Environment International 40 (2012) 15–23

Contents lists available at SciVerse ScienceDirect

Environment International

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

Prediction of environmental concentrations of glucocorticoids: The River Thames, UK, as an example

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ARTICLE INFO

Article history:
Received 14 December 2010
Accepted 20 November 2011
Available online 27 December 2011

Keywords:
Glucocorticoid
Hydrocortisone
Human pharmaceutical
LowFlow2000-WQX

ABSTRACT

Synthetic glucocorticoids (GCs) are consumed in large amounts as anti-inflammatory and immunosuppressive drugs worldwide. Based on what has been learnt from studies of other human pharmaceuticals, they are likely to be present in the aquatic environment. However, to date, information on the environmental concentrations of GCs is very limited. The situation is complicated by the fact that a considerable number of GCs are in everyday use in most developed countries. Hence, obtaining a full picture of GC concentrations in the aquatic environment using the traditional analytical chemistry approach would be time-consuming and expensive. Thus, we took a modelling approach to predict the total environmental concentration of all synthetic GCs (consisting of 28 individual GCs) in the River Thames, as a first step in risk assessment of these drugs. Using reliable data on consumption, the LF2000-WQX model predicts mean concentrations up to 30 ng/L of total GCs in surface water as a best case scenario when the lowest excretion and highest removal rates in sewage treatment works were used, whereas mean concentrations up to 850 ng/L were predicted when the highest excretion and lowest removal rates are considered. We also present the 10th and 90th percentile concentrations (which indicate the likely range of concentrations seen from high flow to low flow conditions in the river) of the highest and lowest consumed GCs, to show the spatial and temporal variations of the concentrations of individual GCs. These data probably provide reliable estimates of the likely range of concentrations of GCs in a typical river impacted by effluent from many sewage treatment plants. Results also identify the hot spots where field studies on fish could be focused. To determine if aquatic organisms face any threat from GCs, laboratory toxicity studies should be conducted using concentrations similar to those reported here.

1. Introduction

A variety of pharmaceuticals and personal care products have been detected in many environmental samples such as sewage treatment plant effluents, surface water, groundwater, soil and sediments worldwide (Heberer, 2002; Ternes, 1998). These compounds may have adverse effects on living organisms, especially aquatic ones (Burkhardt-Holm, 2010; Corcoran et al., 2010; Jobling et al., 1998). Of these pharmaceuticals, steroids are an important group because they can readily enter and accumulate in fish (Maunder et al., 2007). One steroid pharmaceutical, ethinyl estradiol, has been extensively studied; its quantification and impact assessments have been reported from many parts of the world (reviewed in Caldwell et al., 2008). None of the other classes of steroidal pharmaceuticals (androgens, progestogens and glucocorticoids (GCs)) has received much attention, even though they have similar receptor-mediated modes of action. Recent reports on the effects of synthetic progestogens (Paulos et al., 2010; Zeilinger et al., 2009) and GCs (Kugathas and Sumpter, 2011) have confirmed the need to closely assess the risk of other steroidal pharmaceuticals. GCs have already been identified as a potential environmental risk in a model-based study (Sanderson et al., 2004). Therefore we aimed to predict the environmental concentrations of synthetic GCs in UK waters as a first step in the risk assessment of GCs.

Synthetic GCs are used in treating a variety of diseases, including adrenocortical insufficiency, hypersensitivity, asthma, rheumatic disease, inflammatory bowel disease, inflammatory skin, eye and ear conditions (Table 1). These pharmaceuticals are available in the form of tablets, capsules, inhalers, topical creams, ointments, eye/ear drops and injections. Corticosteroids can be administered by the oral and nasal and topical routes and also by the injections, suppositories and ear/eye drops. The average daily dose of corticosteroids varies from 100 μg to 500 mg, depending on the preparation and the route of administrations (BNF, 2006).

Abbreviations: BNF, British National Formulary; EMEA, European Medicines Agency; GC, glucocorticoid; STP, sewage treatment plant.

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doi:10.1016/j.envint.2011.11.007

Table 1
Some physico-chemical and biological information on five of the most prescribed GCs in UK.

