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Inductively coupled plasma mass-spectrometric determination of platinum in excretion products of client-owned pet dogs

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Abstract

Residues of antineoplastic drugs in canine excretion products may represent exposure risks to veterinary personnel, owners of pet dogs and other animal care-takers. The aim of this study was to measure the extent and duration of platinum (Pt) excretion in pet dogs treated with carboplatin. Samples were collected before and up to 21 days after administration of carboplatin. We used validated, ultra-sensitive, inductively coupled plasma-mass spectrometry assays to measure Pt in canine urine, faeces, saliva, sebum and cerumen. Results showed that urine is the major route of elimination of Pt in dogs. In addition, excretion occurs via faeces and saliva, with the highest amounts eliminated during the first 5 days. The amount of excreted Pt decreased over time but was still quantifiable at 21 days after administration of carboplatin. In conclusion, increased Pt levels were found in all measured excretion products up to 21 days after administration of carboplatin to pet dogs, with urine as the main route of excretion. These findings may be used to further adapt current veterinary guidelines on safe handling of antineoplastic drugs and treated animals.

Keywords
chemotherapy, epidemiology, oncology, small animal, small animal internal medicine

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Introduction

Because the use of antineoplastic drugs in veterinary oncology has been gaining popularity in the past decades, the question arises whether these drugs may pose health risks to owners or veterinary personnel handling the pet dogs. In order to keep exposure at 'as low as reasonable achievable' levels, guidelines have been developed, and implemented, on safe handling of antineoplastic drugs, treated animals and associated wastes in veterinary oncology.[1] These also apply to owners of treated pet animals because the dog is usually sent home after treatment. In the Netherlands and Flanders, owners are informed about potential risks associated with exposure to antineoplastic drugs. When owners opt for treatment of their pet with chemotherapeutics, instructions based on the veterinary safe-handling guidelines developed by the European College of Veterinary Internal Medicine-Companion animals (ECVIM-CA)[1] are provided. These describe the handling of their pet during the period of risk. This period varies according the antineoplastic drug of interest.

Veterinary safe handling guidelines are largely based on knowledge from human oncology. Hence, the period of risk during which measures are

taken is, in general, based on the pharmacokinetic behaviour of antineoplastic drugs as observed in humans and experimental animals. However, the pharmacokinetics of compounds are species dependent. To address the question whether the guidelines are completely adequate to diminish exposure in veterinary oncology, it is relevant to investigate the pharmacokinetics of the antineoplastic drugs used in pet animals.

An example of an antineoplastic agent frequently used in pet animals is carboplatin [*cis*-diammine (1,1-cyclobutanedicarboxylato)platinum(II)], a second generation platinum (Pt)-containing compound. It is used in pet dogs for the treatment of numerous solid tumours, especially osteosarcomas and several carcinomas, e.g. thyroid carcinoma and anal sac carcinoma.[2,3] The pharmacokinetics of carboplatin in dogs has only been studied in a limited number of cases, mainly using canine plasma (Table 1). Literature indicates that urine is the principal route of excretion of Pt and carboplatin, but some excretion occurs via faeces as well.[7] Furthermore, human research has demonstrated that Pt originating from carboplatin can be excreted in saliva.[8] Therefore, to evaluate whether the current veterinary safe handling guidelines are adequate for carboplatin, we monitored Pt amounts in urine, faeces and saliva of treated pet dogs. The coat and skin of the dogs may be contaminated with Pt due to an excretory process or as the result of transfer from contaminated surfaces. Because contact with the skin and the coat of pet dogs is rather inevitable when handling them, we also monitored Pt levels in samples collected from treated pet dogs. In addition, Pt in cerumen of pet dogs was determined. The ear canal forms a sheltered environment, which likely prevents contamination of the samples from other sources than the excretion process. Thus, with these samples we aimed to describe potential transdermal excretion.

