La Medicina del Lavoro

Med Lav 2012; *103*, 5: 394-401

Biological monitoring of occupational exposure to antineoplastic drugs in hospital settings

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Key words

Biological monitoring; antineoplastic drugs; health risk

Parole chiave

Monitoraggio biologico; farmaci antineoplastici; rischio per la salute

Summary

Background: *In view of the evidence of cytotoxicity of chemotherapic antineoplastic drugs (AD), current guidelines recommend the evaluation of the health risks of hospital personnel exposed to these compounds. Biological monitoring is the main tool to evaluate all possible drug intake and measure workers' real risk.* ***Objectives:*** *The aim of this study was to assess occupational exposure to AD in a large hospital in Northern Italy in order to verify the effectiveness of the structural and procedural improvements carried out over the last decade.* **Methods:** *Three biological monitoring campaigns were performed using LC-MS/MS analysis of cyclophosphamide (CP) and metotrexate (MTX) as biomarkers of internal dose in the urine of hospital workers. In the first two campaigns, 50 and 81 workers respectively were monitored during AD preparation operations. The last campaign, concerning AD administration activity, was performed after a centralized preparation unit had been set up. Two environmental monitoring campaigns were carried out as well, to complete AD exposure assessment.* **Results:** *During the first monitoring campaign we found positive urinary samples in all the wards studied (total positivity 36%), whereas in the second campaign 11% of the samples were positive and four departments showed negative results in all urine samples. The last campaign showed all urinary CP and MTX levels below the detection limit of the analytical method.* **Conclusion:** *Exposure of oncology ward nurses considerably decreased due to the centralization of AD preparation operations together with training and education of workers. The last biological monitoring results were reassuring; nevertheless, surface contamination still occurred and safety measures should be further improved in order to achieve the lowest reasonably possible contamination levels.*

Riassunto

«Monitoraggio biologico dell'esposizione occupazionale a farmaci antineoplastici in ambiente ospedaliero». **Introduzione:** *Data l'evidenza di citotossicità dei farmaci antineoplastici (FA) le linee guida raccomandano la valutazione del rischio per la salute dei lavoratori ospedalieri esposti a questi composti. Il monitoraggio biologico rappresenta il principale strumento per valutare l'assorbimento e stimare il reale rischio per i lavoratori.* **Obbiettivi:** *È*

Pervenuto il 30.3.2012 - Accettato il 14.6.2012

Corrispondenza: Laura Sabatini, Unità Operativa di Medicina del Lavoro. Policlinico Sant'Orsola-Malpighi, Via Palagi 9, 40138 Bologna - Tel. +39 0516362755 Fax +39 051 6362609 - E-mail: l.sabatini@unibo.it

stata valutata l'esposizione professionale a FA in un grande ospedale del nord Italia al fine di verificare l'efficacia dei miglioramenti strutturali e procedurali introdotti negli ultimi dieci anni. **Metodi:** *Sono state condotte tre campagne di monitoraggio biologico effettuando analisi in LC-MS/MS di ciclofosfamide (CP) e metotressato (MTX) come indicatori biologici di dose interna nelle urine del personale ospedaliero esposto. Nelle prime due campagne sono stati monitorati rispettivamente 50 e 81 lavoratori durante l'attività di preparazione di FA. L'ultima campagna di monitoraggio è stata condotta in seguito alla creazione nell'ospedale di una unità di preparazione centralizzata e ha riguardato l'attività di somministrazione. Sono state inoltre condotte due campagne di monitoraggio ambientale per completare la valutazione dell'esposizione a FA.* **Risultati:** *Durante la prima campagna in tutti i reparti monitorati sono stati trovati campioni di urina positivi (positività totale: 36%), mentre nella seconda campagna sono risultati positivi l'11% dei campioni urinari, con quattro reparti completamente negativi. Infine, nell'ultimo monitoraggio condotto, i valori di CP e MTX sono risultati al di sotto del limite di rivelazione del metodo in tutti i campioni urinari.* **Conclusioni:** *Grazie alla centralizzazione dell'attività di preparazione dei FA e alla formazione e informazione dei lavoratori, l'esposizione degli infermieri dei reparti oncologici è considerevolmente diminuita. I risultati dell'ultimo monitoraggio biologico sono stati confortanti; tuttavia, poiché persiste una diffusa contaminazione delle superfici di lavoro, è auspicabile un ulteriore miglioramento delle procedure di lavoro al fine di ottenere livelli di contaminazione più bassi possibile.*

