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ORIGINAL ARTICLE

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Occupational exposure to antineoplastic agents and parameters for renal dysfunction

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Abstract To study the nephrotoxic effects of occupational exposure to antineoplastic agents, the early renal effect parameters retinol-binding protein (RBP) and albumin (ALB) were determined in the urine of 11 hospital workers involved in the preparation and administration of antineoplastic agents and in 23 hospital workers not involved in drug handling, who served as nonexposed controls. No significant difference was found between the exposed group and the nonexposed control group with respect to the early renal effect parameters RBP and ALB. Although it was demonstrated that the hospital workers were exposed to cyclophosphamide (CP) and probably other antineoplastic agents, the results of the present study show that these exposure levels did not cause nephrotoxic effects.

Key words Antineoplastic agents · Occupational exposure · Hospital workers · Nephrotoxicity · Retinol-binding protein · Albumin

Introduction

Urinary proteins such as β_2 -microglobulin, albumin (ALB), retinol-binding protein (RBP) and the urinary activity of enzymes such as alanine aminopeptidase, β -galactosidase and *N*-acetyl- β -D-glucosaminidase are early renal effect parameters that have proven useful for the early detection of nephrotoxicity. These parameters

are widely used in occupational medicine for the detection of nephrotoxic effects in workers exposed to chemicals [16, 35]. They are also applied clinically to control nephrotoxic side-effects of drugs such as aminoglycosides [3] and antineoplastic agents like cisplatin [2, 3, 6, 8, 9, 12, 14, 15, 19, 30, 32, 33, 35].

In a number of studies we have demonstrated that workers involved in the production, preparation and administration of antineoplastic agents are exposed to these drugs [5, 22–29]. The uptake was assessed by the determination of the parent drug or metabolite in the urine of the workers. Large differences were found in urinary excretion of cyclophosphamide (CP) between several groups, suggesting variable exposure levels [5, 23, 24, 26, 28]. The question is whether these exposure levels will cause nephrotoxic effects in the workers.

Recently, we presented the results of a study in which the urinary CP excretion was determined together with the analysis of chromosomal aberrations in peripheral blood lymphocytes of Dutch and Czech exposed and nonexposed hospital workers [26]. It was shown that chromosomal aberration frequencies were higher in the groups of exposed hospital workers than in their nonexposed controls. The highest amounts of CP were found in the urine samples of 11 exposed Czech hospital workers (0.1–2.9 $\mu\text{g}/24\text{ h}$). For a worst-case approach, this group and the corresponding nonexposed control group ($n = 23$) were selected for monitoring of early renal effects. Urinary ALB and RBP were selected as the most appropriate parameters [35].

Materials and methods**Subjects**

Two groups were studied: 11 nurses, cleaning women and a lab technician involved in the preparation and administration of antineoplastic agents, all working in the same department of a hospital;

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Table 1 Distribution by sex, age, exposure period and smoking habits in the exposed and nonexposed group of Czech hospital workers

	Sex		Age		Years of exposure		Smokers		
	Male	Female	Mean	Range	Mean	Range	N ^b	Number of cigarettes/day	
								Mean	Range
Exposed	11	0	39	28-53	13	3-25	6	10	10
Nonexposed	23	3	44	27-59			4	17	13-20

^aNumber of subjects (smokers and nonsmokers)

^bNumber of smokers

23 control nurses, medical doctors, lab technicians and a cleaning woman not handling antineoplastic agents.

Six, age, profession, exposure period, smoking habits, alcohol use, illnesses, medicine use, inoculation and exposure to chemicals and X-rays were investigated by means of a questionnaire. From this, it appeared that the two groups were rather comparable. There were no indications that persons involved in this study could bring about a confounding effect. Some characteristics of the groups are shown in Table 1. Most of the workers handling antineoplastic agents used gloves, masks and special clothes. The agents were prepared in laminar down-flow cabinets. The amounts of the agents prepared and administered and the periods of handling were registered. CP, isophosphamide, cisplatin, 5-fluorouracil, methotrexate, cytarabine, doxorubicin, etoposide, vinblastine and vincristine were most frequently prepared and administered.

Urine sampling and analysis

Total 24-h urine was collected in portions starting at the end of the preparation/administration of the drugs. The same urine samples were used as in a previous study for the determination of CP [26]. Morning urine samples were used for analysis of RBP and ALB. Both proteins were determined by latex immunoassay [11] and were adjusted for dilution with the urinary creatinine (CREAT-U) concentration [35]. All parameters were analyzed within one run. The mean concentration and the duplicate precision (between brackets) of the determinations of the early renal parameters were: RBP 126.4 µg/l (9.6%); ALB 5.9 mg/l (6.4%).