Patients and methods

Patients and chemotherapy regimes

Client-owned pet dogs treated with single agent carboplatin (Hospira Benelux, Brussels, Belgium; Carbosin, Teva Pharmachemie, Haarlem, the Netherlands) or carboplatin in combination with doxorubicin or epirubicin were eligible for this study. In a normal canine single-agent carboplatin protocol, the drug is delivered every 3 weeks for in total 6–12 times. In a combination protocol with doxorubicin or epirubicin, the anthracycline and carboplatin are alternately delivered every 3 weeks, so the dog receives carboplatin once in 6 weeks. Great heterogeneity exists in the patient population, with regard to body weight and body surface area, because of the limited number of eligible dogs. Dogs were enrolled in the study between October 2009 and May 2012. The characteristics of the dogs are presented in Table 2. No abnormal renal function was reported for any of the dogs. A signed informed consent form was obtained from the owners. The study was reviewed by the Netherlands Cancer Institute Independent Medical Ethical Evaluation Committee.

Sample collection

All samples were collected by the pet owners prior to the treatment and on the day of drug administration up until day 21 postinfusion, using a new pair of nitrile gloves (Klinion, Medeco, Oud-Beijerland, the Netherlands) for each sample, as described earlier.[9,10] Urine samples were collected in 30 mL polypropylene tubes (Sarstedt AG, Nümbrecht,

Table 1. Pharmacokinetics of carboplatin in dogs

Dose	Compound	Period (h)	*n*	V_d (L/m^2)	C_{max} (μg/mL)	CL_T [L/(h m^2)]	$t_{1/2\,el}$ (h)	Urinary excretion (% dose)	References
12 mg kg^{-1} IV	Carboplatin	96	3	5.7 ± 0.4	83 ± 7	5.4 ± 0.2	1.2 ± 0.4	37 ± 15 (over 24 h)	Gaver *et al.*[4]
12 mg kg^{-1} IV	Pt	96	3	5.1 ± 0.4	93 ± 14	5.2 ± 0.3	0.9 ± 0.1	61 ± 9 (over 96 h)	Gaver *et al.*[4]
150 mg m^{-2} IV	Pt	24	3	34 ± 2.8	–	6.5 ± 1.0	3.7 ± 0.29	31.7 ± (over 4 h)	Page *et al.*[5]
250 mg m^{-2} IV	*Carboplatin*	*8*	*9*	*4.3 ± 0.58*	–	*4.3 ± 0.44*	*0.79 ± 0.06*	–	Villarino *et al.*[6]

C_{max}: peak plasma concentration of a drug after administration, CL_T: total body clearance, IV: intravenous, *n*: number of subjects, period: period of sample collection, $t_{1/2\,el}$: biological half-life, V_d: volume of distribution, – : not available.

Table 2. Characteristics of pet dogs treated with carboplatin

Dog	Age[a]	Breed	Gender	Tumour type	Administered dose[bc]	Cumulative dose[d]
1	9	Airedale terrier	F	Transitional cell carcinoma	270	270
2	10	German Shepherd dog	M	Thyroid carcinoma	350	350
3	7	West Highland white terrier	F	Lung carcinoma	72	72
4	2	Bullmastiff	M	Osteosarcoma	460	460
5	4	×Rottweiler	M	Squamous-cell carcinoma	300	300
6	10	×Labrador retriever	M	Adenocarcinoma	210	210
7	8	Irish setter	F	Thyroid carcinoma	270	270
8	7	Boxer	M	Squamous-cell carcinoma	390	390
9	11	Jack Russell terrier	M	Thyroid carcinoma	100	100
10	11	Bemese Mountain dog	M	Sarcoma of the nasal cavity	350	1060

F: female, M: male, ×: cross-breed.
[a]Age at treatment (in years)
[b]Administered dose at sample collection (in mg).
[c]Cumulative dose at sample collection (in mg).
[d]Dose was calculated using 300 mg m^{-2} (when body weight is above 15 kg), else: 15 mg kg^{-1}.

Germany) using voided urine. Canine faecal samples were collected in 50 mL polypropylene tubes (Falcon, Becton Dickinson Labware, Franklin Lakes, NJ, USA). Canine saliva samples were collected by letting the dog chew on Salivette® cotton swabs (Sarstedt AG) and by inserting the swab between the teeth and the cheek of the dog, both while holding the swab, until the swab was soaked with saliva or the dog persistently resisted sampling. Saliva production was stimulated by exercise or the presentation of food. Sebum sampling was performed by wiping a body surface area on both the coat (of the thorax) and the skin (of the lower abdomen) of the dog. All wipe samples were collected using a uniform sampling procedure by wiping a predefined body surface of 10 × 10 cm three times. Cerumen sampling was performed by wiping the accessible part of the ear canal using Kimtech Science precision wipes (Kimberley- Clark Professional, Irving, TX, USA). Wipe samples were stored in 30 mL disposable polypropylene tubes. The owners stored the samples at −20 °C, until the samples were transported to the laboratory. All samples were then stored at −20 °C until analysis.