Introduction

Antineoplastic drugs (AD) represent a wide class of therapeutic agents used daily in large amounts in the treatment of different diseases, e.g. cancer. The cytotoxic effects of these drugs are well known and affect healthy cells as well. Hospital staff who handle these drugs are exposed to a possible risk of adverse health effects, in particular nurses and pharmacy technicians. In fact, exposure risk is particularly high during preparation and administration of AD. There are two main possible absorption routes of these drugs for hospital staff: transdermal absorption and inhalation of aerosolized drugs (5, 11, 19).

For this reason, good working practices and correct use of protective disposables can considerably reduce the risk of exposure. However, several studies have reported high contamination of workplace surfaces and high levels of these drugs in workers' urine (15-17). In fact, reducing exposure to zero is not possible given that surface contamination can occur via incorrect working procedures and accidental events (spilling during preparation or administration, contact with patients' body fluids, prolonged wearing of gloves, incorrect cleaning practices, etc).

Despite the high human health hazard, no exposure limit values (either biological or environmental) are available for these drugs. In fact, their toxic effects are mainly stochastic and no safe threshold of exposure can be established. However, the higher the dose, the higher the probability of adverse effects. Therefore, guidelines were published based on the implementation of handling procedures, use of specific protective equipment and training and education of workers in order to keep the occupational exposure level "as low as reasonably achievable" (ALARA principle) (10, 13, 14). Moreover, guidelines recommend the creation of a pharmacy unit with specific requirements for the separate preparation of cytotoxic drugs in a centralized area restricted to authorized and skilled personnel in order to minimize exposure to AD.

To verify the application of the ALARA principle, it is essential to perform environmental and biological monitoring so as to periodically assess all possible sources of contamination and measure workers' real exposure.

In order to measure exposure at very low levels, extremely sensitive and reliable analytical methods are necessary for both environmental and biological monitoring; moreover, due to the various active ingredients used in cancer therapy, the simultaneous measurement of more than one agent is critical (22).

Concerning the environmental monitoring of antineoplastic agents, which are non-volatile com-

pounds, the measurement of surface contamination at the workplace is the best way to evaluate exposure doses. The wipe test procedure is recognized as the sampling technique of choice for this purpose (16, 20).

Environmental monitoring is important to determine the contamination of the workplace; on the other hand, the effective risk depends on the real intake of these compounds. For this reason, biological monitoring is the method of choice to evaluate the health risk for workers handling AD. The choice of the biological matrix, usually urine in the case of occupational monitoring, and the choice of biological markers are essential when planning biological monitoring (6). In fact, the biological marker level must be directly related to the external dose and must reflect the actual health risk. Since 1979, when Falck (4) first demonstrated the health risk in workers handling AD, several studies concerning biological monitoring of this class of workers have been published (22). A number of effect biomarkers have been studied (such as urinary mutagenicity, chromosomal aberrations, micronuclei, DNA-damage, etc) to detect early damage, but their reliability in biological monitoring of AD has yet to be demonstrated. Moreover, analytical procedures based on effect biomarkers are non-selective and time-consuming (3, 22). For these reasons, determination of the parent drugs in biological fluids as biomarkers of internal dose is the recommended method to assess biological monitoring of exposure to low levels of AD (11, 15). To choose the marker compounds, it is essential to take into account several aspects such as the drug toxicity, the amounts handled and the availability of reliable procedures for sampling and analysis. Although little data are available on CP and MTX excretion, especially after occupational exposure at low doses, previous studies indicated that most of any unmodified CP and, likewise, over 80% of MTX were excreted in urine as intact drugs during the 24 h after drug administration (5, 7, 18).

