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Analysis, occurrence, fate and risks of proton pump inhibitors, their metabolites and transformation products in aquatic environment: A review

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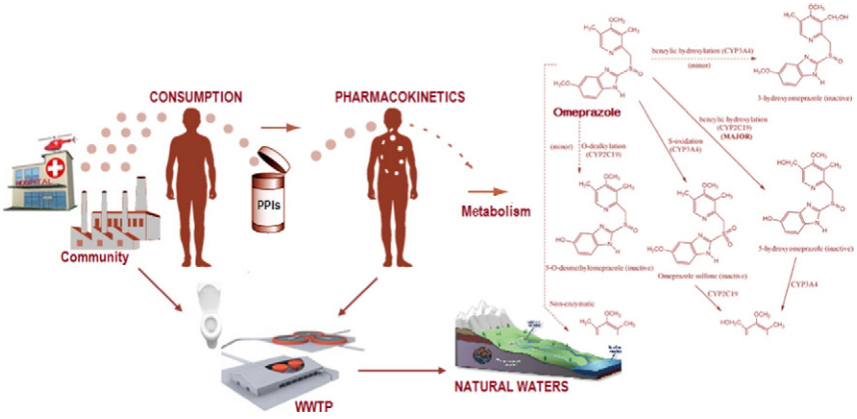
HIGHLIGHTS

- Occurrence and fate of PPIs and their metabolites/TPs in the aquatic environment
- Overview of the analytical methods applied, using LC-MS techniques
- Omeprazole attended the most frequent analysis
- Determination and behavior of omeprazole's metabolites/TPs in the environment
- More ecotoxicological research is needed to assess the risks of PPIs.

GRAPHICAL ABSTRACT



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ABSTRACT

Proton pump inhibitors (PPIs) which include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole, are extensively used for the relief of gastro-intestinal disorders. Despite their high worldwide consumption, PPIs are extensively metabolized in human bodies and therefore are not regularly detected in monitoring studies. Very recently, however, it has been shown that some omeprazole metabolites may enter and are likely to persist in aquatic environment. Hence, to fully assess the environmental exposures and risks associated with PPIs, it is important to better understand and evaluate the fate and behavior not only of the parent compound but also of their metabolites and their transformation products arising from biotic and abiotic processes (hydrolysis, photodegradation, biodegradation etc.) in the environment. In this light, the purpose of this review is to summarize the present state of knowledge on the introduction and behavior of these chemicals in natural and engineering systems and highlight research needs and gaps. It draws attention to their transformation, the increase contamination by their metabolites/TPs in different environmental matrices and their potential adverse effects in the environment. Furthermore, existing research on analytical developments with respect to sample treatment, separation and detection of PPIs and their metabolites/TPs is provided.

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1. Introduction

Proton pump inhibitors (PPIs) or gastric acid pump inhibitors are among the most commonly used drugs worldwide and are used for the treatment of gastro-intestinal disorders (such as dyspepsia, peptic ulcer, *Helicobacter pylori* infection, gastroesophageal reflux disease, gastrointestinal complications and Zollinger-Ellison syndrome) where reduction of gastric acid secretion is beneficial (Pilbrant, 1993; Roche, 2006; Shi and Klotz, 2008). Omeprazole was the first proton pump inhibitor which was introduced in the market in 1989, and next lansoprazole (1995), pantoprazole (1997), rabeprazole (1999) and esomeprazole (pure *S*-isomer of omeprazole) (2001) became available (Shi and Klotz, 2008). All PPIs contain a 2-pyridylmethylsulfinylbenzimidazole pharmacophore (Table 1) and differ only in the nature of substituents on the pyridine and benzimidazole rings (Addo et al., 2014).

PPIs produce a long-lasting and potent non-reversible inhibition of the gastric proton pump H+/K + ATPase in paretal cells (Guo et al., 2011; Horn, 2000; Olbe et al., 2003). They bind strongly to serum proteins and are extensively metabolized by CYP450 family of enzymes. In addition, CYP2C19 isoform is particularly important and influences the pharmacokinetics, pharmacodynamics and clinical outcome of PPIs (Horn, 2000; Roche, 2006; Shi and Klotz, 2008).

Since, PPIs are extensively metabolized in human bodies (Li et al., 2004; Shi and Klotz, 2008), it seems that they have a low potential to reach the environment at large amounts. In this sense, the occurrence of PPIs in aquatic environment can be attributed to human metabolism as well to various degradative/transformative processes (hydrolysis, photodegradation, biodegradation etc.) that take place in different environmental compartments. This statement is supported by recent attempts (Boix et al., 2013, 2014; Kosma et al., 2014b) to correlate their use with the concentration detected in the aquatic environment, in which the parent compounds of PPIs are scarcely detected. For example, low concentrations of omeprazole were detected in urban and hospital WWTPs as well as in surface and river waters (Gómez et al., 2007; Kosma et al., 2014b; Pedrouzo et al., 2008; Valcárcel et al., 2011). Although, PPIs are not regularly detected, considering their high use (Godman et al., 2009, 2011; Woldegiorgis et al., 2009) its analytical monitoring becomes relevant. In addition, in view of the recent reports dealing with the detection of many metabolites and environmental Transformation Products (TPs) in aqueous samples (Boix et al., 2013, 2014, 2016; Boleda et al., 2013; Hernández et al., 2011; Gracia-Lor et al., 2014; Ibáñez et al., 2016; López et al., 2014; Ibáñez et al., 2016), environmental contamination by PPIs should be checked and evaluated more thoroughly.

