Sustainable Chemistry and Pharmacy 4 (2016) 46–56

Contents lists available at ScienceDirect

Sustainable Chemistry and Pharmacy

journal homepage: www.elsevier.com/locate/scp

Modelling and sensitivity analysis of urinary platinum excretion in anticancer chemotherapy for the recovery of platinum

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ARTICLE INFO

Keywords:
Platinum excretion
Precious metal recovery
Sustainable materials management
Cancerostatic platinum compounds
Modelling
Sensitivity analysis

ABSTRACT

Platinum (Pt) based antineoplastics are important in cancer therapy. To date the Pt which is urinary excreted by the patients ends up in wastewater. This is disadvantageous from both an economic as from an ecological point of view because Pt is a valuable material and the excretion products are toxic for aquatic organisms. Therefore, efforts should be made to recover the Pt. The urinary excretion of Pt from two antineoplastics are taken under consideration, i.e. cisplatin and carboplatin. Using these reference compounds, a scenario analysis based on administration statistics from Ghent University Hospital in combination with compartmental models for urinary Pt excretion was performed to simulate the average Pt excretion profile during common treatment schemes. These average profiles can be used to assess the technical, social and economic feasibility of Pt-recovery from urine or wastewater. A one-compartment model is used for cisplatin, which is calibrated using the experimental data of six patients. In contrast, a two-compartment model with parameters from literature is used for carboplatin. A Global Sensitivity Analysis revealed k_{el}, the rate constant of elimination, is the most sensitive parameter in the one-compartment model whereas Q_u, the urine production rate, was the most sensitive in the two-compartment model for the Pt concentration C_u in urine and the excreted mass of Pt via urine. A GLUE uncertainty analysis showed that all experimental data are within the 95% uncertainty boundaries.

1. Introduction

1.1. Background

Platinum (Pt) is a precious metal having a high relevance in different types of industry. Because of its unique properties and the difficulties to substitute it, it is considered critical to the economy and the average commodity price of EUR 33,000 kg^{-1} in August 2016 resembles that of gold (Peck et al., 2015). Besides speculations on a future price increase under form of investments (9%) and use in jewellery (33%), a large share of Pt (37%) is allocated for the production of car catalytic converters. The catalytic properties of Pt are furthermore required in different industrial fields (Cowley, 2015).

In medicine, it is the central element in a type of antineoplastics called Cancerostatic Platinum Compounds (CPC) which are used for cancer therapy. Depending on the cancer-type, three different drugs are commonly applied: cisplatin, carboplatin and oxaliplatin (Fig. 1). Nedaplatin is added to that list in Japan and more CPC are currently in the clinical research phase, especially for oral administration, with satraplatin being in the most advanced stage (Desoize and Madoulet,

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http://dx.doi.org/10.1016/j.scp.2016.10.001
Received 27 May 2016; Received in revised form 27 September 2016; Accepted 1 October 2016

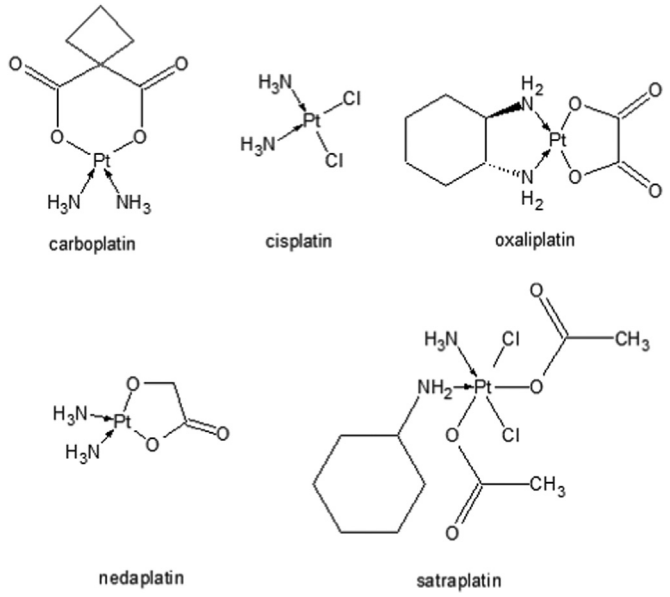

Fig. 1. Chemical structure of different CPCs used in cancer therapy.

2002). The CPC mechanism is universal: after dissociation of the prodrug, a bidentate coordinative bond is formed between Pt and N7 of DNA bases, hence inhibiting further DNA replication. The leaving of chloride or carboxylic ligands is in all cases the rate determining step in the process. For example, the half-life of each chloride hydrolysis in cisplatin is 2.1–3.1 h, whereas the following DNA base adduct is rapidly formed (Howell, 1991).