Since cyclophosphamide (CP) and metotrexate (MTX) are two of the most frequently used drugs in cancer therapy and the kinetics of their excretion allow them to be collected in the same urine sample (6), we chose them as biomarkers of exposure. In addition, we validated a specific and sensitive analytical method to simultaneously analyze MTX and CP in urine samples suitable for biological monitoring of occupational exposure to very low levels of these drugs (2).

In this study we evaluated occupational exposure to AD in a large hospital in Northern Italy over the last 10 years during which several structural modifications and improvements in work procedures were carried out in the wards involved in AD handling. In fact, in the absence of exposure limit values for these drugs, the comparison between different monitoring campaigns in the same occupational setting is the main way to establish whether the levels are actually as low as reasonably possible.

Occupational exposure was assessed from 2001 to 2010 by means of environmental and biological monitoring in order to show the effectiveness of the protective and preventive measures adopted.

Methods

Biological monitoring

In the last decade, three biological monitoring campaigns were carried out in a large hospital in Northern Italy.

The first campaign was conducted in 2001 within the context of a research project supported by the Italian Heath Department with the aim of assessing the long-term risks in hospital nurses exposed to AD (1, 3). In this study, we recruited 50 exposed nurses involved in AD preparation (8 males and 42 females, with a mean age of 35 years) from five oncology wards and 50 non-exposed nurses. An informed consent form was signed by each worker included in the study.

Subsequently, two biological monitoring campaigns were performed during the 2005 and 2010 hospital health surveillance programmes.

In 2005, we monitored 81 exposed workers (12 males and 69 females, with a mean age of 34 years), including both nurses and pharmacy technicians from seven oncology wards and a pharmacy unit. Concerning AD handling, ward nurses usually both prepare and administer AD treatment,

whereas the only task of pharmacy technicians is preparation. However, during this monitoring campaign we monitored all workers only after preparation operations. In fact, after a preliminary risk evaluation and in accordance with guidelines, preparation seemed the most onerous activity.

Finally, we carried out a new biological monitoring campaign in 2010, after a centralized preparation unit (Unità Farmaci Antibalastici, UFA) had been set up. The population was made up of 54 exposed subjects (10 males, 44 females, with a mean age of 40 years) recruited from UFA (preparation activity) and nine oncology wards (AD administration activity). The preparation task consists mainly of drug reconstitution and dilution, whereas administration activity consists of intravenous injection or infusion of the drugs. All personnel monitored reported handling AD during every shift and up to several times in a shift (with a maximum of 30 and 40 AD therapies handled daily on ward C and UFA, respectively), although the AD amounts varied considerably for each treatment. UFA and ward C were observed to be the wards with the highest amounts handled per year (about 2300 g of CP and 500 g of MTX for UFA and 800 g of CP and 190 g of MTX for ward C).

All personnel reported wearing latex gloves, plastic aprons, armlets and masks during AD preparation, whereas only gloves were worn during administration activity. No incidents occurred close to the study periods.

Urine samples for analysis of the biomarkers of internal dose were collected at the end of the work shift, at least 4 hours after the handling of CP and/or MTX. Samples were stored frozen at -20 °C until analysis.

Analyses were performed by liquid chromatography tandem mass spectrometry (LC-MS/MS) after solid phase extraction (SPE) of the samples following previously published methods (1, 2). The limits of detection (LOD) were 0.04 and 0.2 $\mu g/L_{urine}$ for CP and MTX, respectively.

Environmental monitoring

During the research project, we conducted the first environmental monitoring campaign in order to evaluate CP and MTX surface contamination of the five oncology wards studied.

The second environmental monitoring campaign was conducted in 2010 during the health surveillance programme. We monitored the preparation area of the recently constituted UFA and the administration rooms of nine oncology wards.

For both campaigns, wipe samples were taken (at the end of the work day) from several surfaces including preparation hoods, floors, door handles, drip bottles and stands, bedside tables and various objects. Sampling procedures and analyses were performed following Sabatini et al (16).

Briefly, analyses of CP and MTX were performed by LC-MS/MS after cleaning surfaces with ammonium acetate 0.1 M. The LOD of the assay was 1.1 mg/L for CP and MTX on rinsing solution, corresponding to a contamination limit of 0.1 mg/m^2 on surfaces.

