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ORIGINAL PAPER

Environmental risk assessment of platinum cytotoxic drugs: a focus on toxicity characterization of hospital effluents

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Abstract Platinum-based cytotoxic drugs are complexes of Pt used in 50–70% of cancer patients. This study was performed during 2015, in two oncology wards of Qom hospitals in Iran. Sampling was carried out using effluent of the oncology wards for measurement of total Pt concentration. Analysis was performed by ICP–OES, and limit of detection was determined (LODs = 1 μg/L). During the sampling days, the total Pt concentration in the wastewater effluent oncology ward ranged from 5 to 762 μg/L at Shahid Beheshti Hospital and from 3 to 629 μg/L at Hazrat Masoumeh Hospital. According to the results from concentration of cytotoxic drugs, the predicted environmental concentrations (PECs) (ng/L) in wastewater treatment plant effluent and river for cisplatin, carboplatin and oxaliplatin were determined. Calculated RQ_{hww} showed that $\sum RQ_{hww} = 1.19$. Thus, the total platinum compound drug could have potential toxicity effect on aquatic organisms. It was concluded that monitoring of cytotoxic drugs residue in hospital effluent must be considered because of their toxicity and impact on aquatic pollution. The results also revealed that PEC < 10 ng/L for all the platinum compound drugs and sum of the PEC calculation ($\sum PEC_{cis,carbo,oxali}$).

Keywords Cisplatin · Carboplatin · Hospital effluent · Oxaliplatin

Introduction

Pharmaceuticals in water have received a growing attention from environmental and health agencies all over the world and become one of the emerging pollutants due to their frequent detection in the water environment. The fact that pharmaceuticals are manufactured with the intention to cause biological effects has raised concerns about the impacts of unintentional pharmaceutical exposure on the health of humans and ecological communities' (Parrella et al. 2014). As they are discharged into receiving streams, the fate and risk of pharmaceuticals in the aquatic environment have been studied. Pharmaceuticals are released to wastewaters after excretion and due to incomplete removal in wastewater treatment plants (WWTPs) (Jaafari et al. 2017). Thus, traces of pharmaceuticals have been detected in hospital effluents, influent/effluent wastewaters and surface and groundwaters (Fuerhacker et al. 2007; Hoseini et al. 2013; Jaafari et al. 2015; Safari et al. 2015). The World Health Organization has reported that cancer is classified as the second cause of death

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(21%). Cytotoxic compounds have grown in recent years, as a group of antineoplastic agents that function by interacting with DNA and interfering with the process of cell division (Ferrando-Climent et al. 2014). Three cancerostatic platinum compounds, cisplatin (cis-diamminedichloroplatinum(II)), carboplatin (cis-diammine 1,1-cyclobutanedicarboxylato platinum) and oxaliplatin ([(1R,2R)-1,2-cyclohexanediamine-N,NV]oxalate(2-)-O,OV-platinum), are complexes of Pt used in 50–70% of cancer patients which have gained undisputed relevance in cancer therapy for treating testicular tumors, ovarian carcinomas and blood cancer. Platinum-based antineoplastic agents cause cross-linking of DNA as monoadduct, interstrand cross-links or DNA protein cross-links. The resultant cross-linking inhibits DNA repair and/or DNA synthesis in cancer cells (Vyas et al. 2014). Platinum drug compounds are classified as probably carcinogenic to humans (group 2A) by the International Agency for Research on Cancer (1987). The platinum of cytostatic agents is excreted by the patients and reaches the municipal sewer system. The environmental distributions and impacts of these drugs and their metabolites are, however, particularly poorly defined (Negreira et al. 2014). In recent years, there has been an increase in the rate of cancer disease and platinum drug consumption in oncology wards of Qom hospitals. In light of the increasing environmental concentration of cytotoxic and in view of the possible exposure to aquatic organisms and human, the aim of this study was to assess environmental and ecological risk of Platinum cytotoxic drugs in aquatic environment.

Materials and methods

Study area

This study was performed during 2015, in two oncology wards of Qom hospitals, Iran, including Shahid Beheshti Hospital with 400 active beds (and a 20-bed oncology ward) and Hazrat Masoumeh with 120 active beds (and a 15-bed oncology ward) located in the central part of Qom Province. The studied hospitals provide general medical, surgical, maternity, pediatric, and a range of specialist services. The population of the urban area selected for this study has been approximately 1,000,000 habitants. The wastewater treatment plants considered in this study serve population between 100,000 and 150,000 and have primary and secondary biological treatment processes ($Q = 0.5$ m^3/s).