Statistical analysis

The nonnormal distributions of the renal effect parameters ALB and RBP were transformed logarithmically. Differences in both parameters between the exposed group and the nonexposed control group were tested with Student's *t*-test. Correlations were quantified with the Pearson correlation coefficient, *r*. *P*-values (two-tailed) below 0.05 were considered to be of statistical significance. The statistical analysis were carried out on a personal computer using the InStat 1.1 software package.

Results

The mean concentrations of the renal effect parameters ALB and RBP in the exposed group and the nonexposed control group are presented in Table 2. No significant difference was observed between the two groups in the concentrations of these parameters. No

Table 2 Mean concentrations of the renal effect parameters albumine (ALB) and retinol-binding protein (RBP) in the exposed and nonexposed group of Czech hospital workers

Parameter	Geometric means (range)		<i>P</i> ^a
	Exposed (<i>n</i> = 11)	Nonexposed (<i>n</i> = 23)	
ALB (mg/mol CREAT-U)	0.44 (0.09-2.33)	0.30 (0.03-0.95)	0.27
RBP (µg/mol CREAT-U)	7.9 (3.0-18.9)	8.8 (1.2-28.0)	0.71

^aTwo-tailed *t*-test

correlation was found between the number of years of exposure and the urinary ALB (*r* = 0.31; *P* = 0.50) or RBP concentration (*r* = 0.25; *P* = 0.59). In addition, ALB and RBP concentrations were not related (*r* = 0.33; *P* = 0.33). The effect of smoking was also investigated. To this end, the exposed group and the nonexposed control group were subdivided into smokers and non-smokers. Two-way analysis of variance (SAS General Linear Models procedure, software version 6.07) was used to study the influence of smoking and exposure. No significant effect of smoking was found upon the urinary ALB and RBP excretion.

Discussion

Urinary renal effect parameters are widely used for the detection of early renal dysfunction in workers exposed to nephrotoxic chemicals such as organic solvents, heavy metals and silica [16, 20]. In patients treated with some antineoplastic agents, nephrotoxic side-effects are observed [2, 3, 6, 8, 9, 12, 14, 15, 19, 30, 32, 33, 35]. The question is whether nephrotoxic effects occur in hospital workers who are occupationally exposed to antineoplastic agents. Up to now, no such data have been published.

Several studies have shown that groups of hospital workers are exposed to antineoplastic agents [4, 5, 13, 17, 23, 24, 26-29, 34]. This was found by measurement of the parent compound or metabolites in the urine of the workers. Pharmacokinetic studies

have shown that large amounts of antineoplastic agents administered to patients are excreted unchanged in their urine [1, 7, 10, 21, 31]. These levels are much higher than those found in the urine of hospital workers involved in the preparation and administration of these agents. However, it remains unclear to what extent chronic exposure to low amounts of antineoplastic agents will cause adverse health effects. In a previous study, we showed that occupational exposure to these drugs may cause genetic effects [26]. It appeared that chromosomal aberration frequencies in peripheral blood lymphocytes of hospital workers handling antineoplastic agents were increased over those in their controls. The highest increase was observed in the exposed smokers, suggesting an additive effect of exposure and smoking. Therefore, it is not impossible that these exposure levels may cause other health effects, such as nephrotoxicity. In order to detect possible nephrotoxic effects at an early stage, the excretion of urinary ALB and RBP was determined.

Recently, it was found in a large study involving 5670 people that urinary ALB concentrations were significantly higher in smokers than in nonsmokers [18]. Hence, it is reasonable to assume that smoking is a possible confounder. However, in our study no significant effect of smoking on urinary ALB and RBP excretion was found. One explanation could be that our study was conducted in 34 hospital workers.

In conclusion, our results show no difference in urinary ALB and RBP excretion between the exposed group and the nonexposed control group of hospital workers. However, it should be noted that in our (pilot) study rather small groups were monitored. No increase in urinary RBP excretion indicates no tubular dysfunction. No increase in urinary ALB excretion and urinary RBP excretion indicates no tubular and no glomerular renal dysfunction. Although a previous study demonstrated that the hospital workers handling antineoplastic agents were exposed to one of these drugs, the results of the present study indicate that these exposure levels do not result in clear nephrotoxic effects.

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