Results

The results of biological monitoring performed during the research project are reported in table 1. All wards monitored presented positive samples (total positivity 36%), for either one or both marker compounds with the highest positivity percentage in the Day Hospital ward. Highest CP and MTX concentration levels were found in the Pediatric Oncology Department.

In 2005 biological monitoring was conducted in the same five previously monitored departments and three additional wards (table 2). As in the research project, we studied nurses only involved in preparation tasks. Overall, 11% of urine samples were positive and four departments tested negative. The Day Hospital ward continued to show the highest percentage of positive subjects.

In accordance with Italian legislation (9), a centralized unit for cytotoxic drug preparation (UFA) was created within the pre-existing pharmacy department at the end of 2009. Following Italian guidelines (10), UFA was set up with specific engineering requirements for the separate manipulation/preparation of cytotoxic drugs in a centralized area restricted to authorized and skilled personnel.

Table 1- Results from biological monitoring of exposure to AD performed in 2001 (research project)

Hospital Ward (No. of subjects monitored)	CP concentration ($\mu g/L_{urine}$)	MTX concentration ($\mu g/L_{urine}$)	No. of positive samples (%)
Ward A: Haematology I (12)	0.16	nd	2 (16%)
	0.40	nd	
Ward B: Haematology II (16)	0.21	nd	5 (31%)
	0.20	nd	
	2.00	0.31	
	0.22	1.10	
	nd	1.05	
Ward C: Haematology Day Hospital (5)	0.06	0.52	4 (80%)
	0.50	0.30	
	0.43	nd	
		0.41	
Ward D: Haematology Transplant Unit (7)	0.07	nd	2 (28%)
	0.08	nd	
Ward E: Pediatric Oncology (10)	10.00	nd	5 (50%)
	0.72	2.01	
	2.04	1.10	
	3.20	nd	
	1.00	nd	

nd: not detectable (below LOD of the method)

Table 2- Results from biological monitoring of exposure to AD performed in 2005 (health surveillance programme)

Hospital Ward (No. of subjects monitored)	CP concentration ($\mu g/L_{urine}$)	MTX concentration ($\mu g/L_{urine}$)	No. of positive samples (%)
Ward A: Haematology I (15)	nd	0.58	2 (13%)
	0.24	nd	
Ward B: Haematology II (16)	nd	0.40	1 (6%)
Ward C: Haematology Day Hospital (5)	0.25	nd	4 (80%)
	0.15	0.56	
	0.19	nd	
	0.08	nd	
Ward D: Haematology Transplant Unit (4)	nd	nd	- (0%)
Ward E: Pediatric Oncology (21)	nd	nd	- (0%)
Ward F: Oncology I (16)	0.25	nd	2 (12%)
	0.09	nd	
Ward G: Radiotherapy (1)	nd	nd	- (0%)
Pharmacy Unit (3)	nd	nd	- (0%)

nd: not detectable (below LOD of the method)

Table 3 - Summary of results from biological monitoring of exposure to AD performed in 2001 (research project), 2005 and 2010 (health surveillance programme)

Hospital Ward	% positive samples (No. of subjects monitored)		
	2001	2005	2010
A	16% (12)	13% (15)	0% (15)
B	31% (16)	6% (16)	0% (18)
C	80% (5)	80% (5)	0% (2)
D	28% (7)	0% (4)	0% (2)
E	50% (10)	0% (21)	0% (7)
F	-	12% (16)	0% (2)
G	-	-	0% (1)
H	-	-	0% (2)
I	-	-	0% (1)
L	-	0% (1)	-
Pharmacy Unit	-	0% (3)	-
UFA	-	-	0% (4)
Total	**36% (50)**	**11% (81)**	**0% (54)**

Due to the fact that UFA has provided most of the antineoplastic treatments required by the entire hospital since 2009, the remaining most hazardous activity in the oncology departments is administration. For this reason, in 2010 we carried out biological monitoring of the personnel exposed to AD mainly during administration of treatments and patient care activities. We monitored 50 nurses from nine oncology wards and four pharmacy technicians from UFA: as shown in table 3, all urinary CP and MTX results were below the LOD of the assay.