Sample collection, preparation and analytical methodology

The sampling was carried out using effluent of the oncology wards of the hospitals. Wastewater samples containing 24-h composite samples were collected during February and May 2015 over 30 days from each hospital. Upon arrival to the laboratory, the samples were acidified to PH < 2 with hydrochloric acid solution (6M). A total of 50 ml of the samples was vacuum-filtered through filter paper (pore size = 2.7 μm). A stock solution (1000 mg/l) of platinum at the highest purity (99.9%) was prepared along with the calibration solution of the target compound of 1, 10, 15, 20 and 30 μg/L. The method fitted a linear model with ($R^2 = 0.999$) and the apparatus limit of detection (LOD) was determined as 1 μg/L. The analysis was performed by ICP–OES.

Environmental risk assessment

In order to evaluate the environmental risk assessment of platinum cytotoxic drugs, risk quotients (RQs) were calculated for each compound. According to Eq. (1)

$$\mathrm{RQ} = \mathrm{PEC}/\mathrm{PNEC} \quad (1)$$

RQ is calculated according to EU guidelines (Ferrando-Climent et al. 2014), as the ratio between predicted environmental concentrations (PEC) and (PNEC) that is predicted no effect concentration. Amount of PNEC is based on toxicity data related to fish, daphnia or algae and determined by applying "safety factor" that for acute study safety factor of 1000 is applied to the EC50 value. At the present study, PNEC for Pt-based anticancer drugs was taken from literature data and 1.22 (μg/L) was selected (Frédéric and Yves 2014).

In this method, the interpretation of data on probable ecological risk effects of contaminated water contains:

RQ < 1.0 indicates no significant risk;
$1.0 \leq$ RQ < 10 indicates a small potential for adverse effects;
$10 \leq$ RQ < 100 indicates significant potential for adverse effects (Franquet-Griell et al. 2015).

At this study, two types of RQ were calculated including RQ for hospital wastewater risk (RQ_{hww}) and RQ for effluent wastewater treatment plant into surface water (RQ_{sw}) (Escher et al. 2011; Daouk et al. 2016).

Predicted environmental concentration (PEC)

The predicted environmental concentrations (PECs) are used to calculate the amounts of drugs expected to be discharged into the environment, and this model plays an important role in risk assessment. According to PEC model, PEC value >10 ng/L is evaluated for any of the cytotoxic drugs as compounds with environmental risk (Grung et al. 2008; Besse et al. 2012). This model or equivalent has been extensively used with or without

refinements to estimate PECs of pharmaceuticals, especially cytotoxic drugs in surface and wastewaters (Negreira et al. 2014). The PECs (ng/L) were calculated to estimate the amounts of cytotoxic drugs in wastewater effluents and surface waters in Qom Province (Chen et al. 2013). Using the following equation

$$\mathrm{PEC} = \frac{\text{consumption} \times \mathrm{Fexc} \times \mathrm{Fstp}}{\mathrm{WWinhab} \times \mathrm{inhab} \times \text{dilution} \times 365} \times 10^6 \qquad (2)$$

where consumption (mg year^{-1}) is the amount of drug consumed by the population over 1 year in a defined zone; inhab is the number of inhabitants. WWinhab is the volume of wastewater per person per day (which was calculated as 200 l inhabitants^{-1} day^{-1}). Dilution is the dilution factor from wastewater treatment plant (WWTP) effluents to surface waters (default value set at 10); F_{excreta} is the excretion fraction of the active molecule (considered based on previous studies (0.6) for evaluation of elimination process) (Toolaram et al. 2014); and F_{stp} is the fraction of the drug emission from WWTPs directed to surface waters, which can be defined as 1-WWTP removal fraction. In most cases, WWTP removal rates were not available, and therefore, we assumed an F_{stp} value of 1, which corresponds to a worst-case scenario (i.e., no removal in WWTPs) (Rowney et al. 2011; Besse et al. 2012). Prediction of environmental fate and other physiochemical properties that play critical roles in determining environmental behaviors and fate in this study were determined by a theoretical model (EPI Suite 4.1).

Using this model, various physiochemical parameters such as boiling point, bioconcentration factor (BCF), bioaccumulation factor (BAF), octanol–water partition coefficient (Kow), solubility, vapor pressure, environmental fate of organic compound and efficiency of elimination process were assessed (Chen et al. 2013).

