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Review Article

Identification of Knowledge Gaps Regarding Healthcare Workers' Exposure to Antineoplastic Drugs: Review of Literature, North America versus Europe

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ABSTRACT

We have been examining the issue of healthcare workers' exposure to antineoplastic drugs for nearly a decade and have observed that there appears to be more publications on the subject matter originating from Europe than from North America. The concern is that findings from Europe may not be generalizable to North America because of differences in handling practices, regulatory requirements, and training. Our objective was to perform a literature review to confirm our observation and, in turn, identify gaps in knowledge that warrants addressing in North America. Using select keywords, we searched for publications in PubMed and Web of Science. All papers were initially classified according to the originating continent and then categorized into one or more subject categories (analytical methods, biological monitoring, occupational exposure, surface contamination, and probability of risk/exposure). Our review identified 16 papers originating from North America and 55 papers from Europe with surface contamination being the subject matter most often studied overall. Based on our results, we are of the opinion that North American researchers need to further conduct dermal and/or urinary drug contamination studies as well as assess the exposure risk faced by healthcare workers who handle antineoplastic drugs. Trends in exposure levels should also be explored.

1. Introduction

A number of health risks associated with healthcare workers' exposure to antineoplastic drugs have been established since the 1970s [1]. Occupational exposure to these agents have led to a range of health outcomes reported in healthcare workers including acute effects [2], cardiotoxicity [3], reproductive toxic effects [4–6], and chromosomal damage—a precursor to cancer development [7,8]. Nearly 40 years after the association between healthcare workers and the adverse effects of antineoplastic drug exposure was established, the matter remains a concern today for a number of reasons. First, the incident rate of cancer is steadily increasing and, in turn, the use of antineoplastic drugs is growing [9]. Second, existing safe drug handling practices may not effectively eliminate the risk potential as drug contamination of surfaces is prevalent in multiple departments within a hospital [10,11]. Lastly, the number and variety of healthcare workers potentially exposed to antineoplastic drugs has increased because the use of these agents for treating nonmalignant diseases has expanded [1]. Compounding the problem is the fact that occupational exposure limits have not been established for these drugs by any of the recognized agencies that produce such exposure thresholds (e.g., American Conference of Governmental Industrial Hygienists threshold limit values, German maximum workplace concentration).

Our group of researchers at the University of British Columbia in Vancouver, Canada, have been examining the issue of healthcare workers' exposure to antineoplastic drugs for more than a decade. During our review of the literature for background and research purposes, we noticed a peculiar finding that a larger proportion of the publications on this subject matter originate in continental

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Europe. Connor et al [10] mentioned this phenomenon as well. Although the information from Europe is of value, the findings and conclusions may not necessarily be transferable to North American healthcare facilities due to differences in standards of practice, legislative requirements and education/training protocols between the two continents. Although results from Europe may not necessarily be generalizable to North America, they are of value by initiating meaningful discussions and acting as an impetus for similar research projects to be conducted in North American facilities. (We know that there are publications based in other continents such as Asia and Australia that have examined the issue of healthcare workers' exposure to antineoplastic drugs. However, we have observed that the work focuses primarily on cross-sectional evaluations of current exposure conditions and do not elucidate contributing factors related to the risk of exposure. We are confident that future work from these other continents will offer valuable insight into this subject matter).

The purpose of this paper was to test our observation that more publications regarding healthcare workers' exposure to antineoplastic drugs originate from Europe than in North America. We conducted a review of the published literature for articles that addressed this topic, categorized them according to subject matter, and then tallied the findings to determine where knowledge gaps exist, if any, between the two continents. From the potential knowledge gaps identified, our goal was to identify and prioritize additional research that is worthy of consideration in North American facilities to better our understanding of healthcare workers' exposure to antineoplastic drugs and the underlying risk that these exposures may present.

