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ScienceDirect
Chemosphere 71 (2008) 1754–1764
CHEMOSPHERE
www.elsevier.com/locate/chemosphere

Occurrence, fate and assessment of polar metamizole (dipyrone) residues in hospital and municipal wastewater

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Received 13 July 2007; received in revised form 9 November 2007; accepted 9 November 2007
Available online 31 December 2007

Abstract

The occurrence and fate of residues from the therapeutic use of the non-steroidal anti-inflammatory drug metamizole have been studied in investigations of sewage effluents from a military hospital, municipal sewers and a sewage treatment plant (STP) in Berlin, Germany. The loads of the metabolites aminoantipyrin (AA), 4-acetylaminoantipyrin (AAA) and 4-formyl-aminoantipyrin (FAA), rapidly formed after the application of metamizole, were predicted from pharmacokinetic data and based on the evaluation of extensive data sets of on the administration in hospitals and private households. In parallel, the actual concentrations were measured within three field trials.

For the military hospital, the estimated average annual discharges of AA/AAA and FAA were 10.5 and 3.2 kg, respectively. For the STP, annual loads of 333 and 133 kg were determined for AA/AAA and FAA, respectively. During sewage treatment, an average decrease of 26% of the loads was measured for AA/AAA whereas no changes were observed for FAA. Generally, the prediction of the loads resulted in an overestimation of the residue levels compared to those measured in the respective sewers. Thus, modeling of predicted loads or concentrations alone will not be sufficient for a realistic assessment.

Concerns for human or other mammals' health are not expected from the occurrence of metamizole residues in the aquatic system measured at concentrations up to 7 $\mu g\,l^{-1}$ in STP effluents. However, a rest of uncertainty remains as it was not possible to derive a no observed effect level for the induction of rare but potentially fatal toxicological side effects reported for metamizole.

Keywords: PhACs; Drugs; Pharmaceuticals; Sewage; Loads; Risk assessment

1. Introduction

Residues of pharmaceuticals are frequently detected in the aquatic environment (Daughton and Ternes, 1999; Heberer, 2002; Kolpin et al., 2002). In municipal areas, the largest amount of these anthropogenic compounds results from the medical administration of drugs to the human population. Residues from the application of the parent drugs or their physiological metabolites are excreted by the human organism and discharged into the sewer systems. Two different sources of discharges might be distinguished: (1) wastewater from private households and (2) medical facility effluents, e.g. from hospitals (Kümmerer, 2004). These two types of wastewater are different regarding the occurrence and composition of pharmaceutical residues including the metabolites of the parent drugs. Wastewater from households contains a variety of residues from prescription drugs including analgesics, antibiotics, blood-pressure regulating drugs, hormones but it also contains residues from some other over-the-counter medicinal products. Hospital effluents are sources for pharmaceuticals also used in private households but additionally for some other substances typically or almost exclusively administered in hospitals such as X-ray contrast media (Kümmerer et al., 1998), special diagnostic agents (Flöser,

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0045-6535/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.chemosphere.2007.11.032

1999), cytostatic compounds (Kümmerer and Al-Ahmad, 1997), and for *reserve antibiotics* used almost exclusively in hospitals to limit the risk of the formation of resistant bacteria. Pharmaceuticals specifically administered in hospitals also include some strong highly effective analgesics (Feldmann, 2005) to be classified as opioid analgesics (derivatives of the opium poppy alkaloid morphine) and non-opioid analgesics. In the group of the non-opioid analgesics, the non-acidic pyrazole derivate metamizole (dipyrone, Novalgin®) is the substance with the highest analgesic potential. This drug is particularly active as a killer for pain originating from spasms of smooth muscles but it also possesses very good antipyretic properties and possesses some antispasmodic activity. Due to its rare but potentially fatal side effects such as agranulocytosis (an acute condition involving a severe and dangerous reduction in the number of white blood cells (leukopenia)), metamizole is currently not registered in some countries (e.g. USA, UK, Sweden). Under controlled conditions the use of metamizole is regarded as being safe. Therefore, and in view of its unique analgesic properties, the use of this compound is getting more popular again in Germany (Reinhardt et al., 2006). Currently, metamizole is registered for use with humans in some European countries, in Africa, Asia and in Middle and South America. In Japan and Australia the use of metamizole in human medicine is possible but restricted. Accounting for the quantities administered, metamizole is the most important analgesic in some German hospitals. Especially orthopedic and surgical faculties prefer this quick-acting analgesic compound. Nevertheless, metamizole is also prescribed in private medical practices all over the country. Thus, it will not be possible to assign metamizole residues found in the municipal wastewater to hospital effluents alone.