Determination of Pt by inductively-coupled plasma-mass spectrometry

We recently developed and validated assays for the determination of Pt originating from carboplatin in canine urine, faeces, oral fluid, sebum and cerumen.[9,10] The methods are based on the quantification of Pt by inductively-coupled plasma-mass spectrometry (ICPMS), and allow lower limits of quantification of 7.50 ng L^{-1} Pt in canine urine (in 15 µL of matrix), 15.0 ng L^{-1} Pt in canine oral fluid (in 15 µL of matrix) and 0.105 ng g^{-1} Pt in canine faeces (in 5 µg of matrix), 0.15 pg cm^{-2} Pt in canine sebum (in 15 µL of extraction solution) and 7.50 pg per sampled external ear canal (in 15 µL of extraction solution).[9,10] Sample pretreatment mainly involved dilution with appropriate diluents. In brief, urine samples were thawed, whirl mixed and then diluted 100 times with 1% HNO_3 (v/v) solution. Canine faecal samples were thawed, weighed, homogenised [1:3 faeces:ultrapure water (Aqua B. Braun Medical, Melsungen, Germany)] and whirl mixed. The samples were then centrifuged at 2100 g for 5 min. The supernatant was centrifuged at 10 300 × *g* for 5 min and subsequently diluted 100-fold with 1% HNO_3 solution. The resulting solution was filtered using a 0.2 µm filter (Sartorius minisart, Sarstedt AG, Nümbrecht, Germany). A procedure similar to the pretreatment of urine samples was followed for canine oral fluid samples. However, these were diluted with a 0.01% (g/v) ammonium ethylenediaminetetraacetic acid (EDTA, Sigma-Aldrich, St. Louis, MO, USA) and Triton X-100 (Sigma-Aldrich) solution (in water) and if necessary successively with oral fluid: 0.01% EDTA/Triton X solution (1:100, v/v). To each 2 mL diluted sample, 20 µL of internal standard solution was added. Subsequently, diluted samples were transferred to autosampler tubes. Sebum and

cerumen wipes were extracted with 10 mL 1% HCl (Mallinckrodt Baker, Philipsburg, NJ, USA) (v/v), and vessels were kept in an ultrasonic bath at 40 °C for 60 min. Then, samples were filtered using a 0.2 μm filter. Later an internal standard was added [iridium (Merck, Darmstadt, Germany), 100 ng L^{-1}, 10 μL per mL sample]; 2 mL of sample were introduced directly into the ICPMS (Varian 810-MS, Victoria, Australia).

Results

Due to pollution by car exhaust catalysts, Pt is ubiquitous in the environment.[11] By measuring Pt background in healthy untreated pet dogs, and in the treated pet dogs prior to the first treatment with carboplatin, we were able to distinguish a rise in Pt levels, as a result of administration of carboplatin, from normal Pt background variation.

Pt levels in urine, faeces and saliva of pet dogs treated with carboplatin

The Pt levels were determined in 114 urine samples collected at several time points before and after administration of carboplatin in 10 pet-dogs (Table 3 and Fig. 1). Because of cross-contamination issues and analytical errors, 20 samples had to be excluded from the study. Median Pt level in urine samples on day 1 (after administration) is 30.9 mg L^{-1}. The median urinary Pt concentration rapidly declines to 1.1 mg L^{-1} on day 5. Later, median Pt concentration decreases more slowly in urine to 0.1 mg L^{-1} (day 20).

The Pt levels were monitored in 90 faecal samples of eight treated pet dogs collected at different time points before and after administration of carboplatin (Table 3 and Fig. 1). Because of analytical errors, 11 samples had to be excluded from the study. The pretreatment sample of dog 2 showed a higher than usual background level of Pt. Median Pt level on day 1 is 318 ng g^{-1} faeces, then raises to 1178 ng g^{-1} faeces on day 2 and falls rapidly after achieving maximal levels to 43.8 ng g^{-1} faeces on day 5. Pt levels in faeces continue to decrease at a slower rate to day 21 (median: 29.0 ng g^{-1}).