Concerning workplace surface contamination, in 2001 all wipe samples were positive for at least one drug marker (table 4). After centralization of preparation operations, the positivity percentage decreased and we found about 25% of workplace surfaces uncontaminated; moreover, the CP median value was 12 times lower in 2010 than in 2001 even if the mean values seem to be similar. In fact, the mean values are affected by few very high values found both in 2001 and 2010, caused by occasional deviation from standard procedures.

Discussion

The three biological monitoring campaigns carried out in the last 10 years have shown a progressive decrease of AD intake in exposed personnel, reaching complete negativity in 2010 (undetectable levels of CP and MTX in all urinary samples, as shown in table 3).

Between 2001 and 2005 the number of positive urine samples significantly decreased in all wards (except ward C), probably due to an increase in workers' risk awareness. In fact, after the 2001 monitoring campaign, the hospital personnel involved in AD handling attended a further special training on health working procedures to be adopted when preparing/administering AD treatments. Moreover, the research project results were presented to the study participants and, in the light of the environmental and biological contamination found, they improved AD handling procedures and the use

Table 4 - Results of AD environmental monitoring performed in 2001 and 2010

	2001 Research project		2010 Health surveillance programme	
	CP (mg/m^2)	MTX (mg/m^2)	CP (mg/m^2)	MTX (mg/m^2)
No. of monitored wards (No. of wipe samples)	5 (39)		10 (63)	
mean	128.4	50.8	156.0	28.0
median	21.4	nd	1.7	nd
min	0.1	nd	nd	nd
max	1084.1	2514.8	3757.7	168.5
positivity	100%	46%	75%	14%

nd: not detectable (below LOD of the method)

of personal protective equipment (PPE). Indeed, the education and training of personnel required by law are essential to reduce exposure; however, it is the sense of responsibility of each individual worker that drives observation and maintenance of the safety practices during daily work routine. Only in ward C (Haematology Day Hospital) did we find no reduction in AD absorption from 2001 to 2005; however, it was observed that in this department there was a significant amount of drug preparation activity in an inadequate preparation room with the surfaces presenting the highest contamination values found during environmental monitoring (data not shown). Our results are in line with previous studies in which biological monitoring of nurses handling AD was performed in Italian hospitals (12, 15, 21). In these studies similar percentages of positive samples (about 30%) were reported, with the lowest percentages for the nurses involved only in administration tasks.

In 2010 when nurses were responsible mainly for AD administration or infusion, the biological levels of marker compounds were all below the LOD of the analytical method. The UFA pharmacy technicians, despite the heavy work load (high numbers of AD daily preparations), also showed negative urine analyses. After all, even in 2005 the technicians involved in the same task in the old pharmacy ward also resulted negative for biological monitoring. These results agree with earlier observations where biological monitoring on Pharmacy Units showed all urine as negative when administration activity is the specific task of skilled personnel (23).

Moreover, since the end of 2009, when all AD treatments were provided by the centralized UFA, we noticed a remarkable decrease in workplace contamination in the wards. Notwithstanding, further improvement is advisable, as we have already found a high percentage of positive samples with some high peak values (table 4). In contrast, despite the increased work load for the pharmacy technicians, we still found an ideal situation in the UFA for both biological (table 3) and environmental monitoring (data not shown).

The setting up of a centralized pharmacy unit considerably improved the exposure level of oncology ward nurses by reducing the handling of AD only to administration and patient care activities. The centralization did not worsen the pharmacy technicians' exposure thanks to their special training and skill in AD handling, the UFA engineering control systems and the unvaried nature of their single task.

In the light of our results, it is reassuring that no drugs were detected in workers' urine samples; however, it must be noted that undetectable AD markers do not guarantee a total lack of absorption and health risk. It is therefore necessary to maintain and further improve safety measures and working procedures in order to finally achieve the lowest reasonably possible contamination levels.

No potential conflict of interest relevant to this article was reported

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