2. Materials and methods

We sought articles from two common literature databases: PubMed and Web of Science. Select keywords were used to identify articles for the purposes of this review. The keywords were antineoplastic drugs (along with its synonyms antineoplastic agents and cytotoxic drugs), healthcare, occupational exposure, analytical methods, biological monitoring, risk assessment, surface contamination, and exposure monitoring. The keywords were systematically combined together in order to conduct the literature search. For example, "antineoplastic drugs" AND "occupational exposure" AND "healthcare" was one combination. There were a total of 18 combinations of keywords and all combinations were applied to each of the two databases.

We aimed to identify original research articles (i.e., nonreview) using the aforementioned keywords with the following exclusion criteria: (1) not written in English; (2) not published between January 1, 2004 and December 31, 2012. The year 2004 was chosen as this was the release date of the original NIOSH (National Institute for Occupational Safety and Health) Alert regarding antineoplastic and other hazardous drugs [1]; (3) research conducted outside of North America or continental Europe (as defined by worldatlast.com [12]); (4) nonhuman studies; and (5) not full reports (i.e., letters to the editor).

Every full-text article that met the inclusion criteria was initially classified according to the continent of origin of the study (North America or Europe). Next, the paper was reviewed and categorized into one or more of the following five categories based on its subject matter: analytical methods (e.g., development and validation of a novel laboratory analytical method), biological monitoring (e.g., blood or urine samples), occupational exposure, surface contamination, and probability of risk/exposure. For the purposes of this paper, "occupational exposure" was defined as those instances where dermal and/or airborne contamination levels were measured. "Probability of risk/exposure" was defined as determinants of exposure and/or studies in which comparisons between exposed and nonexposed populations were made. The number of articles was tallied according to the five subject categories, stratified by the continent, using the COUNTIF function in Microsoft Excel (Microsoft, Redman, WA, USA).

3. Results

Our search of the two literature databases resulted in a total of 80 publications that matched our inclusion criteria. Of these, nine were removed because they were deemed irrelevant (i.e., conference proceedings, not concerning occupational health, or not related to healthcare settings). Therefore, 71 papers remained in the study—16 from North America and 55 that originated in continental Europe.

When these 71 papers were categorized according to their subject matter, the topics discussed in order of frequency (from highest to lowest) were surface contamination, probability of risk/exposure, biological monitoring, occupational exposure, and analytical methods. For each of the five topics, there were always more instances of European-based publications than North American, with a minimum 3-fold difference (Table 1).

4. Discussion

Our analysis suggests that European scientists have been more active in researching the area of healthcare workers' exposure to antineoplastic drugs than their North American counterparts. From 2004 until 2012, there were three times as many papers from Europe compared to North America. We therefore believe that there are opportunities in North America to further our understanding of this occupational health issue.

Surface contamination was the topic most commonly examined in the literature. As Connor et al [10] recently indicated, every paper that has examined surface contamination has found at least one instance of drug residual present. Therefore, we suggest that there is likely no need to explore this particular topic any further. However, as no occupational exposure limits have been established, we recommend that North American researchers and/or occupational hygienists consider developing suitable hygienic guidance values based on surface contamination levels that have been recently obtained from Canadian and American healthcare facilities. Such hygienic guidance values have previously been proposed in two European countries—one for Germany [63] and another set of values for Sweden [39]. Given the potential difference in practices and training regimens, the hygienic guidance values developed in Europe may not be practical or suitable to North American facilities.

European researchers have provided leadership in the area of developing methods for quantifying antineoplastic drug contamination in various matrixes. Researchers in North America can simply adopt and refine these analytical methods according to local needs without the need for rigorous validation. However, it would be ideal if a research facility in North America were capable of performing some of these reported analyses because there may be sample stability concerns if these samples were to be shipped overseas. Upon review of the papers that have developed analytical methods, there appears to be a need to find biological markers of exposure that are specific to the different types of antineoplastic drugs [83] as well as address the issues associated with the large interindividual variability of volume output when collecting urine samples [37].

