

Determination of platinum surface contamination in veterinary and human oncology centres using inductively coupled plasma mass spectrometry

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Abstract

The objective of this study was to determine the surface contamination with platinum-containing antineoplastic drugs in veterinary and human oncology centres. Inductively coupled plasma mass spectrometry was used to measure platinum levels in surface samples. In veterinary and human oncology centres, 46.3 and 68.9% of the sampled surfaces demonstrated platinum contamination, respectively. Highest platinum levels were found in the preparation rooms (44.6 pg cm^{-2}) in veterinary centres, while maximal levels in human centres were found in oncology patient-only toilets (725 pg cm^{-2}). Transference of platinum by workers outside areas where antineoplastic drugs were handled was observed in veterinary and human oncology centres. In conclusion, only low levels of platinum contamination attributable to carboplatin were found in the sampled veterinary oncology centres. However, dispersion of platinum outside areas where antineoplastic drugs were handled was detected in veterinary and human oncology centres. Consequently, not only personnel, but also others may be exposed to platinum.

Keywords

chemotherapy, comparative oncology, oncology, small animal, small animal internal medicine

Introduction

Falck *et al.* (1979)¹ were the first to report the mutagenicity of urine of workers occupationally exposed to antineoplastic drugs. Since then numerous studies have been performed using environmental and biological monitoring methods to evaluate occupational exposure to these drugs.^{2–6} Research demonstrated that the implementation of appropriate staff training, guidelines on safe handling of antineoplastic drugs, and protective measures were able to diminish the exposure, although a certain amount of exposure cannot be avoided.^{4,7–10} Most

of the studies have focussed on workers in human oncology. However, there are other populations that are occupationally exposed to antineoplastic drugs as well.¹¹ One of the fields at risk is veterinary medicine. In response, guidelines on safe handling of antineoplastic drugs have been developed by the European College of Veterinary Internal Medicine of Companion Animals (ECVIM-CA).¹² These guidelines are based on knowledge acquired in human oncology. Usage of chemotherapy in veterinary oncology is still not as widespread as in human oncology. In addition, veterinarians and

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their clients are generally less willing to accept a high degree of side effects, resulting in lower doses of the same drugs than those used in human oncology.¹³ On the other hand, animals do not always comply with the strict measures necessary for safe handling of antineoplastic drugs and related wastes. Thus, extrapolating knowledge on the excretion of antineoplastic drugs from human patients to veterinary patients is difficult. However, research on occupational exposure in veterinary oncology is scarce.^{11,14–18}

The objective of this study was to investigate the current level of environmental contamination by platinum (Pt) attributable to Pt-containing antineoplastic drugs in veterinary oncology centres. To achieve this objective, we measured the surface contamination by Pt originating from carboplatin in five veterinary oncology centres and a veterinary pharmacy using inductively coupled plasma mass spectrometry (ICPMS). To be able to place the data in a broader perspective, we also evaluated the Pt surface contamination originating from Pt-containing drugs in two human oncology centres.

Materials and methods

Determination of surface contamination in veterinary oncology centres

The wipe samples were collected in five veterinary oncology centres (sites 1–5a) and one veterinary pharmacy (site 5b) in the Netherlands and Flanders. The chosen facilities provide a representation of the diversity in veterinary oncology centres in the Netherlands and Flanders, in terms of size and amount of carboplatin (carboplatin, Hospira Benelux, Brussels, Belgium; Carbosin, Teva Pharmachemie, Haarlem, the Netherlands) handled annually. Table 1 describes the characteristics of the centres. One of those centres (site 5a) was associated with a veterinary pharmacy (site 5b), where the antineoplastic drug applications were prepared. Hence, the pharmacy was included in the study.