The reliability of the PEC in this study was determined by the PEC/MEC (measured environmental concentrations) ratio with an acceptable range of 0.2–4 (Zhang et al. 2013). Moreover in this study, platinum drugs were measured in the wastewater from oncology wards of the hospitals, and then, $\mathrm{PEC_{hww}}$ were calculated by dividing the consumed mass of drugs (M) multiplied by the excretion factor by the volume of wastewater (V) as shown in Eq. (3) (Daouk et al. 2016).

$$\mathrm{PEC_{hww}} = M \times F_{\mathrm{excr}}/V \qquad (3)$$

In this study for $\mathrm{PEC_{hww}}$ calculation, M was average total dosage of injected platinum-based drug complex including cisplatin, carboplatin and oxaliplatin in two hospitals, volume of wastewater in the Shahid Beheshti was 2 L/s and Hazrat Masoumeh was L/s and total volume of wastewater 3 L/s was considered. F_{excr} was taken as (0.6).

Consumption data

Table 1 shows that the consumption data of platinum drugs were extracted from healthcare centers in Qom Province in 2015. The results revealed that a larger portion of platinum compounds was widely consumed in hospitals other than the ones investigated in this study.

Results and discussion

Environmental fate and physiochemical properties of platinum drugs

The physiochemical properties of platinum drugs for occurrence and fate of these compounds in aquatic environment are presented for illustrative purpose in Table 1.

According to results of Table 1, platinum cytotoxic drugs are highly water soluble and log $K_{\mathrm{ow}} < 1$ suggests that the compounds are highly mobile in the aquatic environment. Therefore, the likely behavior platinum drugs less likely to sorb onto the sediments or sludge in the environment. BAF and BCF factors are also low, suggesting that none of these compound drugs are expected bioaccumulation in aquatic organisms.

Determination of quantities of platinum drugs in the hospital effluents of oncology wards

During sampling days, the total Pt concentrations in the wastewater effluent from oncology ward ranged from 5 to 762 μg/L at Shahid Beheshti Hospital and from 3 to 629 μg/L at Hazrat Masoumeh Hospital, as listed in Tables 1 and 2. The results showed that the platinum drugs were found in 100% of samples. Equivalent quantities of Pt administered as cisplatin, carboplatin and oxaliplatin were derived from the distribution of the ratio of Pt to the total molecular mass of each compound. Therefore, the average concentration of platinum drugs containing: cisplatin, carboplatin and oxaliplatin was, respectively, determined as 146.2, 55.4 and 170 μg/L for Shahid Beheshti Hospital and as 47.2, 225.6 μg/L, 0 for Hazrat Masoumeh Hospital. In the study of Lenz et al. (2007), Pt concentration from wastewater of a hospital in Vienna Austria was ranged from 3 to 250 μg/L (Lenz et al. 2007). In another study by Vyas et al. (2014) on platinum-based anticancer drugs from wastewater of a UK hospital, total Pt was measured and the concentration was ranged from 0.02 to 140 μg/L in the oncology effluent and from 0.03 to 100 μg/L in the main drains (Vyas et al. 2014). It seems that higher concentration of total Pt in this study is related to direct sampling of separated wastewater oncology wards from hospital sewer and optimization of sampling condition.

Table 1 Platinum drugs consumption in Qom province in 2015

Compound	Shahid Beheshti (gr/year)	Hazrat Masoumeh (gr/year)	Total of urban consumption (gr/year)
Cisplatin	150	100	325
Carboplatin	180	145	422
Oxaliplatin	110	95	266

Table 2 Basic information of platinum drug base about physio-chemical properties

Compound	Cisplatin	Carboplatin	Oxaliplatin
Boiling point	575	772	780
Water solubility (gr/l)	2.5	11.7	8.1
Vapor pressure (mm hg)[a]	1.16e−0.19	4.59e−0.19	4.8e−0.19
Log k_{ow}	−2.19	−0.46	−0.58
Log BCF	0.5	0.049	0.5
Log BAF	−0.049	−0.049	−0.049
Biodegradation (% STP)[b]	0.09	0.09	14
Sludge adsorption (%STP)	1.75	1.75	1.75
Total Removal (%STP)	1.85	1.85	1.85