Inhalation, dermal, urine, and blood samples have been collected by various researchers in order to understand healthcare workers' exposure to antineoplastic drugs. Our results suggest that European researchers have examined occupational exposures

Table 1
Summary of literature review findings with tally of articles based on continent of origin and topics addressed

Author and year	Continent		Topical categories				
	North America	Europe	Occupational exposure	Biological monitoring	Analytical methods	Surface contamination	Probability of risk/ exposure
Acampora et al 2005 [13]		×				×	×
Barbieri et al 2006 [14]		×			×		
Brouwers et al 2007 [15]		×			×	×	
Bussieres et al 2007 [16]	×					×	
Caciari et al 2012 [17]		×		×			×
Castiglia et al 2008 [18]		×				×	
Cavallo et al 2005 [19]		×		×		×	×
Cavallo et al 2009 [20]		×		×			×
Chappuy et al 2012 [21]		×			×	×	
Chu et al 2012 [22]	×					×	
Connor et al 2005 [23]	×					×	×
Connor et al 2010 [10]	×		×	×		×	×
Constantinidis et al 2011 [24]		×	×				×
Crauste-Manciet et al 2005 [25]		×	×			×	
Fabrizi et al 2012 [26]		×			×	×	
Favier et al 2012 [27]		×				×	
Forges et al 2011 [28]		×				×	
Fransman et al 2004 [29]		×	×			×	
Fransman et al 2005 [30]		×	×			×	×
Fransman et al 2006 [31]		×	×			×	
Fransman et al 2007 [32]		×	×				×
Fransman et al 2007 [33]		×	×	×		×	×
Harrison et al 2006 [34]	×					×	×
Hedmer et al 2004 [35]		×	×		×	×	
Hedmer et al 2005 [36]		×				×	
Hedmer et al 2008 [37]		×		×			
Hedmer et al 2008 [38]		×		×		×	
Hedmer and Wohlfart 2012 [39]		×				×	
Hon et al 2011 [40]	×		×				
Hon et al 2011 [41]	×		×			×	
Konate et al 2011 [42]		×	×	×		×	×
Kopp et al 2012 [43]		×		×		×	x
Kopp et al 2012 [44]		×				×	x
Lalande et al 2012 [45]		×	×				x
Mader et al 2009 [46]		×		×			×
Mason et al 2005 [47]		×	×	×		×	
Massoomi et al 2008 [48]	×		×				×
McDiarmid and Condon 2005 [49]	×						×
Ndaw et al 2010 [50]		×		×	×		
Nussbaumer et al 2010 [51]		×			×	×	
Nussbaumer et al 2012 [52]		×			×	×	
Nygren et al 2005 [53]		×	×		×		
Nygren et al 2008 [54]							
Odraska et al 2011 [55]		×	×			×	
Odraska et al 2012 [56]		×				×	×
Pieri et al 2010 [57]		×		×			×
Pretty et al 2012 [58]	×		×	×	×	×	
Roberts et al 2006 [59]		×				×	×
Rubino et al 2006 [60]		×		×	×		×
Sabatini et al 2005 [61]		×			×	×	
Sabatini et al 2012 [62]		×		×		×	×
Schierl et al 2009 [63]		×				×	×
Schierl et al 2010 [64]		×				×	
Schierl et al 2012 [65]		×	×			×	
Schulz et al 2005 [66]	×					×	
Sessink et al 2011 [67]	×					×	
Sottani et al 2004 [68]		×		×	×		
Sottani et al 2005 [69]		×		×	×		

(*continued on next page*)

Table 1 (*continued*)