All centres used the veterinary safe handling guidelines developed by the ECVIM-CA.¹² Only trained veterinarians and pharmacists were allowed to handle antineoplastic drugs. Only trained veterinary technicians were allowed to assist when storing antineoplastic drugs and handling treated

pets and antineoplastic drug wastes. All centres appeared to implement the following measures to the same degree: instruction of involved employees about the potential risks and used procedures, use of good personal protection and hygiene practice, implementation of an emergency and contamination procedure and use of a cytotoxic spill kit. Each centre consisted of a preparation room with one biological safety cabinet (BSC), apart from site 1 and the pharmacy, which used a laminar air flow (LAF) hood. Apart from site 1, which uses a separate room for administration, the centres administered the antineoplastic drugs in the consultation room. Centres used the PhaSeal[®] drug transfer device (TD; Carmel Pharma AB, Goteborg, Sweden) or the Tevadaptor[®] drug-handling device (DHD; Teva Medical, Netanya, Israel).

Samples were taken at locations that were prone to contamination. Floors, tables, work benches, (refrigerator) door handles, waste bin tops and transport box in the administration, consultation and preparation rooms were sampled. Additionally, handles of telephones and computer mouse devices in the administration, consultation and preparation rooms, and floors, tables and kitchen work surfaces in the canteens, waiting rooms and at the receptions were sampled. Not all locations were present at each centre. Additionally, the wiping method described in this study can only be applied to smooth surfaces. As some standard locations had rough surfaces, sampling could not be performed. Table 3 shows the locations sampled for each centre. Single samples were taken of each location.

Determination of surface contamination in human oncology centres

The wipe samples were taken in one inpatient (site 1) and one outpatient (site 2) oncology department of a human hospital in the Netherlands. The selected facilities provide a representation of medium-sized human oncology departments in the Netherlands. Table 2 delineates the characteristics of the departments.

Each department consisted of a preparation room, an administration room with adjacent patient-only sanitary facilities, a waiting room and reception. The antineoplastic drugs were

Table 1. Characteristics of the sampled veterinary oncology centres

	Site					
	1	2	3	4	5a	5b
Total amount of Pt processed, annually (mg ^a)	9538	0–1200 ^b	5600	^c	6350	6350
Number of years in service ^a	26	4	8	8	4	<1

^a At time of environmental monitoring, with amount of Pt in mg.

^b Estimation, depends on number of treated patients, annually.

^c Not available.

Table 2. Characteristics of the sampled human oncology centres

	Site	
	1	2
Type	Inpatient	Outpatient
Total amount of Pt processed, annually (mg ^a)	43 000	175 000
Number of years in service ^a	5	<1

^a At time of environmental monitoring.

prepared in the pharmacy of the hospital and then transported to the medication room of each department, where the preparations were stored before administration to the patient. Depending on the department, a canteen, non-restricted sanitary facilities and rooms for other patients were present. Samples were collected at locations that were likely to be contaminated, Floors, tables, work benches, door handles, waste bin tops, outer packaging of the infusion bag, transport box, chair, infusion pump, bell, control system of the bed/chair, shower, toilet seat and toilet cover in the administration rooms, preparation rooms, sluice room and patient-only sanitary facilities were sampled. Samples were also collected at floors, tables, kitchen work surfaces, door handles, handles of telephones and computer mouse devices in the canteens, waiting rooms and at the receptions. Table 4 shows the locations sampled for each centre. Single samples were taken of each location.

Wipe sampling procedure

The surface sampling was announced in advance. The same person performed the sampling by wiping a surface area of 10 × 10 cm. If a 10 × 10 cm area could not be sampled, the complete top of the

device was wiped and the area was estimated. The wiping procedure involved wiping the predefined surface three times in different directions. A new pair of disposable, nitrile gloves (Klinion, Medeco, Oud-Beijerland, the Netherlands) was used for each wipe sample. The wiping tissue (Kimtech Science precision wipes, Kimberly-Clark Professional, Irving, TX, USA) was moistened with 500 µL pure water (Aqua B. Braun Medical, Melsungen, Germany) before wiping the surface. During each visit, two procedural blank samples were prepared by moistening the wiping tissues with 500 µL water, followed by storing of the wipes in 30 mL polypropylene tubes (Sarstedt AG&Co, Numbrecht, Germany). The collected surface wipe samples were stored also stored in 30 mL polypropylene tubes. After the visit, all samples were stored at –20 °C until further processing.

