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OCCUPATIONAL EXPOSURE TO ANTIPROLIFERATIVE DRUGS IN HEALTH CARE WORKERS

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Summary. - *A survey is presented of the information available on the occupational hazard caused by exposure to anticancer drugs. Emphasis is laid on the need for stricter and safer measures to protect the sanitary personnel, who should also be constantly and thoroughly informed on the risk run when manipulating antiproliferative agents. Possible strategies for effectively preventing occupational diseases in this field are finally outlined.*

Riassunto (Esposizione professionale a farmaci antiproliferativi del personale sanitario). - *Viene presentata una breve rassegna delle informazioni disponibili circa i rischi a cui sono esposti gli operatori coinvolti nella manipolazione di farmaci antitumorali. Si evidenzia la necessità per misure più rigorose e sicure per la protezione del personale sanitario, che deve peraltro essere costantemente ed esaurientemente informato circa il pericolo connesso all' uso di tali sostanze. Si fa cenno infine allo sviluppo di procedure per l' effettiva prevenzione di malattie professionali in questo settore.*

Introduction

Numerous factors contribute to making the sanitary working environment hazardous for medical and nursing staff. Apart from exposure to harmful agents of a physical (electricity, noise, ionizing radiation), chemical (it has been estimated that in a hospital environment there can be over 130 mutagenic substances) and biological nature, other aspects should be taken into account: for example, easy access to psychotropic drugs, rotation of working hours with day and night shifts, the stress of coping daily with own fears of vulnerability and mortality [1].

Within this area there are also certain sectors which due to the specific diagnostic and/or therapeutic tools employed are situations unto themselves. One of these sectors is oncology where, apart from the occupational hazards already present in any health setting, there is additional risk due to exposure to antiproliferative drugs. By this term we mean a class of heterogeneous chemical compounds, the common characteristics of which is to inhibit cell proliferation. This inhibition occurs through the interaction of the drug or its active metabolites with one or more of the systems in cells which regulate the replication of DNA, its transcription into RNA, the syntesis of proteins from messenger RNA and the consequent cell division [2].

Present knowledge

The particular mechanism of action intervening in cell proliferation and the essential structural and functional similarity of systems operating in normal as well as tumoural cells, give reason to believe that a certain level of mutagenicity, carcinogenicity and/or teratogenicity is innate to the action of these drugs (Table 1) [3-5]. Within anticancer chemotherapy, this aspect is reflected in the possibility of second primary tumours induced by treatment [6] or toxic effects in the embryo or fetus if the mother has undergone treatment during pregnancy [7].

Therefore, with the increasing awareness of the importance of late effects induced by anticancer drugs, the need arose to verify the possibility of occupational exposure to such substances and the eventual risks involved for sanitary staff responsible for their preparation and administration [8, 9]. The first study on this subject dates back to 1979 when Falck *et al.* [10] furnished data on the results of a mutagenicity assay on urine from patients treated with antiproliferative drugs as well as nurses handling these substances. Mutagenic activity was present not only in the urine of patients undergoing therapy but also, even if at lower level, in the majority of the assisting personnel [10]. When the same personnel was re-examined with an identical procedure but after substantial improvements in the handling procedures of cytostatics, a significant decrease

in the previously established mutagenic activity was demonstrated [11]. Similar results were later reported by another independent group [12]. Likewise, a significant increase in the urinary excretion of thioethers in nurses regularly handling cytotoxic drugs, indicating an exposure to alkylating agents, was also reported [13]. In 1984 Hirst *et al.* [14] clearly demonstrated the exposure and consequent absorption of such drugs by sanitary personnel, determining measurable amounts of cyclophosphamide in the urine of two nurses for 32% of the days examined in which drugs had been handled. The above-mentioned studies demonstrated that personnel involved in preparation and administration of anticancer drugs is actually susceptible to absorption of such agents. Proofs that such levels of exposure are genotoxically harmful can be found in investigations on the induced early cytogenetic effects, i.e. the chromosomal damage in peripheral blood lymphocytes. Studies to date have demonstrated that sanitary personnel exposed at length suffer genetic damage in the form of increased sister chromatid exchange frequencies [15, 16] or chromosomal aberrations [16, 17].