Name of GC	Hydrocortisone	Prednisolone	Betamethasone	Beclomethasone	Fluticasone
Treatment	Adrenocortical insufficiency Hypersensitivity Asthma Rheumatic disease Inflammatory bowel disease Eczema	Rheumatic disease Immunosuppression in lymphoma/leukaemia Asthma Inflammatory bowel disease Inflammation of eyes/ears	Eczemas Psoriasis Eczematous inflammation of external ear Inflammation of eyes	Prophylaxis of asthma Acute ulcerative colitis	Prophylaxis of asthma Eczema Prophylaxis and treatment of allergic and perennial rhinitis
Route and average daily dose	Oral; 30 mg Intravenous/intramuscular; 500 mg, 6 hourly Topical; 15–30 mg for 2 weeks	Oral; (95%) 20–40 mg (maximum 60 mg/day) Rectal enemas/suppositories; 20 mg Ophthalmic/oral drops; 2–3 drops–3 hourly	Topical (30%); 1–2 times/day Oral; 2–3 drops/day	Nasal inhalation (70%); 400–1000 μg/day Topical (15%); 5 mg	Nasal inhalation; (70%) 100–500 μg/day Topical cream or ointment; 1–2 times/day 100–200 μg/day
Molecular formula (and molecular weight)	$C_{21}H_{30}O_5$ (362.4)	$C_{21}H_{26}O_5$ (358.4)	$C_{22}H_{29}FO_5$ (392.5)	$C_{22}H_{29}ClO_5$ (408.9)	$C_{22}H_{27}F_3O_4S$ (444.5)
Log P	1.61	1.66	1.93	2.12	3.70
Water solubility (mg/L at 25 °C)	219.6	221.4	75.14	49.39	27
Vapour pressure (mm Hg at 25 °C)	3.44E−15	2.13E−15	2.81E−15	6.19E−17	2.79E−15
Henry's constant (atm m^3 mol^{-1} at 25 °C)	5.77E−8	2.71E−8	7.15E−8	1.27E−8	3.15E−8

GCs are relatively soluble in water, with logP values from 1 to 3 (Table 1). This helps them to be removed from the body through metabolism and excretion. Their very low vapour pressures and Henry's constants (Table 1) mean that they are non volatile in the aquatic environment. In most of the synthetic corticosteroids, the H on the 6th and/or 9th carbon is substituted by F or Cl (see Fig. 1 for numbering). This halogen substitution increases the stability of these compounds in the human body, so that frequent administration is avoided. Therefore it is anticipated that the halogenated corticosteroids would degrade relatively slowly in the environment, and hence might be found in the aquatic environment. In fact, the occurrence of synthetic GCs in surface waters and effluents has recently been reported from some parts of the world (Table 2), but the values reported vary from country to country. There has been no quantification of GCs in UK waters.

Quantification of the concentrations of different groups of pharmaceuticals in the aquatic environment is necessary in order to assess the risk posed by these compounds to aquatic organisms. There are two approaches for making this estimate: actual measurements and model predictions, both of which have their advantages and disadvantages (discussed in Johnson et al., 2008a). Chemical (GC/MS, LC/MS) and biological (GR-CALUX) methods can in theory provide precise values. Since the pharmaceuticals can be found in the environment in low ng per litre concentrations and they might be present as a mixture of similar compounds, extraction and quantification will be expensive and time consuming. Measured values are very much dependent on the time of sampling, sampling point, extraction efficiency prior to measurement and detection limit of the technique employed; hence they fail to give real spatial and temporal variation, which is a function of the hydrology of river and inflow variations (Johnson, 2010). This is why the papers to date provide only a partial picture of the concentrations of GCs in the aquatic environment (Table 2), and probably explain why the measured concentrations vary from 0.3 ng/L to up to 1900 ng/L in different environmental samples. Moreover, quite a large number (about 30) of different GCs are in use. Therefore, the modelling approach is justified, as it is possible to predict the environmental concentrations of all GCs, either individually or in combination, throughout a river catchment, and for different seasons.

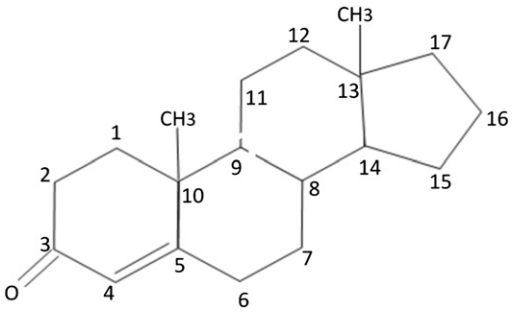

Fig. 1. Generalised ring structure and numbering of corticosteroids.

This paper presents predictions of environmental concentrations in the river Thames of a total of 28 GCs, using the LowFlow2000-WQX model (Williams et al., 2009). Two spatial simulations are presented, in order to represent the uncertainties in the excretion rates of the chemicals by humans and their removal rates in sewage treatment. We also present the 10th and 90th percentile concentrations (which indicate the likely range of concentrations seen at high flow to low flow conditions in the river) of the GCs consumed in the highest and the lowest amounts, to show both the degree of variation in concentration dependent on the flow rate of the river, and also very different concentrations of different GCs.

2. Materials and methods

2.1. Calculation of total consumption of GCs in the UK

The total amount of synthetic corticosteroids used as human pharmaceuticals in the UK was calculated as described before (Runnalls et al., 2010). Briefly, the calculation was based on the Prescriptions Cost Analysis database for England, Wales, Scotland and Northern Ireland (obtained from the regional National Health Service (NHS) websites, which referred to the year 2006/07). For each individual preparation, the total amount of active ingredient prescribed was calculated by multiplying the value in the quantity column by the amount of active ingredient in each unit. Where the drug was dispensed as a gel, the percentage of active principle was calculated (obtained from the British National Formulary 2006 standard). In those cases of multiphase drugs, containing units with different strength and composition in each pack, the different compositions were taken into account. The amounts of GCs used as veterinary pharmaceuticals have been kindly provided by the Veterinary Medicines Directorate of the UK.