Analytical procedures

Pt analyses were performed as reported elsewhere.¹⁹ In brief, extraction was accomplished by adding 10 mL 1% HCl solution (v/v) to the wipe samples, followed by ultrasonification for 60 min at 40 °C. The extraction solution was then filtrated using 0.20 µm filters (Sartorius minisart, Sarstedt AG&Co, Numbrecht, Germany). When Pt concentrations appeared to be higher than the highest concentration validated (1.00×10^4 ng L⁻¹ in extraction solution), the filtrated solution was further diluted using 1% HCl until the Pt concentration was within the validated range. Subsequently, 10 µL internal standard solution (iridium, 100 ng L⁻¹; Merck, Darmstadt, Germany) is added to each mL sample, to measure Pt concentrations. The extraction solutions are then introduced directly into the ICPMS (Varian

Table 3. Pt contamination in veterinary oncology centres in the Netherlands and Flanders

Sampled surface	Pt contamination (in pg cm ⁻²)					
	Site					
	1	2	3	4	5a	5b
Waiting room: floor	a	a	0.1	0.1	b	0.7
Reception: floor	a	a	b	a	b	b
Consultation room						
Floor	b	a	0.1	0.1	b	b
Table	0.1	a	a	a	b	a
Door handle	0.4	a	a	a	b	a
Handle phone	0.1	b	a	0.1	b	1.4
Mouse computer	0.2	b	0.1	a	b	a
Door handle refrigerator	0.1	a	b	b	b	b
Waste bin top	2.7	a	0.1	b	b	1.7
Administration room						
Floor	0.4	b	b	b	b	b
Table	a	b	b	b	b	b
Door handle	0.4	b	b	b	b	b
Waste bin top	0.3	b	b	b	b	b
Preparation room						
Floor	0.5	a	8.9	0.2	0.2	b
Work bench	2.0	0.1	0.2	2.1	0.4	0.4
Door handle	a	a	b	a	a	b
Door handle refrigerator	a	a	44.6	a	0.3	b
Waste bin top	0.1	0.1	a	b	a	b
Transport box	b	b	b	b	1.1	b
Canteen						
Floor	b	a	0.1	0.1	a	0.1
Table	a	a	a	a	a	a
Kitchen surface	a	a	a	a	a	b

^a Below threshold (0.1 pg cm⁻²).

^b Sample was not available.

810-MS, Mulgrave, Victoria, Australia). The lower limit of quantification (LLOQ) of the assay is 0.500 ng L⁻¹ Pt (corresponding to 0.050 pg Pt cm⁻² of the sampled surface).¹⁹ The assay was validated according to the FDA guidelines.²⁰

Results

Contamination was calculated in pg cm⁻². The presence of Pt in the environment is ubiquitous, due to pollution by car exhaust catalysts.²¹ Below a threshold of 1.00 ng L⁻¹ Pt, corresponding to 0.100 pg cm⁻², it was not possible to address the source of contamination.¹⁹ Consequently, only results 'at or above the threshold' are described.

Determination of Pt surface contamination in veterinary oncology centres

The wipe samples were collected in five veterinary oncology centres between October 2009 and February 2011. The results are presented in Table 3.

None of the procedural blank samples prepared in each centre, contained concentrations of Pt exceeding the LLOQ level.

Forty-six percent of the surface samples contained levels that were at or above the threshold. There was variation in the level of contamination between the centres. Centre 2 showed the lowest overall Pt contamination, with only 2 out of 15 (13.3%) of the wipe samples containing Pt at or above the set threshold. Centre 1 showed the highest overall Pt contamination with 12 out of 19 (63.2%) of the samples containing Pt at levels at or above the threshold. Of centre 3, 8 out of 14 (57.1%) surface samples showed Pt contamination. Centre 4 had 6 out of 14 (42.9%) surface samples that demonstrated Pt contamination. Of centres 5a and 5b, four out of nine (44.4%) and five out of nine (55.6%) surface samples showed Pt contamination, respectively. The highest level of Pt contamination was detected in the preparation rooms (up to 44.6 pg cm⁻²). Pt was found in all wipe samples taken from the middle of the BSC workbench.