Saliva was difficult to obtain. One dog did not allow sampling. The others did, but sampling did not always generate enough saliva. Twenty-eight

Table 3. Excretion of Pt in urine, feces and saliva of pet dogs treated with carboplatin

Day	Urine Mean[a] (range)[ab]	*n*	Faeces Mean[a] (range)[ab]	*n*	Saliva Mean[a] (range)[ab]	*n*
Pretreatment	<LLOQ	1	0.2	3	<LLOQ	2
1	55.9 (0.3–138)	9	659 (17.3–1641)	3	658 (299–1017)	2
2	13.2 (0.07–82.8)	7	1518 (21.4–4328)	7	212 (36.4–388)	2
3	4.4 (0.06–28.4)	8	796 (51.4–2022)	7	150	1
4	1.7 (0.02–4.6)	4	265 (17.6–605)	6	63.7 (15–112)	2
5	0.8 (0.03–1.2)	6	108 (13.7–367)	5	3.7 (0.5–6.9)	2
6	0.9 (0.7–1.4)	5	25 (14–44.5)	4	2.7 (2.2–3.2)	2
7	0.4 (0.01–0.8)	5	34.9 (7.9–112)	7	2.6 (0.2–5)	2
8	0.4 (0.2–0.6)	3	17.6 (9.2–26.1)	2	1.7 (1.1–2.4)	2
9	0.5 (0.4–0.5)	3	15.1 (10.4–17.8)	3	2.2 (0.4–4.1)	2
10	0.3 (0.05–0.5)	5	24.1 (15.5–31.9)	5	–	0
11	0.2 (0.2–0.3)	3	31	1	1.2	1
12	0.3 (0.2–0.5)	4	12.7 (5.1–18.7)	3	0.6	1
13	0.3 (0.006–0.7)	7	30.5 (6–90.9)	5	0.2	1
14	0.2 (0.1–0.2)	2	14.1 (8.6–19.6)	2	0.7	1
15	0.2 (0.2–0.2)	2	7.6 (6.4–8.9)	2	–	0
16	0.07 (0.02–0.1)	3	8.7 (5.6–10.5)	3	1	1
17	0.4 (0.07–0.7)	3	12.3 (7.6–17)	2	–	0
18	0.2 (0.002–0.3)	4	7.1 (5.7–8.6)	3	0.6 (0.3–0.9)	2
19	0.1 (0.003–0.3)	6	15.9 (13.4–18.3)	2	0.4	1
20	0.2 (0.1–0.4)	3	7.4 (7–7.8)	2	–	0
21	–	0	29 (18.6–39.3)	2	–	0
22	0.08	1	–	0	–	0

LLOQ: Lower limit of quantitation; *n*: number of samples.
[a]In mg L^{-1} (urine); ng g^{-1} (feces) or μL^{-1} (saliva).
[b]Minimum—maximum concentrations.

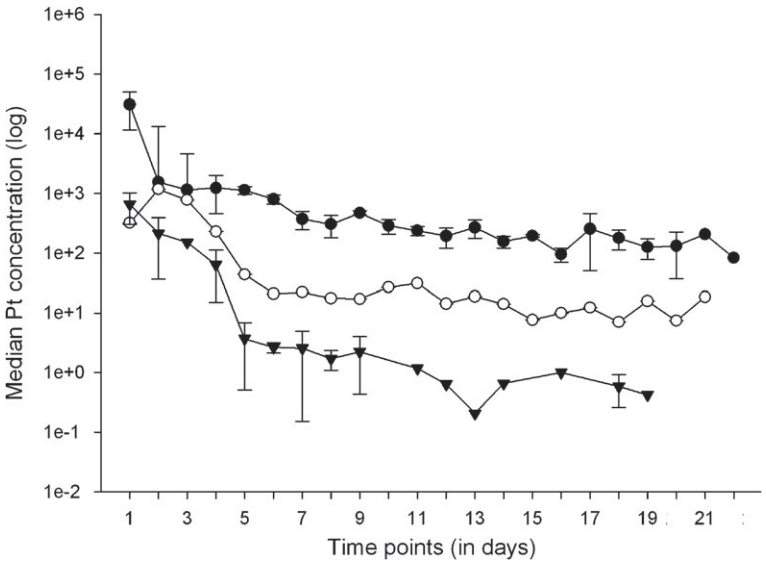

Figure 1. Depiction of median Pt concentrations in urine (●, $\mu g\,L^{-1}$, $n = 10$), faeces (○, $\mu g\,kg^{-1}$, $n = 8$) and saliva (▼, $\mu g\,L^{-1}$, $n = 2$) of pet-dogs treated with carboplatin, up to 22 days after administration. The LLOQ of the urine assay ($7.5 \times 10^{-4}\,\mu g\,L^{-1}$) is delineated in the figure as a horizontal line. Error bars are based on standard error × 2. The sample size was variable at each time point. For sample sizes see Table 3.