[a] At 25 °C

[b] Secondary treatment plant

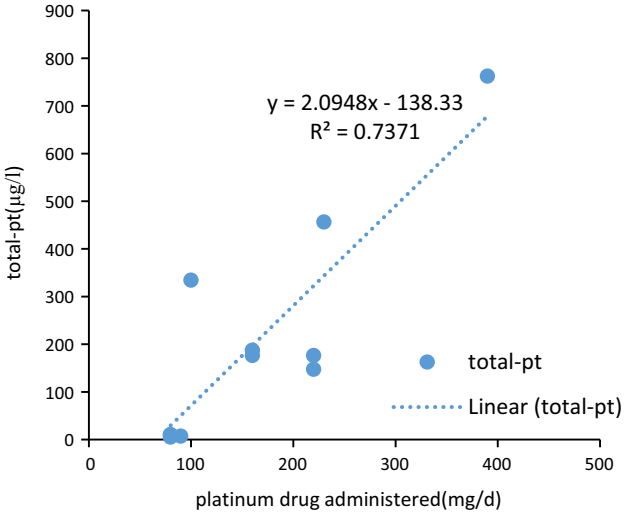

Fig. 1 Correlation of platinum drug administered and total platinum measured in wastewater of the oncology wards of Shahid Beheshti Hospital

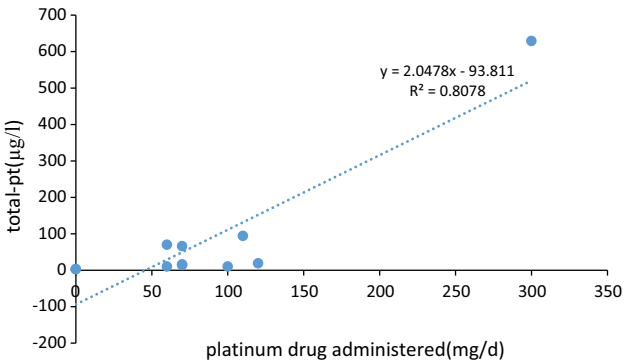

Fig. 2 Correlation of platinum drug administered and total platinum measured in wastewater of the oncology wards of Hazrat Masoumeh Hospital

The results of studies show that the concentration of total Pt during the sampling depends on the rate of excretion of drugs and time of sampling, which are highly variable. Figures 1 and 2 represent the correlation observed between drug-administered quantities of platinum complex versus and total Pt measured in the wastewater effluent.

The results are shown in Fig. 1 ($R^2 = 0.73$, $P_{value} < 0.05$) and Fig. 2 ($R^2 = 0.8$, $P_{value} < 0.05$). Accordingly, existence of a better correlation was between the dosage of drug injected to patients versus total Pt measured in the hospital of Hazrat Masoumeh to decreased range of total Pt concentration in the hospital effluent.

Results of risk estimation

For risk estimation, at first PEC_{hww} and PEC of each compound of platinum drugs were calculated and in other stage RQ_{hww} and RQ_{sw} were determined that results are represented in Table 5. To determine the PEC_{hww}, amounts of each platinum compound calculated according to measured results of total Pt concentration in Tables 3, 4, sum of average amounts calculated for two hospital including, cisplatin (193.5 µg/L), carboplatin (280 µg/L) and oxaliplatin (170 µg/L), were considered. PEC determination was carried out by total of urban consumption (gr/year) for platinum complex drugs (Table 1) and considering effluents of wastewater treatment plants ($Q = 0.5$ m^3/s) (Table 5).

In order to evaluate the reliability of risk estimation, PEC_{hww}/MEC ratios for all drug compounds containing cisplatin, carboplatin and oxaliplatin were determined. The results were in an acceptable range (0.2–4). In a study about PEC value estimation of common cytostatic drugs (carboplatin) in Europe, PEC values were determined in

Table 3 Quantities of platinum drug administered and total platinum measured in the wastewater of Shahid Beheshti Hospital

Day	Platinum drug administered (mg/d)			Platinum drug calculated in wastewater (μg/L)			Total Pt
	Cisplatin	Carboplatin	Oxaliplatin	Cisplatin	Carboplatin	Oxaliplatin	
1	70	20	–	8.74	2.5	–	7
2	50	–	30	5.28	–	3.18	5
3	170	50	–	184.3	54.2	–	147.7
4	130	–	100	444	–	341.5	456
5	110	–	50	214.3	–	94.4	187
6	110	–	110	154.4	–	154.4	175.9
7	100	60	–	181.7	109.5	–	175.6
8	100	–	–	320	–	254.5	334
9	390	–	–	1145.8	–	–	762
10	80	–	–	15.2	–	–	10
11	80	–	–	15.2	–	–	10
Min	50	20	30	5.28	2.5	3.18	5
Max	390	60	110	1145.8	109.5	254.5	762
Sum	1310	130	290	2709	166	850	2207.2
Average	120	43	72.5	146.27	55.4	170.01	206.4

Table 4 Quantities of platinum drug administered and total platinum measured in the wastewater of Hazrat Masoumeh Hospital