Table 4. Pt contamination in two human oncology centres in the Netherlands

Sampled surface	Pt contamination (in pg cm ⁻²)	
	Site	
	1	2
Entrance: door handle	0.1	^a
Non-restricted area:	1.3	^b
patient room: door handle		
Waiting room: floor	4.3	1.4
Reception		
Floor	1.0	1.6
Handle telephone	^a	^a
Computer mouse	0.1	0.1
Preparation room		
Floor	^b	^b
Door handle	^b	^b
Work bench	0.1	0.1
Transport box	^a	^a
Outer packaging infusion bag	^b	^a
Administration room		
Floor next to bed/chair patient	10.8	9.2
Infusion pump	1.4	0.3
Bell	3.9	^b
Control system bed/chair patient	1.4	0.3
Chair	0.7	^b
Door handle	^a	1.0
Table	0.1	0.1
Waste bin top	0.4	0.2
Patient-only sanitary facilities		
Toilet: door handle	^b	2.3
Toilet: seat	725	0.6
Toilet: cover	350	^b
Toilet: floor	0.3	4.8
Shower	0.4	^b
Sluice room		
Work bench	1.4	^b
Floor	271	^b
Canteen		
Floor	1.5	2.5
Table	0.1	0.1
Kitchen surface	^a	^b

^a Below threshold (0.1 pg cm⁻²).^b Sample was not available.

Thirteen out of 27 samples (48.1%) from the consultation rooms demonstrated Pt contamination. In the administration room of site 1, three out of four samples (75.0%) showed Pt contamination. In the preparation rooms 15 out of 25 samples (60.0%) contained Pt at or above the threshold level. Not only work benches were contaminated

in these rooms, but a door handle (one out of nine, 11.1%), refrigerator door handles (three out of seven, 42.9%), handles of telephones (three out of four, 75.0%) and computer mouse devices (two out of four, 50.0%) as well, up to 44.6 pg cm⁻². We detected Pt contamination up to 0.7 pg cm⁻² on the floors of the canteen and the waiting room at three centres (sites 3, 4 and 5b).

Determination of Pt surface contamination in human oncology centres

The wipe samples were collected in two human oncology centres in May 2011.

Surface contamination of all standard locations is presented in Table 4. Mean and maximum Pt concentrations at human and veterinary oncology units are presented in Table 5. None of the procedural blanks prepared in each centre contained levels of Pt exceeding the LLOQ.

In 21 out of 25 (84.0%) of all surface samples collected at site 1 (inpatient department), Pt at levels at or above the threshold were found. In site 2 (outpatient department), 15 out of 19 surfaces (79.0%) demonstrated contamination with Pt at or above the threshold. There was variation in the level of contamination between the oncology centres, especially with regard to the patient-only sanitary facilities. The samples collected in the patient-only toilet, the sluice room and on the floor next to the patient's bed (site 1) or chair (site 2) showed the highest level of Pt contamination (up to 725 pg cm⁻² at site 1 and up to 9.2 pg cm⁻² at site 2). Pt contamination was demonstrated in 12 out of 16 samples (75.0%) collected at the waiting room, reception and the canteen (up to 4.3 pg cm⁻²).

Discussion

This article describes environmental contamination by Pt attributable to Pt-containing antineoplastic drugs at veterinary and human oncology centres in the Netherlands and Flanders.

Determination of surface contamination with antineoplastic drugs in veterinary oncology centres is rarely reported in the literature. Meijster *et al.* (2006)¹¹ measured environmental contamination with carboplatin in two veterinary oncology

Table 5. Summary of Pt surface contamination

	n ^a	Samples ^b	Mean ^c	Median ^c	Min ^c	Max ^c	SD ^c
Veterinary oncology centres	5	33/71	3.2	0.4	0.1	44.6	9.7
Veterinary hospital pharmacy	1	4/9	0.5	0.4	0.2	1.1	0.1
All veterinary facilities	6	37/80	1.9	0.2	0.1	44.6	7.4
Human oncology centres	2	37/45	45.1	1.37	0.103	724.5	148.1

Min, minimal concentration; Max, maximal concentration; SD, standard deviation.