samples from two dogs, collected at different time points before and after administration of carboplatin, were monitored (Table 3 and Fig. 1). Because of analytical errors, one sample had to be excluded from the study. The highest median amount of Pt excreted via saliva was on day 1 ($658\,\mu g\,L^{-1}$). The levels of Pt declined rapidly at first (day 4: median of $64\,\mu g\,L^{-1}$), and then more gradually until day 18 (median of $0.6\,\mu g\,L^{-1}$).

Pt levels in sebum and cerumen of pet dogs treated with carboplatin

From seven dogs, 100 sebum samples of the skin, collected on various time points before and after administration of carboplatin, were available for monitoring (Table 4 and Fig. 2). Because of analytical errors three samples had to be excluded from the study. Of the two dogs with higher than usual Pt background levels, one lived in the garden and only rarely entered the house, while the other lived in a city. Median Pt concentration was highest on day 1 ($367\,pg\,cm^{-2}$). The median Pt level declines until day 4 to $86.2\,pg\,cm^{-2}$, and more slowly until day 21 ($4.8\,pg\,cm^{-2}$).

A total of 109 sebum samples of the coat were monitored in eight dogs, at several time points prior to the treatment with carboplatin and postinfusion (Table 4). Because of analytical errors five samples had to be excluded from the study. Maximal median amount of Pt was found on day 3 ($38.6\,pg\,cm^{-2}$). The median Pt level falls quite slowly to $7.2\,pg\,cm^{-2}$ on day 5 and, later, even slower to $1.4\,pg\,cm^{-2}$ on day 21.

The Pt levels were monitored in 106 cerumen samples from eight dogs, collected at different time points prior to treatment and after administration of carboplatin (Table 4). Because of analytical errors, three samples had to be excluded from the study. Highest median level of Pt was found on day 3 (689 pg per sample). Later, median Pt levels gradually decline to 95.1 pg per sample on day 21.

Discussion

We report increased levels of Pt in several canine excretion products, up to at least 3 weeks after administration of carboplatin to pet dogs. Validated methods were used. Clinical applicability was previously demonstrated and described using samples from a pet dog treated with carboplatin collected up to 4 days postinfusion.[9,10] In the current study, samples collected from 10 dogs up to 21 days after administration were used.

Table 4. Excretion of Pt in sebum and cerumen of pet dogs treated with carboplatin

Day	Sebum (skin) Mean[a] (range)[ab]	*n*	Sebum (coat) Mean[a] (range)[ab]	*n*	Cerumen Mean[a] (range)[ab]	*n*
Pretreatment	0.3 (0.2–0.5)	6	<LLOQ	6	<LLOQ	6
1	560 (105–1948)	6	35 (1.4–161)	8	3468 (2.3–19878)	6
2	258 (111–516)	7	50 (2.6–120)	7	1517 (34.8–4901)	7
3	166 (4.6–665)	7	30.7 (0.9–65.9)	7	1543 (76.2–4737)	8
4	106 (18–335)	7	31.4 (0.5–125)	7	411 (1.1–1395)	7
5	102 (7.8–338)	6	90.1 (1–555)	7	703 (54.8–2442)	6
6	36.2 (2.1–110)	7	6 (1.2–19.8)	5	526 (23.8–2257)	7
7	40 (0.5–126)	6	5.6 (0.3–19.2)	7	460 (11.6–1935)	7
8	65 (2.3–124)	4	2.9 (2.3–3.6)	2	596 (13.1–1713)	4
9	42.4 (1.6–106)	4	7.4 (0.4–19.3)	4	353 (50.8–1083)	4
10	14.5 (2.2–23.8)	4	3.3 (0.7–6.1)	4	536 (105–1203)	4
11	19.8	1	3.6 (0.2–5.4)	3	828 (30.3–1627)	2
12	4.1 (1.5–8.5)	3	2.1 (0.3–4.6)	4	372 (120–981)	4
13	19.1 (1.2–30.5)	4	2.1 (0.4–4)	5	354 (32.2–1128)	5
14	8.4	1	3.8 (3.6–4)	2	563 (201–925)	2
15	5.1 (0.9–10.4)	4	1.8 (0.3–5.3)	4	408 (128–1178)	4
16	6.4 (1.1–16)	4	1.5 (0.6–2.7)	4	465 (71.6–1351)	4
17	3.9 (2.1–5.7)	2	2.6 (0.8–4.4)	2	115	1
18	5 (3.1–6.2)	3	2.4 (0.3–5.9)	4	382 (30.6–1375)	4
19	5.4 (1–9.8)	6	1.9 (0.8–3.2)	6	174 (35.1–482)	5
20	2 (1.6–2.3)	2	2.1 (1.6–2.5)	2	547 (106–988)	2
21	4.8 (2.6–7)	2	1.3 (0.2–2.3)	3	90.1 (62–113)	3
22	0.8	1	0.6	1	248	1