1.2. Pharmacokinetics of Pt excretion

High chloride levels in the blood (98–106 mmol L^{-1}) (Wians, 2016) initially protect the parent precursor of cisplatin. The neutral character allows for passive migration through cellular membranes and only in the cytosol, where a lower chloride content prevails, exchange with water molecules yields the active substance (Lippert, 1999). Pt(II) subsequently forms both intra- and interstrand combinations of linked double-stranded DNA (dsDNA) fragments through the sp^2 hybridised N7 atoms of guanine or adenine. From the administered dose, a rapid clearing from the plasma occurs by renal elimination, while a small fraction of Pt is associated to plasma proteins in the blood (Graham et al., 2000).

The pharmacokinetics of the Pt excretion can be described by compartmental models, which are thoroughly described in literature (Rowland and Tozer, 2011; Gabrielsson and Weiner, 2007). Each theoretical compartment contains part of the Pt dose for metabolism, where reciprocal exchange is possible. Specific to the CPC is the duality in physiological processes, covering both the fast excretion phase and slower metabolism of active Pt associates up to lifelong permanent binding of Pt residues in certain tissues. In order to account for this, the central compartment in the model is often extended with a secondary peripheral compartment, resulting in a two-compartment mathematical model. The resulting overall rate of excretion is found to be irrespective of sex, age or dose. Faecal excretion represents only a very minor elimination route. Eventually, most Pt as such ends up in the patient's urine and is discharged with the wastewater.

1.3. Toxicology and recovery of Pt in the environment

CPCs are susceptible to degradation in aqueous phases, both *in vivo* and *ex vivo*, yet around 75% of cisplatin and 100% of carboplatin is expected to reach sewage treatment systems intact (Lenz et al., 2007). This, in combination with the low immobilization by adsorption on sediments, leads to potentially high remaining toxicity and cancerogenicity of the drugs (Falter and Wilken, 1999). The European Commission undertakes actions in this context to reduce the environmental exposure to pharmaceuticals as part of the Water Framework Directive. It imposes a threshold of 0.01 μg L^{-1} to distinguish potential harmful pharmaceuticals. However, no exceedance has been observed so far in wastewater for individual antineoplastics (Kümmerer et al., 1999).

The fate of antineoplastics after excretion remains mostly unexplored (Lenz et al., 2007). Whereas the overall Pt recycling rate reached 28% in 2016, recovery from aqueous streams is non-existing today. The average value of Pt loss per oncological hospital bed can be estimated at 500 EUR y^{-1} based on the average administered dose of 60 mg Pt and 75% occupancy. Despite the limited fraction of Pt used in pharmacological applications, great recovery potential can be found on a global scale. Knowledge on the expected average excretion profile can help to evaluate the economic profitability of systems designed and put in place to avoid CPC release in the environment.

1.4. Modelling urinary Pt excretion

The pharmacokinetics of CPC have been intensively studied for medical purposes as the models can be used to determine the optimal dose (Desoize and Madoulet, 2002; Duffull and Robinson, 1997). Research has mainly focused on Pt concentrations in plasma, but in this contribution we focus on urinary excretion, which is less relevant from a medical perspective. However, since CPC are potentially harmful to the environment and they contain a precious metal, urinary excretion can be interesting from an economic and ecological perspective. The expected average excretion profile of Pt can help to evaluate the economic profitability of systems to avoid CPC release into the environment and simultaneously recover Pt. Therefore, the model parameters of the compartmental models for the Pt excretion via urine after a cisplatin and carboplatin treatment are respectively determined by calibration or based on literature. Next, these models are used to simulate the excretion of Pt during common treatment schemes used at the Ghent University Hospital. Moreover, two modelling tools, i.e. a Global Sensitivity Analysis (GSA) and an uncertainty analysis are applied to obtain more detailed process knowledge.

2. Theory

The objectives of this contribution are multiple. First, determination of the model parameters of the compartment models for the Pt excretion after a cisplatin treatment is pursued. For the carboplatin treatment, the model parameters found in literature are used. Next, these models are used to simulate the excretion of Pt via urine for common treatment schemes in the Ghent University Hospital. The experimental data for cisplatin is used to calibrate the one-compartment model. Furthermore, a GSA has been conducted for gathering process knowledge and to reveal the most sensitive parameters. Finally, a Generalised Likelihood Uncertainty Estimation (GLUE)-uncertainty analysis has been performed to detect interactions between parameters and to develop model output uncertainty boundaries on the basis of the gathered experimental data.

3. Materials and methods

3.1. Clinical study data

After approval of the ethical commission and personal consent, a total of 7 patients receiving chemotherapy (1 man, 6 women) participated in the study between February and April 2015. Data for body weight (kg), creatinine clearance (mg dL^{-1}) and body surface area (m^2) were collected individually. After administration of antineoplastics, urine samples were collected at the Medical Oncology Research Unit of