^a Number of sampled centres.

^b Number of samples at or above threshold per total number of samples.

^c Expressed in pg cm⁻².

centres in the Netherlands. They sampled 12 surfaces in the administration and preparation rooms, and detected contamination in all samples, ranging between approximately 0.3–6730 pg cm⁻². Kandel-Tschiederer *et al.* (2010)¹⁵ measured Pt surface contamination at the preparation room, administration room and canteen of one German veterinary oncology centre. The authors reported Pt contamination ranging between 20 and 4610 pg cm⁻² in 12 out of 28 samples. The Pt contamination detected in our study ranged between 0.1 and 44.6 pg cm⁻², with the highest level of contamination generally found in the preparation rooms. The majority of the contaminated surfaces had Pt levels roughly 10–1000 times lower than the results reported by Meijster *et al.* (2006) and Kandel-Tschiederer *et al.* (2010).^{11,15} The two veterinary centres monitored by Meijster *et al.* (2006),¹¹ were evaluated by our study as well (site 1 and site 5b). This difference in Pt surface contamination cannot be easily explained. In this study, we are unable to exactly address the cause of the diminished Pt surface contamination. Nowadays, the veterinary centres use the PhaSeal[®] TD or the Tevadaptor[®] DHD when handling anti-neoplastic drugs. Kandel-Tschiederer *et al.* (2010)¹⁵ also describe the introduction of the PhaSeal[®] TD, which led to a marked decrease in Pt contamination. This reduction of surface contamination after introducing a TD has been reported in human oncology centres as well.^{22,23} The use of a TD or a DHD could, therefore, explain the reduction in Pt contamination of surfaces in site 1 and site 5b. Heightened awareness of involved personnel, improved training and stricter implementation of the veterinary safe handling guidelines may also have caused the observed reduction. In addition, all visits to the centres were announced in advance. It

is possible that a thorough cleaning was performed prior to the surface sampling. On the other hand, all centres used a daily cleaning procedure and visits occurred during normal working hours. A reduced patient load would also explain the lower Pt surface contamination found at site 1 and site 5b. However, neither veterinary oncology centre reported a decline in patient load.

The variation in surface contamination between veterinary oncology centres reported in this article can be correlated with the amount of Pt processed annually in the centres. Yet, there also seems to be an influence of cleaning and working procedures as evidenced by the similar Pt levels found in site 1 and 3, since site 1 processed a considerably higher amount of carboplatin. Site 1 uses a laminar air flow (LAF) hood and has a separate room for administration, while site 3 uses a BSC and does not have a separate administration room. As to the implementation of the other measures described in the veterinary safe handling guidelines provided by the ECVIM-CA (2007),¹² no difference between the centres was apparent. However, in daily practice small differences in implementation of the guidelines might result in the similar Pt levels found in site 1 and 3. In this study, we only measured surface contamination with Pt once at each centre. As a consequence, we cannot determine whether implementation of a specific measure has influenced the Pt surface contamination.

The environmental contamination by Pt in the human oncology centres ranged from 0.1 to 725 pg cm⁻². This is comparable with the Pt levels at surfaces in human oncology centres reported in the literature.^{24,25} Furthermore, this Pt contamination in the human oncology centres is up to 16 times higher than the levels found

at the veterinary oncology centres, and up to 8 times lower than the Pt contamination found in Dutch hospital pharmacies, published previously by our research group (minimum–maximum range: 0.105–5760 pg cm⁻², with 108 out of 124 surface samples demonstrating Pt contamination).¹⁹ Our findings indicate that hospital admission of human patients treated with Pt-containing compounds leads to a generally higher Pt surface contamination of the oncology centre. Consequently, the difference in environmental contamination by Pt between veterinary and human oncology centres, as found in this study, is likely the result of differences in total amounts of Pt-containing antineoplastic drugs handled annually and the result of sending the treated pet home after dosing.