n: number of samples.
[a]In pg cm^{-2} (sebum) or pg per sample (cerumen).
[b]Minimum–maximum concentrations.

Although the sample size of this study is rather small, a constant excretion pattern can be observed in all sampled matrices. This provides valuable information on the excretion pathways for Pt and on the duration of excretion, which can be used to further enhance the veterinary safe handling guidelines. To our knowledge, this is the first article describing Pt excretion in faeces, saliva, sebum and cerumen of pet dogs treated with carboplatin.

The Pt was mainly excreted via urine in pet dogs in this study. This is in agreement with the literature. Gaver *et al.*[4] and Page *et al.*[5] also described urine as the primary route of Pt excretion when carboplatin is administered to dogs (Table 1). Our results demonstrate that Pt was excreted to a lesser extent in faeces and saliva of treated pet dogs. Faecal excretion[7,12,13] of carboplatin has been reported in mice and rats, while salivary excretion[8] has been described in humans, though urine is the main route of excretion in these species as well.[12,14] Furthermore, we were able to detect traces of Pt in canine sebum and cerumen samples. No reports regarding these excretion products could be traced.

As mentioned above, we theorised that the external ear canal is a sheltered environment, thereby reducing the contribution of potential external Pt contamination. Therefore, the marked increase in Pt levels in cerumen after administration of carboplatin indicates that transdermal excretion of Pt occurred. This may be the result of Pt secretion into sebum and cerumen. However, this is rather unlikely given the time lapse between sebum production and its excretion onto the skin surface (on average 8 days in humans, though unknown in dogs).[15] Transcellular transport, on the other hand, would require transition through the virtually impenetrable intracellular matrix of the keratinocytes.[16] Intercellular transport across the skin involves interaction with hydrophobic and hydrophilic environments,[16] but carboplatin is a hydrophilic compound[17,18] with an affinity for hydrophobic environments.[17] Moreover, both carboplatin and Pt are polar compounds, and very polar solutions have been reported to permeate the stratum corneum.[16] Even though this applies to external-to-internal transdermal