Day	Platinum drug administered (mg/d)			Platinum drug calculated in wastewater (μg/L)			Total Pt
	Cisplatin	Carboplatin	Oxaliplatin	Cisplatin	Carboplatin	Oxaliplatin	
1	100	–	–	15.38	–	–	10
2	70	–	–	21.53	–	–	14
3	–	120	–	–	36	–	19
4	–	70	–	–	3.44	–	16
5	–	300	–	–	1196.7	–	629
6	–	110	–	–	168.8	–	94
7	–	–	–	–	5.7	–	3
8	–	–	–	–	5.7	–	3
9	–	70	–	–	125.56	–	66
10	–	–	–	133.8	–	–	70
11	60	–	–	19	–	–	10
Min	60	–	–	15.38	5.7	–	3
Max	60	300	–	133.8	1196.7	–	629
Sum	100	670	–	189	1580	–	934
Average	290		–	47.27	225.6	–	82.9

wastewater effluent (ng/L) and PEC in river (ng/L) as 21.9, 0.59, respectively (Daouk et al. 2016). These results are approximately similar to the results obtained in the current study. Study of anticancer drugs in surface water shows that the conservative PEC values (ng/L) calculated based on platinum drugs consumption containing carboplatin, oxaliplatin and cisplatin in France were 1.91, 0.76 and 0.52, respectively. If converted to value for the present study, our results are very higher than to these calculated in this study (Besse et al. 2012). In addition, results of study on concentration of cytotoxic drugs by Cristian Gomez-Canela, et al. show that PEC (ng/L) in wastewater effluent treatment plant and river was determined as 2.23, 0.16 for cisplatin with annual consumption (4.09 g/d, 2012) and

Table 5 PEC, PEC_{hww} and risk estimation of platinum cytotoxic drug from effluent wastewater

Drug compound	MEC (μg/L)	PEC_{hww} (μg/L)	PEC_{hww}/MEC	PEC (μg/L)	PNEC (μg/L)	RQ_{hww}	RQ_{Sw}
Cisplatin	193.54	46.96	0.24	2.78 E−3	122	0.38	22 E−6
Carboplatin	280.4	61.05	0.21	3.6 E−3	122	0.5	29 E−6
Oxaliplatin	170	38.5	0.22	2.27 E−3	122	0.31	18 E−6

5.24, 0.22 for oxaliplatin with annual consumption (9.08 g/d, 2012), respectively. Given the mean annual consumption of platinum drugs containing, cisplatin (0.41 g/d) and oxaliplatin (0.34 g/d), obtain in this, it can be concluded that the results in this study were reasonable to those Gomez-Canela (Franquet-Griell et al. 2015). In this study, RQ_{hww} (risk ratio related to hospital fraction) and RQ_{Sw} (risk ratio related to river and surface water) were determined. The RQ_{hww} calculated value ($\sum RQ_{hww} = 1.19$) and risk ratio assessment of hospital wastewater showed that the total platinum compound drug could have the potential toxicity effect on aquatic organisms after dilution in urban sewerage and receiving water body and calculation of RQ_{Sw}, and risk ratio was considerably reduced. In a study by Silwan Daouk (2016) on the load of pharmaceutical ingredients in a Swiss university hospital wastewater and prediction of Pt-based anticancer drug in surface water, PEC (0.001 ng/L) and RQ (<0.001) were calculated which were also confirmed in the present study (Daouk et al. 2016).

Conclusion

In spite of limitations of toxicity estimation in ecological risk assessment by PEC model such as direct detection and measurement of platinum complex, especially fate of metabolite of these compounds in aquatic environment, the results of study give a comprehensive preliminary on the risk of oncology wastewater of hospitals and, the criterion of the ratio of PEC_{hww}/MEC can be considered as a primary stage in risk estimation of aqueous environments. It must be noted that although the predicted environmental concentration for Pt-based drugs was observed to be lower than that of the EMEA guideline (EMEA 2006), no safe level of exposure was obtained regarding this compound and its presence in resource water is very harmful. This study indicated that considering the large consumption of Pt-based anticancer drugs, investigation and monitoring of the residual of cytotoxic anticancer drugs should be taken into account considering their role in contamination of water resources and aquaculture. Management of cytotoxic waste and human excretion (urine and fecal) from oncology wards in hospital, wastewater separation and treatment on-site is vital for environmental pollution control. Considering the low efficiency of conventional wastewater treatment systems in removing platinum cytotoxic pharmaceutical compounds, the values of consumption of these drugs should be evaluated both at both local and at regional scales.

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