The alarm created by the flow of data published was an essential prerequisite to initiate epidemiologic investigations and draw attention of numerous institutions throughout the world to the problem, leading to the introduction of safe handling policies and procedures [18-21]. Finally, epidemiologic evidence of damage resulting from occupational exposure to antiproliferative drugs was gathered from two studies published in 1985. Selevan *et al.* [22] in a case-control study of nurses in 17 Finnish hospitals analyzed 124 cases of fetal loss during the period 1973-80, thereby demonstrating a significant association between fetal loss and exposure to cytotoxic drugs during the first trimester of pregnancy. Hemminki *et al.* [23] in a similar case-control study of nurses in Finnish hospitals investigated 46 cases of congenital malformations occurring during the period 1973-79 and ascertained a significant association between congenital malformations and exposure to anticancer drugs during the first three months of pregnancy. The association moreover was correlated to levels of exposure in as much as the higher the exposure the stronger the association.

From data above a conclusion can be drawn regarding the possibility and consequence of occupational exposure to antiproliferative agents and it is clear that priority should be given to adopting protectional measures for safeguarding workers in this field. In order to do this it is essential to know under what conditions such substances arrive in the working environment and how they are absorbed by the personnel handling them. If these drugs are handled without any special precautions they are almost certainly introduced into the environment depending on working habits and handling techniques as well as individual manipulative skill [12]. The aerosols generated during preparation, reconstitution, dilution, transferring and administration of drugs are particularly dangerous [24]. These aerosols can form when glass vials are opened, when inserting or disconnecting a needle in flasks with

Table 1. - *Available data on mutagenicity, teratogenicity and carcinogenicity of antiproliferative drugs as summarized by IARC*

Drug	Mutagenicity *(a)*	Teratogenicity *(b)*	Carcinogenicity *(c)*
Alkylating agents			
busulfan	+	+	+
chlorambucil	+	+	+
cyclophosphamide	+	+	+
mechlorethamine	+	+	-
melphalan	+	+	+
thiotepa	+	+	-
carmustine (BCNU)	+	+	-
lomustine (CCNU)	+	+	-
cisplatin	+	-	-
Antimetabolites			
5-fluorouracil	(*)	+	-
6-mercaptopurine	+	+	-
methotrexate	+	+	-
Plant alkaloids			
vinblastine	-	+	-
vincristine	-	+	-
Antitumour antibiotics			
actinomycin D	+	+	-
adriamycin	+	-	(*)
bleomycin	-	+	-
Miscellaneous			
dacarbazine	+	+	-
procarbazine	+	+	-

(a): in eukaryotic cells; *(b)*: in experimental animals; *(c)*: in humans; *(*)* no data available.

perforable rubber stoppers, expelling air or excess drug from the syringe, leaving open vials or flasks containing residual drug in working areas, disposing of excess drugs in the wastepaper basket or by dropping vials and flasks containing drug residues. Aerosols can also deposit on food and beverages which might be present in the same room where solutions are being prepared [24]. Just as dangerous are dripping and minor leaks of drugs in solution as well as the materials, cotton-wool or gauze, used to stop these leaks. Dejections of patients in therapy, especially urine, are harmful because of their content of drugs and/or active metabolites. The anticancer agents thus introduced into the environment are absorbed by the staff in the same way as any other chemical substance: a) inhalation of aerosols; b) percutaneous diffusion; c) ingestion of food or beverages accidentally contaminated.

Conclusions

If it is so easy for such substances when handled without special precautions to contaminate the working environment, is it than possible to prevent personnel exposure with timely safeguarding measures? The answer is definitely yes, even though with some reservations. Although it is not feasible here to detail all the suggestions put forward by various institutions and professional associations, we would however point out that in order to correctly put into effect these suggestions it is absolutely necessary that the health workers involved are amply informed of the problem and thereby personally motivated to understand the theory and operating methods behind any such safeguards.

Finally, it is necessary to have, possibly on the basis of an internationally harmonized agreement, a health surveillance protocol for periodical checks on the levels of exposure to which high-risk personnel is subjected. However in this regard there is still no unanimous agreement on the most suitable type of test. Some, in fact, recommend biological monitoring methods through determination of urinary levels of the drugs [20, 25] or the DNA adducts [26], while others are in favour of utilizing environmental monitoring [24]. This last group of people are critical of the use of biological indicators as standards because these only reflected an exposure which already took place; they maintain that as the aim of any program to prevent occupational illnesses is the environmental contamination control, the assessment of its effectiveness should come from environmental measures. In the particular case of occupational exposure to antiproliferative drugs it should be borne in mind that many of them are known as carcinogens. The fact that it is not yet possible to demonstrate an association between an increased risk of tumours and an occupational exposure to such agents, could only indicate that the levels of exposure are so low that the potential risk of cancer, if it exists at all, cannot be detected by epidemiological studies. If this is the case, safeguarding measures and effectiveness monitoring should be applied with the aim to further reduce the level of exposure and not simply to maintain the level of risk below the threshold of epidemiological detectability.

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