In both human and veterinary oncology centres, wipe samples obtained from, e.g. the computer mouse, the floor at the canteen and the handle of the door of a non-restricted patient room, demonstrate that transference of Pt may occur. The determination of antineoplastic drugs in areas outside the rooms where these compounds or their wastes (e.g. patient's excreta) are handled or outside the sanitary facilities for treated patients, has rarely been reported in the literature. Some contamination of these surfaces has been described in a human hospital pharmacy (e.g. dressing room)²⁶ and some human oncology centres (e.g. writing desk).²⁷ The transference of antineoplastic drugs to surfaces that are not expected to be contaminated (e.g. computer mouse) in areas where antineoplastic drugs are handled, is more frequently investigated and contamination of these surfaces has been reported.^{19,28,29} In veterinary oncology, dispersion of carboplatin or Pt by workers has also been reported.^{11,15} As a result, surfaces deemed 'safe' may be contaminated, resulting in the potential exposure of workers, patients and visitors.

The Dutch human oncology centres monitor surface contamination with several antineoplastic drugs, including Pt-containing agents, annually. The cut-off values for evaluation of surface contamination used in the human oncology centres in the Netherlands are: <100 pg cm⁻² (only an annual surface monitoring is required), 100–10 000 pg cm⁻² (risk assessment, followed by surface monitoring and implementation of

measures if necessary), and >10 000 pg cm⁻² (implementation of measures, followed by surface monitoring).³⁰ Most surfaces at the human oncology centres measured in this study had Pt levels lower than 100 pg cm⁻² and none were higher than 1000 pg cm⁻², while none of the levels measured in veterinary oncology centres exceeded 100 pg cm⁻². The measurements during annual surface monitoring of Dutch human oncology centres are carried out using analytical techniques that are not as sensitive, but less expensive than the method reported in this article. The less sensitive assays suffice for monitoring in areas where contamination can be expected. However, with regard to the areas that should not be contaminated (e.g. canteen) our results indicate that contamination with Pt does occur and that the contamination levels may not be detectable using the less sensitive analytical assays. The presence of contamination on these surfaces indicates failure of working procedures, according to the criteria set by the human oncology centres in the Netherlands.³⁰ Therefore, to ensure a more accurate depiction of the actual transference of antineoplastic drugs, the use of an ultra-sensitive assay (e.g. ICPMS) could be considered, for specific surfaces. This may also be considered for surface monitoring in veterinary oncology centres.

Conclusion

Even though we only found low levels of Pt contamination attributable to carboplatin in the sampled veterinary oncology centres, we did discern a contamination pattern. The amount of antineoplastic drugs annually handled is of importance, as can be expected. The data also indicate that protective measures, working and cleaning procedures, and the use of a TD or a DHD can greatly influence environmental contamination. Highest contamination can be found in the drug preparation rooms, but there is evidence that transference outside the areas where antineoplastic drugs and their wastes are handled occurs. Therefore, not only those who actively work with antineoplastic drugs, but others as well might be exposed.

The level of contamination is higher in the human oncology centres than in the veterinary

oncology centres, as can be expected on the basis of the amounts of antineoplastic drugs annually handled. As in the veterinary oncology centres, spreading of Pt outside the areas where antineoplastic drugs and their wastes are handled occurs, which might result in exposure of workers, patients and visitors.

ICPMS allows detection of Pt at ultra-sensitive levels, thus providing a more accurate evaluation of exposure routes and working procedures. However, by only measuring Pt we are unable to distinguish between the Pt-containing compounds or their (active) metabolites. We are, therefore, presently monitoring Pt levels in the urine of veterinary personnel and we are evaluating the biological activity of the Pt found in urine samples of treated pet dogs, to further investigate potential clinical implications of the observed contamination.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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