Author and year	Continent		Topical categories				
	North America	Europe	Occupational exposure	Biological monitoring	Analytical methods	Surface contamination	Probability of risk/ exposure
Sottani et al 2007 [70]		×			×	×	
Sottani et al 2008 [71]		×		×	×		
Sottani et al 2010 [72]		×		×		×	
Sottani et al 2012 [73]		×	×	×		×	
Stover and Achutan 2011 [74]	×					×	×
Testa et al 2007 [7]		×		×			×
Touzin et al 2009 [75]	×					×	
Touzin et al 2010 [76]	×					×	×
Tuerk et al 2011 [77]		×			×	×	
Turci et al 2011 [78]		×		×		×	×
Turk et al 2004 [79]		×					×
Ursini et al 2006 [80]		×	×	×		×	
Villarini et al 2011 [81]		×		×			×
Zock et al 2011 [82]	×					×	
North American subtotals	16		5	2	1	13	7
European subtotals		55	16	23	16	37	23
Overall totals	71		21	25	17	50	30

levels more often than North Americans (Table 1). This may be because some researchers consider the collection of surface contamination samples to be sufficient markers of exposure and therefore personal samples do not need to be collected [63]. This is understandable given that surface wipes are more convenient to collect and are not invasive, and one can obtain a larger sample size with less stringent ethical considerations compared with samples taken from individuals. However, this may mask the true extent of exposure as we have recently reported that, although surface contamination is widespread within a healthcare facility, surface contamination levels are not necessarily indicative of the exposure risks faced by healthcare workers [11,84]. As such, it is recommended that surface contamination be used to identify those job categories at risk of exposure but that personal samples, such as dermal wipes or biological samples, be collected from healthcare workers to evaluate their actual level of risk [84]. Not only have our European colleagues conducted more studies on occupational exposure than we have, but they have also looked at trends in exposure levels over time [33,46,72]. This is an important consideration as analysis of trends is a means to evaluate the effectiveness of control measures in reducing the risk of exposure, and we recommend that North American researchers consider initiating this type of study.

Table 1 indicates that 30 papers determined the probability of risk/exposure due to occupational exposure to antineoplastic drugs—more than two-thirds of which ($n = 23$) originated from Europe. One of the means to confirm that workers are at risk of exposure to antineoplastic drugs and their associated health effects is to perform studies comparing workers that are exposed versus those that are not exposed. Our review found seven such studies—six from European researchers [7,17,19,20,60,81] and only one originating in North America [10]. Because there are likely differences in handling practices and training regimens, the findings reported in Europe may not be representative of the conditions in North American facilities. We, therefore, suggest that more North American researchers adopt a mandate to assess the level of risk associated with the antineoplastic drug exposure levels faced by their healthcare workers by conducting exposed versus nonexposed studies.

Limitations regarding this project need to be mentioned. We treated all antineoplastic drugs alike; however, these drugs differ in their physical and chemical properties that affect their pharmacokinetics as well as their toxicity. This review had a limited scope whereby publications from other continents and gray literature, including dissertations, were not considered. Some of the studies resulted in multiple related publications; however, they were treated as independent papers in our review. When we combined these related publications, the ratio of European to North American publications remained greater than 3:1 and did not change our conclusions (not shown). In addition, the number of search terms used was somewhat limited. We did attempt to use other terms such as “healthcare facilities” and “anticancer drugs”, but this either resulted in no hits or duplicate results.

In conclusion, our review of the literature indicates that since 2004, more publications regarding healthcare workers’ exposure to antineoplastic arise from Europe than in North America. We believe there are a number of research initiatives that can be undertaken in North America to better understand this subject matter. This includes occupational exposure studies (i.e., personal samples quantifying antineoplastic drug contamination levels in healthcare workers) and the subsequent assessment of the risk associated with these exposure levels. In addition, an analysis of the trends in exposure levels from North American facilities is also suggested. Given the known health effects of antineoplastic drugs, we need to better understand the occupational exposures to antineoplastic drugs in North American workplaces and, where necessary, implement control measures to protect our healthcare workers to reduce the level of risk.

Conflicts of interest

The authors declare no conflicts of interest.

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