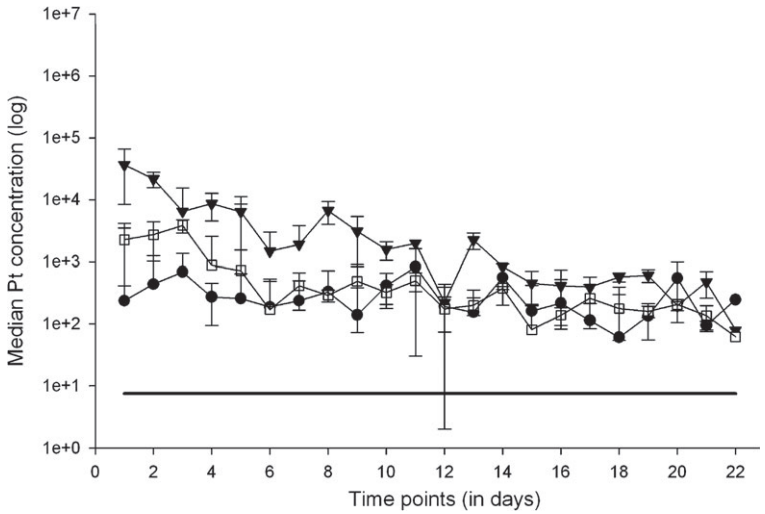

Figure 2. Depiction of median Pt concentrations in sebum of the skin (▼, pg per 100 cm^2, $n = 7$), sebum of the coat (□, pg per 100 cm^2, $n = 8$) and cerumen (●, pg per sample, $n = 8$) of pet-dogs treated with carboplatin, up to 21 days after administration. The LLOQ of the cerumen assay (7.5 pg per sample) is delineated in the figure as a horizontal line. Error bars are based on standard error × 2. The sample size was variable at each time point. For sample sizes see Table 4.

transport, intercellular transport of Pt still seems the most probable route for its excretion into sebum and cerumen in dogs.

The Pt concentrations detected in sebum of the coat are roughly 2–20 times lower than what is found in sebum of the skin. This difference in Pt levels may be the result of common dog behaviour (e.g. licking), droplet formation when urinating or topical histological differences of the skin (e.g. variation in number of sebaceous glands, thickness of epidermis and stratum corneum).[19]

Our findings demonstrate that Pt is excreted in pet-dogs up until at least 21 days after administration of carboplatin. However, the duration of sample collection in this study, only covered the first 3 weeks after dosing. On the basis of the reports in the literature, Pt excretion may occur over longer periods of time. For example, prolonged excretion of Pt has also been reported in humans, with urinary Pt levels measurable up to 17 years after treatment with Pt-containing compounds.[20,21] This can be explained by the Pt retention that occurs in various organs (e.g. liver and kidney) and major tissues such as skin, bone and muscle.[20,22–24] From these distinct body compartments, Pt is then slowly released into the bloodstream,[21] probably as the result of normal cell turn over.[24–26] Another process likely contributing to the prolonged excretion of Pt is the persistent circulation of Pt in blood due to protein binding.[27]

The guidelines on handling antineoplastic drugs, treated animals and associated wastes in veterinary oncology list 5 days as being an expected period of risk for carboplatin.[1] This is in accordance with the period of fast elimination reported here. Moreover, the guidelines consider all excreta, namely urine, faeces, saliva and vomit, as potentially hazardous. However, our findings indicate that sebum may be a potential source of exposure by dogs. Furthermore, the results demonstrate that low levels of Pt are excreted via all routes, up to at least 3 weeks after the administration of carboplatin.

It is not clear whether the Pt levels reported in this article represent true health risks. Occupational exposure of nurses and pharmacy personnel to antineoplastic drugs in human oncology centres is associated with increased genotoxic responses.[28] However, doses given to pet-animals are relatively low compared with human oncology patients. Thus, we may conclude that the exposure of owners and veterinary personnel via canine excretion products is lower than the occupational exposure encountered in human oncology. Nevertheless, Pt-containing compounds have been associated with an increased risk of cancer in human patients[29,30] and any exposure to carcinogenic

compounds could, theoretically, result in adverse health effects.[31] Importantly, using the ICPMS, we do not distinguish between carboplatin and its (active) metabolites (e.g. serum albumin adducts and cisplatin).[27,32] Consequently, we are unable to provide information on the biological activity of the measured Pt. We are, therefore, presently investigating the biological activity of the Pt measured in canine urine.

Conclusion

Considering the safe-handling of pet dogs treated with carboplatin, this study demonstrates the importance of not only urine but also other excretion products, such as saliva and sebum, which contain increased Pt levels after administration of carboplatin. Furthermore, Pt could be measured in urine, faeces, saliva, sebum and cerumen of pet dogs, up to at least 21 days after administration of carboplatin. These findings may be used to further adjust the veterinary guidelines on safe handling of pet dogs treated with antineoplastic drugs.

Conflicts of interest

Conduct of the study was financially supported by: Dutch Animal Cancer Foundation (NKFD), Collaborating Dutch and Belgian Veterinary Cancer Centers (SDK), the Netherlands Organization for Health Research and Development, ZonMw (OND1307436) and Pfizer Animal Health.

J. P. d. V. is chairman of the Dutch Animal Cancer Foundation (NKFD). For the remaining authors none were declared. The authors declare that there are no conflicts of interest.

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