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Reduction in the environmental exposure of pharmaceuticals through diagnostics, Personalised Healthcare and other approaches. A mini review and discussion paper

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ABSTRACT

Pharmaceuticals enter the environment from production, through incorrect disposal as well as from patient use and excretion. Patients' excretions into wastewater have been judged to form the highest fraction of pharmaceuticals released to the environment. There are concepts and technologies available to address pharmaceuticals emissions from production, incorrect disposal and patient excretion. However, while normal physiological excretion in patients cannot be prevented, there may still be ways to optimise the administration of pharmaceuticals with a view to reducing environmental exposure, while ensuring satisfactory pharmacologically active concentrations in the patient. Towards this goal, state-of-the-art diagnostics emerge as critically important. Describing different approaches for a reduction of environmental exposure, specifically addressing interindividual differences in drug metabolism and personalised healthcare, with recognising antibiotics administration as a related problem, this paper is not strictly speaking a scientific research article but is meant to be more of a compilation of existing and new ideas and a thought-starter.

Contents

1. Introduction

The presence of pharmaceuticals in the environment (PIE) is increasingly seen as a concern, (a) for environmental organisms in their natural habitat (e.g., Barceló 2012; Kümmerer 2008; Oldenkamp et al. 2013); (b) through maintaining or fostering

Abbreviations: AB, Antibiotic; API, active pharmaceutical ingredient; DDD, defined daily dose; PHC, personalised healthcare; MAb, monoclonal antibody; PIE, pharmaceuticals in the environment; WWTP, wastewater treatment plant

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antimicrobial resistance genes that endanger the future availability of life-saving antibiotics (ABs) (WHO 2014); and (c) for human health through consumption of drinking water, fish or crops containing active pharmaceutical ingredients (APIs) (Boxall 2004; Oldenkamp et al. 2013), but also (d) due to concerns about the environmental presence of human metabolites or environmental transformation products of APIs that may maintain pharmacological potency or may gain increased toxicological activity through the transformation process (Michael et al., 2014). APIs may enter the environment from production, through incorrect disposal by draining into wastewater and in particular from patients' excretions (Boxall 2004; START 2008), which are estimated to constitute the major contribution to PIE (START 2008). Concerns about PIE may be rationally addressed through environmental risk assessment; because risk is a product of exposure and effects, a decrease of the environmental concentrations of PIE would directly reduce their potential risks, as noted by several publications (e.g., Barceló 2012; Kümmerer 2008, 2010; Boxall 2004).

The present contribution collates existing proposals and presents new ideas on how APIs in environmental compartments could possibly be reduced. Special emphasis is given to optimisation of administration by application of various approaches, with emphasis on Personalised Healthcare (PHC) through determination of individual dosages and selection of optimal APIs. As such, this is not meant to be a scientific research paper but rather a compilation of different ideas for discussion and further development.

2. Reduction of PIE from production

Losses of APIs from chemical, biotechnological or galenical production were estimated to be minor and of no environmental concern. However, Larsson et al. (2007) showed that in a pharmaceutical industrial park in India such emissions from chemical production result in very high local concentrations of APIs both in the WWTP and in the receiving water. Losses from production, albeit on a lesser scale, were subsequently also documented from the USA (Phillips et al., 2010) and from Europe (e.g., Prasse et al., 2010; Sanchez et al., 2011), in one case through evidence of histological effects in feral fish downstream of the effluent site (Sanchez et al., 2011). Despite these instances of analytical detections and the histological effects, however, not all pharmaceutical productions cause a risk to the environment (Hoerger et al., 2010).

Whereas APIs excreted by patients have hopefully fulfilled their intended pharmacological role, emissions of APIs from production serve no medicinal purpose. Hence, production losses can be minimised without jeopardising the intended function. On the other hand, such losses cannot be completely avoided unless all wastes including wastewaters from the processes are incinerated, but then this would lead to high costs in terms of carbon dioxide emissions. Also, minimisation may cause other costs in terms of technical installations, energy and secondary waste streams that need to be disposed of as well. Therefore, it makes sense to assess potential losses and their risks to the environment, and to selectively manage and reduce where indicated by environmental risk assessment (Hoerger et al., 2010). Recently, an industry consortium presented concepts and measures adopted by different pharmaceutical companies as examples for how to investigate, assess and reduce the release of APIs from pharmaceutical production (Caldwell et al., 2015). In view of this publication, reduction of API release to the environment from production will not be discussed further here.

3. Reduction of PIE through addressing incorrect disposal

Several publications and programmes over the past two decades have investigated disposal practices of unused pharmaceuticals, both in Europe and the USA (Bound & Voulvoulis 2005; Donovan & Blake 1992; Kuspis & Krenzelok 1996; Musson & Townsend 2009; Seehusen & Edwards 2006; START 2008). According to these publications, between 10% and 65% of prescription medications are not taken as per the doctor's orders, mostly through patient noncompliance, sometimes as a consequence of too large packs for the treatment prescribed or through the medicines going past their use-by date. Data from the German START programme show that up to 15.7% of tablet and up to 43.4% of liquid medicines waste is occasionally or regularly disposed of via wastewater; the total incorrect disposal to the sewer for Germany was estimated in 2007 at 346 t of APIs per annum (START 2008), with zero therapeutical benefit but 100% environmental load.

As one example to improve this situation, the START (2008) guide recommends on one hand to install customer-friendly take-back schemes for all unused pharmaceuticals or alternatively to ensure safe destruction by other means; on the other to launch education programmes about the importance of, and their own role and responsibility in, correct and environmentally safe medicines disposal for prescribers, pharmacists, medical personnel and in particular the public at large as the final users (and often disposers) of medicines. The importance of environmentally conscious and responsible consumers, also in the field of medicines, has been recognised and taken up by EU member states, e.g., by Germany (http://www.arzneimittelentsorgung.de/), and also by the European pharmaceutical industry umbrella organisations (medsdisposal 2015).

4. Reduction of PIE through upgrading municipal wastewater treatment

Patient excretions contain APIs or human metabolites thereof. While in some instances the collection of patient urine has been advocated for the express purpose of separating and preventing concentrated or hazardous APIs from entering the environment, several research programmes have investigated the improvement of API removal in WWTPs and drinking water production (e.g., Aga 2008; POSEIDON 2006; Ternes & Joss 2006). While prolonged hydraulic and sludge retention times improve the overall removal, many APIs are not significantly reduced using biodegradation alone. Additional physico-chemical treatment steps, viz., chemical oxidation or adsorption to activated charcoal, were shown to achieve a high degree of removal for certain APIs; e.g., in Switzerland the potential of ozonation and activated charcoal was tested in full-scale WWTPs (Götz 2010). It was found that overall, most APIs plus other micropollutants were removed by $>80\%$ through either of the technologies, but not necessarily to the same extent; for a given API either ozonation or activated charcoal gave better results (Abegglen & Siegrist 2012; Götz 2010).

Based on this long series of assays, Switzerland decided to retrofit approximately 100 WWTPs over the next 20 years with one of the two tested micropollutant removal technologies, in function of the site-specific wastewater mix. It was estimated that this upgrading, covering the biggest of a total of above 700 WWTPs in Switzerland, would reduce the overall micropollutant load in the receiving waters by around 50% (Abegglen & Siegrist 2012; Götz 2010). Comparable investigations and plans to upgrade WWTPs with forced oxidation or activated charcoal technology are under way in Germany as well, e.g., in the project RiSKWa (2015). However, while from a purely technological point of view a far