In this regard, the aim of this article is to provide an overview of the current state of knowledge on: a) the transformation mechanisms and pathways that contribute to the input of PPIs in the aquatic environment, b) the analysis and occurrence of their metabolites/TPs in WWTP influents and effluents and receiving surface waters c) the application of advanced treatment processes such as advanced oxidation processes (AOPs) in the degradation of PPIs and d) the potential hazards associated with the occurrence and persistence of PPIs in the environment. From analytical point of view, we set out the analytical methods applied, using liquid chromatography mass spectrometry (LC-MS) techniques, focusing on their capabilities and potentials concerning their application for identifying the unknown contaminants (metabolites and/or TPs) in environmental matrices. We state examples of applications and when it is possible we try to give future points that have not been totally investigated yet. Under this aspect, over the past few years a growing number of articles have been published and are presented in Fig. 1.

2. Consumption of PPIs

Recent studies have reported the increment of PPIs utilization and consumption, in European countries year by year (Godman et al., 2009, 2011; Woldegiorgis et al., 2009). In particular, Godman et al. (2009), captured utilization of dispensed prescriptions of PPIs in ambulatory care from 2001 to 2007, using defined daily doses (DDD) as well as DDDs/1000 inhabitants/day (DDD/TID) for patients covered by the social health insurance system, in Austria. According to the results, since generics of omeprazole and lansoprazole became available in 2003, there was an increase in prescribing of both products. By 2007, 89.5% of omeprazole dispensed on a DDD basis was generic omeprazole, while it was lower for lansoprazole (65.2%). This fact was helped by larger package sizes of these PPIs, as well as higher strength of generic omeprazole (40 mg) becoming available without prior approval (Godman et al., 2009). In another recent study, Godman et al. (2011), studied the utilization (DDDs) and expenditure (Euros and local currency) of PPIs in 19 European countries and regions from 2001 to 2007. These were Austria, Croatia, Estonia, France, Finland, Germany, Italy, Lithuania, Norway, Portugal, Poland, Republic of Ireland, Serbia, Slovenia, Spain, Sweden, Turkey, and the United Kingdom. The results showed that in both Lithuania and Poland, there was approximately a twofold difference in the rate of increase in utilization (DDD basis) versus the rate of increase in reimbursed expenditure of the PPIs between 2001 and 2007. For instance, Lithuania utilization increased 10.8 fold between 2001 and 2007 and Poland over 150 fold between 2002 and 2007. This appreciable increase in utilization, was considerably greater than in the other European countries. General findings from the study, showed more limited utilization of the PPIs among Central and Eastern European countries compared with Western European countries (Godman et al., 2011). Furthermore, Woldegiorgis et al. (2009), reported that omeprazole and esomeprazole belong to the top-40 selling drugs in Nordic countries during 1997–2007. In all Nordic countries, omeprazole is the major PPI substance on the markets. In November 2000 the enantiopure version of omeprazol, esomeprazole, was granted market admission and from 2001 there is sales statistics also for esomeprazole. In most countries one can observe a decline in the sales of omeprazole accompanying the rapid sales increase of esomeprazole in the years 2001–2003. Nevertheless for both compounds sales in Sweden have increased by 63% (from 1 tonne in 1997 to approximately 2.5 tonnes in 2007). In Denmark, and Norway the consumption has increased in a similar fashion (74–77%), while the sales increase in Finland and Iceland in amounts of 89–90%, respectively (Woldegiorgis et al., 2009). Finally, Ortiz de García et al. (2013), estimated the consumption of PPIs sold taking into account the number of packages commercialized in 2009, and the results showed that the consumption of omeprazole, pantoprazole, lansoprazole and esomeprazole was 13,850–27,710, 3410–6820, 2020 and 806–3226 kg/year, respectively.

3. Sources and pathways of PPIs in the environment

Since after administration, PPIs are extensively metabolized in the human body (Li et al., 2004; Shi and Klotz, 2008), little if any unchanged drug was excreted into the effluent and reach the wastewater treatment plant (WWTP). Looking at all compounds, approx. 70–95% of the consumed amount of PPIs is excreted as inactive or pharmaceutically active metabolites (e.g hydroxyl-omeprazole, hydroxy-lansoprazole, desmethyl-pantoprazole) in urine and feces (Fig. 2). For example in the case of omeprazole, the majority of the dose (about 77%) was eliminated in urine whereas the remainder of the dose was recoverable in feces, implying a significant biliary excretion of the metabolites of omeprazole (Andersson et al., 1993). At least six metabolites were identified in urine, from which two were identified as hydroxyomeprazole and the corresponding carboxylic acid (Petsalo et al., 2008). Three metabolites have been identified in plasma, the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole (Espinosa Bosch et al., 2007; Song and Naidong, 2006).

PPIs and their metabolites are only partially eliminated in WWTPs (Rosal et al., 2010). If they are not eliminated during the purification process, they pass through the sewage system and may end up in the