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Platinum-based anticancer drugs in waste waters of a major UK hospital and predicted concentrations in recipient surface waters

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HIGHLIGHTS

- Pt-based anticancer drugs have been measured in waste waters from a UK hospital.
- Concentrations of total aqueous Pt were highly variable.
- Median concentrations suggest that the majority of Pt is emitted from outpatients at home.
- Predicted concentrations in recipient waters are below EMEA guidelines.
- Nevertheless, the potential environmental effects of these drugs require investigation.

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ABSTRACT

Concentrations of the cytotoxic platinum-based anticancer drugs, as total Pt, have been measured over a three week period in one of the main drains and in the effluent of the oncology ward of a major UK hospital (Derriford, Plymouth). Concentrations of Pt were highly variable in both discharges, and ranged from about 0.02 to 140 μg L^{-1} in the oncology effluent and from about 0.03 to 100 μg L^{-1} in the main drain. A comparison of drug administration figures over the study period with an estimate of the quantity of Pt discharged through the drains suggests that about 22% of total Pt is emitted to the environment from the hospital with the remainder being discharged by treated patients in the wider community. Administration figures for the three Pt-based drugs used in the hospital (cisplatin, carboplatin and oxaliplatin) coupled with published measurements on the removal of the drugs by conventional sewage treatment allowed the concentrations of Pt arising from each drug to be predicted in recipient surface waters as a function of water flow rate. For conditions representative of the region under study, concentrations of total Pt between a few tens and in excess of 100 pg L^{-1} are predicted, with the principal form of the metal occurring as carboplatin and its metabolites. Although predicted concentrations are below EMEA guidelines warranting further risk assessment, the presence of substances in surface waters that are potentially carcinogenic, mutagenic and teratogenic and yet whose environmental effects are not understood is cause for concern.

1. Introduction

For many years, surgery and radiotherapy were the main means of managing cancer. Although these approaches are able to remove local tumours, they do not have a great impact on general prognosis because most deaths in patients are caused by metastatic spread of the disease. Presently, antineoplastic agents are employed, either alone or in combination with surgery or radiotherapy, to improve the outcome for cancer patients. Most anticancer drugs inhibit the proliferation of cancerous cells but are non-selective inasmuch as they are also toxic to non-cancerous cells. Consequently, a concern arising from the administration of antineoplastic agents is their potential effects on aquatic life once emitted to the environment.

Cytotoxic drugs are a group of antineoplastic agents that function by interacting with DNA and interfering with the process of cell division. Because of their non-selectivity, coupled with potentially genotoxic, mutagenic and carcinogenic properties, it has been hypothesised that all eukaryotic organisms may be at risk from exposure to these chemicals (Johnson et al., 2008) and that threshold values for lowest effect concentrations in the environment are inappropriate (Kosjek and Heath, 2011). Accordingly, there has been an increasing interest in the environmental distributions and behaviour of cytotoxic drugs and their metabolites over the past decade. Recent advances in analytical capabilities have allowed the concentrations and fluxes of many cytotoxic chemicals to

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be established in their principal environmental sources (hospital discharges and treated sewage effluents) and, for fewer cytotoxics, their concentrations in receptors (mainly rivers and tap water) (Kosjek and Heath, 2011). Where cytotoxics are not detectable or data are lacking, concentrations and fluxes have been predicted from information on drug usage and water consumption (Johnson et al., 2008; Rowney et al., 2009; Besse et al., 2012).

Platinum-based cytotoxics are coordination complexes of Pt which are used in 50–70% of cancer patients (Hannon, 2007). The environmental distributions and impacts of these drugs and their metabolites are, however, particularly poorly defined. The chemical and pharmacokinetic properties of the principal complexes in use, cisplatin (*cis*-dichlorodiammineplatinum(II)), carboplatin (*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II)) and oxaliplatin ([1*R*,2*R*]-1,2-cyclohexanediamine-*N*,*N*′)oxalate(2-)-*O*,*O*′platinum(II)), are shown in Table 1. The drugs are mainly used in combination therapy for the treatment of solid tumours and, specifically, ovarian, oesophageal and bladder carcinoma, tumours of the head and neck, testicular tumours, small cell lung cancer and metastatic colorectal cancer (Michalke, 2010). The mechanism of action of cisplatin involves the formation of reactive, aquated complexes (*cis*-$PtCl(OH_2)(NH_3)_2^+$ = monoaquacisplatin; *cis*-$Pt(OH_2)_2(NH_3)_2^{2+}$ = diaquacisplatin) inside the cell through the replacement of the chloro ligands by water molecules:

$$cis - PtCl_2(NH_3)_2 + H_2O \leftrightarrow cis - PtCl(OH_2)(NH_3)_2^{+} + Cl^{-} \quad (1)$$

$$cis - PtCl(OH_2)(NH_3)_2^{+} + H_2O \leftrightarrow cis - Pt(OH_2)_2(NH_3)_2^{2+} + Cl^{-}. \quad (2)$$