In human medicine metamizole is administered orally up to four times per day at doses between 500 and 1000 mg. In Europe, metamizole is also registered for use in veterinary medicine indicated for use in horses, cattle, swine, and as an adjunct to therapy in many inflammatory conditions of the musculoskeletal and locomotor systems. Metamizole is included in Annex II of Council Regulation EEC 2377/90 with maximum residue levels of 50 $\mu g\,kg^{-1}$ for milk (bovine) and 100 $\mu g\,kg^{-1}$ in muscle, fat, liver and kidney set for bovine, porcine and equidae, respectively. The European Agency for the Evaluation of Medicinal Products (EMEA, 2003) established an "acceptable daily intake" (ADI) of 0.01 $mg\,kg^{-1}$ bw for metamizole by applying a safety factor of 1000 to the pharmacological "*no observed effect level*" (NOEL) of 10 $mg\,kg^{-1}\,bw\,d^{-1}$ in mice.

After oral, rectal, intravenous or intramuscular application of metamizole an immediate hydrolytical cleavage of the parent compound results (*in vivo* and *in vitro*) in the rapid formation of the pharmacologically active substance 4-methyl-aminophenazone (MAA) which is the only primary metabolite (Levy et al., 1995; EMEA, 2003). MAA is further metabolized in the human organism to aminoantipyrin (AA), 4-acetylaminoantipyrin (AAA) and 4-formylaminoantipyrin (FAA). Between 2 and 8 h after administration of ^{14}C-metamizole, MAA and its three major secondary metabolites account for approximately 77% of the total residue detected in human serum (EMEA, 2003). Biological half-lifes of metamizol and its metabolites are relatively short (2–10 h) (Volz and Kellner, 1980; Asmardi and Jamali, 1985; Klaus et al., 1997; Charlton, 2005) which may also be important to guarantee a supervised application within the hospital which also considers to control the before mentioned potential side effects.

Significant adsorption of metamizole and its metabolites to organic particulates is not expected and was also not observed in preliminary sorption studies conducted by Zuehlke (2004). In the literature, a $\log K_{ow}$ value as low as 0.00 was reported for metamizole (ARGE, 2003). The high polarity of the metamizole metabolites also necessitated the development of an analytical method that applies an in situ derivatization to convert the analytes into more hydrophobic compounds which are then extractable from the aqueous samples.

This paper presents results from three field trials investigating the occurrence and fate of the main metabolites of metamizole at different sampling sites including a sewer of a medium sized (military) hospital in Berlin (Germany), a sewage pumping station (SPS) containing the combined sewage of several municipal hospitals and some private households, and a large-scale sewage treatment plant (STP) serving a total population of one million inhabitants also including several hospitals. One of the intentions of these investigations was to determine the loads, the distribution and the ratios of the metabolites of metamizole in the effluents from both the hospitals and from private households as well. Furthermore, the ability of modern sewage treatment plants to eliminate or decrease the concentrations of these residues was studied. Finally, the feasibility of an environmental risk assessment was verified.

2. Experimental section

2.1. General remarks

The total amounts of metamizole residues were calculated and measured in three one-week sampling series conducted in the time period between April 2002 and August 2003. In parallel to analytical measurements, data on the actual consumption of pharmaceuticals were collected in all wards of the German Army Military Hospital located in Berlin (Germany). From these data the total amount of metamizole applied during a respective one-wk time period was calculated. Additionally, the amounts of metamizole administered in four other hospitals located in the same wastewater drainage area were investigated and an average use of metamizole by the inhabitants of this area was calculated from sales data obtained for the whole town of Berlin. Using a novel model for the calculation of loads of drug residues in wastewater (Heberer and Feldmann,