk assessment for these anti-cancer drugs is not feasible. Of the nine monoclonal antibodies they evaluated, the authors identified developmental toxicity in all nine and effects on fertility in a number of them. In addition, gemtuzumab ozogamicin has been reported to be mutagenic following release of the calicheamicin from the antibody moiety. It was also reported that there were mixed results to the developing foetus when pregnant women were treated for cancer with two of the monoclonal antibodies, trastuzumab and rituximab.

The authors conclude that dermal and oral uptake is unlikely in the occupational setting. It is felt that pharmaceutical agents with molecular weights greater than 500 Daltons are not able to be taken up by the dermal route[11] and oral ingestion of proteanous agents would result in degradation in the GI tract. Therefore, Halsen and Krämer suggest that pulmonary uptake is possible, but is limited and absorption is low. However, they advise that there is a potential for occupational exposure by inhalation, especially from droplets and aerosolized drug.

Unlike almost all other treatments for illness, cancer drug treatment is truly individualized. Doses of drugs are not only generally based on patient's height and weight but on their laboratory parameters (e.g., neutrophil count and platelet count) on the day of treatment. Thus, a patient may be on one treatment yet receive different doses at different visits. This individuality is required because of the anti-cancer drugs' toxicity and their low therapeutic index. Additionally, since many individually prepared doses have a short 'shelf-life' either due to stability or sterility issues, doses must be prepared in a timely fashion, generally on the actual day of treatment. This is the basis for in-house preparation of anti-cancer treatments.

Government authorities in charge of reducing risk in the workplace say that the first level of risk control is to eliminate the hazard. This can be interpreted to mean do not manipulate anti-cancer drugs. In fact, hospitals and institutions with a small workload should heed this advice and outsource the preparation of their doses. However, while patients continue to require individually prepared treatments, oncology pharmacists and technicians will continue to prepare them. We certainly do not want to stop this activity – after all we might be on the receiving end one day. But we must improve the conditions these professionals work under, to bring to a minimum their likelihood of harm while they are working to provide treatment for others. In the last few decades, we have made big improvements in handling hazardous drugs. However, we have not eliminated surface nor biological contamination entirely. The increasing number and variety of available drugs to treat cancer, that can cause harm to those handling them, behoves us to remain vigilant in seeking and following optimum safe handling conditions.

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