The aquated complexes then bind directly with DNA to form intrastrand cross-links between bases, thereby inhibiting the cell division process (Berners-Price and Appleton, 2000; Lau and Ensing, 2010). The precise modes of action of carboplatin and oxaliplatin are less clear, but appear to involve aquation as a precursor to DNA binding (Desoize and Madoulet, 2002). Compared with cisplatin, carboplatin is considerably more stable and less reactive because of the relatively low lability of the bidentate dicarboxylate ligand in the *cis* position.

The present study is the first to report concentrations of Pt-based cytotoxic drugs, as total Pt, in the waste waters from a UK hospital. We use data on the administration of the drugs in the outpatient oncology ward encompassing the sampling period to evaluate the relative magnitude of environmental sources of the cytotoxic substances from the hospital and from treated patients in the wider community. Published information on the removal of the drugs by conventional sewage treatment is also used to predict concentrations of clinically-derived Pt in recipient surface waters of varying flow rates and the significance of these concentrations relative to those arising from other environmental sources of Pt.

2. Materials and methods

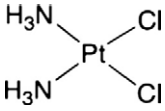
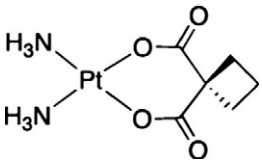
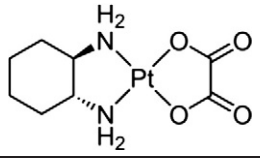
2.1. Study site

Derriford Hospital, Plymouth, is a large university hospital serving about 450,000 people in southwest England. The hospital includes a major cancer care centre and an aseptic facility for manufacturing and dispensing chemotherapy drugs. Solid and liquid wastes arising from the pharmaceutical facility are treated as hazardous and disposed of by incineration. Waste water from the outpatient oncology ward, where drugs are administered intravenously, is carried by an underground, open, semi-circular concrete drain of about 15 cm in diameter (drain 1). After about 10 m, this drain discharges into one of the main drains that receives general waste from about 50 % of the hospital (drain 2). No flow data are available for drain 1, but about 100,000 m^3 of water is annually discharged through drain 2 (~3.2 L s^{-1}).

2.2. Sampling and sample preparation

Samples were collected on week days during June and July 2012 over a 21 day period, thereby encompassing a three week chemotherapy cycle. Drains were accessed through a series of manholes with the assistance of the hospital estates personnel between 12 noon and 1 pm, or midway through the working day (8.30 am to 5 pm) and a few hours after the administration of the first round of infusions. Drain 1 was sampled immediately outside the oncology ward and at a distance of about 5 m from its discharge into drain 2, and drain 2 was sampled a few metres downstream of the input from drain 1. Samples were collected manually by placing a 1 L high density polyethylene bucket into the waste stream with the aid of a 4 m length of nylon string. Once sufficient waste water had been collected, the bucket was carefully raised and a screw-capped 60 mL polyethylene centrifuge tube filled to the mark. The bucket was then rinsed successively with 0.1 M HNO_3, hypochlorite disinfectant solution and distilled water before being stored in a plastic zip-lock bag until required for the next sampling. In the laboratory, 50 mL of sample was vacuum filtered through a Whatman 542 hardened ashless filter paper (pore size = 2.7 μm) using a Pyrex filtration unit.

Table 1
Chemical and pharmacokinetic properties of the three Pt-based anticancer drugs (Lenz et al., 2005; Rowney et al., 2009; National Toxicology Program, 2011 and references therein).

Drug	Formula	Structure	Molecular weight	Water solubility[a], g L^{-1}	Log K_{ow}[a]	Plasma elimination half-life, h
Cisplatin	*cis*-$PtCl_2(NH_3)_2$		300.05	2.5	−2.19	130 ± 24 to 327 ± 91
Carboplatin	*cis*-[$Pt(NH_3)_2$(CBDCA-*O*,*O*′)], (CBDCA = 1,1-cyclobutanedicarboxylate)		371.25	11.7	−0.46	139 ± 38
Oxaliplatin	Pt(dach)ox (dach = cyclohexanediamine; ox = oxalate)		397.29	7.9	−0.05 (±1.32)	273 ± 19

[a] At 25 °C.