PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN THE ENVIRONMENT

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Abstract. Various problems concerning the pharmaceutical and personal care products (PPCPs) in the environment of the Eastern European countries are described. The main classes of PPCPs in the environment, as well as major occurrence pathways and PPCPs fate, are depicted. The influence of specifics of the regional pharmaceutical market, medication consumption culture and pharmaceutical waste disposal techniques on environmental pollution with PPCPs, are discussed. Examples of wrong drugs prescription, drugs misuse, drugs overconsumption, and poor pharmaceutical waste management are presented. The necessity in research and management of PPCPs with emphasize on the local specifics and practices are concluded.

Keywords: PPCPs, pharmaceuticals, personal care products, drugs overconsumption, drugs prescription, pharmaceutical waste.

Abbreviations:

AA – 4-aminoantipyrine
AAA – 4-acetylaminoantipyrine
CAFOs – confined animal feeding operations
CNS – central nervous system
FAA – formylaminoantipyrine
NSAID – non-steroidal anti-inflammatory drug
PPPCs – pharmaceutical and personal care products
STP – sewage treatment plant

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1. Introduction

Pharmaceuticals and personal care products represent a group of environmental micro-pollutants that could be detected recently due to development of new sensitive analytical methods. Their fate in natural ecosystems is poorly understood and their effects on different organisms are largely unknown. While large studies concerning PPCPs in the environment problems have been performed in the US and Western European countries [1–3], a little is known about their occurrence and fate in the Eastern European and other developing countries. Therefore, it is necessary to determine and to analyze the major problems that can influence PPCPs presence in the environment taking in consideration all the regional aspects.

2. Analysis and discussion

PPCPs have been present in the environment since their industrial production and mass application started. Development of the more sensitive analytical methods made it possible to detect their presence in residual concentrations. Recently, standard methods of PPCPs determination in water, soil, sediment, and biosolids, have been developed [4, 5].

Though, the individual environmental concentrations of the PPCPs are very low, effects of their mixture on the living organism are largely unknown and, therefore, unpredictable. Besides, their constantly increasing inflow lets assign them to the group of persistent organic pollutants and makes it necessary to study their influence on the living organisms.

There are several important questions that need to be solved regarding the presence of PPCPs in the environment:

- Assessment of PPCPs' origins concerning the specifics of the area/community using them and development of the new effective strategies of their release prevention
- Determination of fate and trends of the most environmentally occurring, persistent PPCPs
- Determination of the influence of their low and ultra low individual concentrations and multi-component mixtures on the non-target organisms that might be affected

Main classes of PPCPs detected in the environment are: antidepressants, antiepileptics, antihypertensives, antimicrobials, antineoplastics, antiseptics, β_2-sympathomimetics, contraceptives, hypnotic agents, lipid regulators, musks, painkillers/NSAIDs, CNS stimulants, sunscreen agents, X-ray agents [6].

The main routes of their penetration in the environment are described in the picture below (Fig. 2.1) [7].

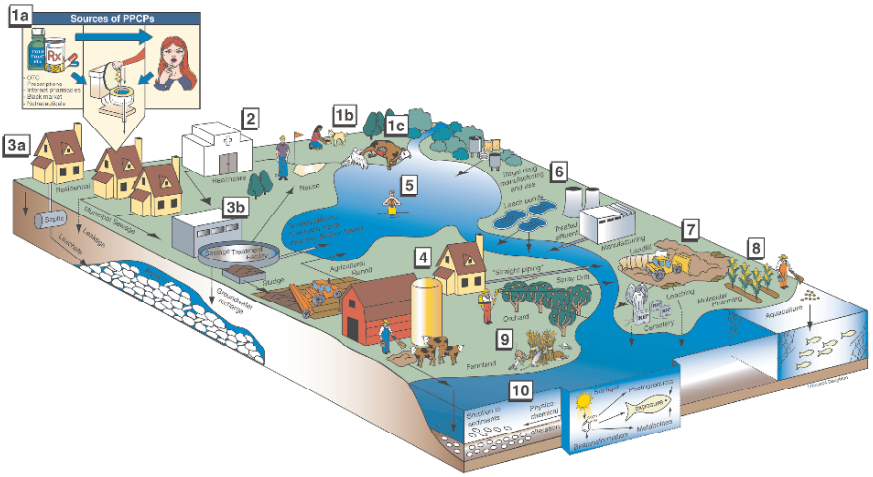

Fig. 2.1. Origins and fate of PPCPs in the environment.

Thus, the PPCPs enter in the environment as a result of:

1. Usage by individuals (1a) and pets (1b): metabolic excretion (non-metabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomits, excretion exacerbated by disease and slow-dissolving medications; disposal of unused/outdated medication to sewage systems; underground leakage from sewage system infrastructure; disposal of euthanized/medicated animal carcasses serving as food for scavengers (1c)
2. Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus
3. Release to private septic/leach fields (3a); treated effluent from domestic sewage treatment plants discharged to surface waters, re-injected into aquifers (recharge), recycled/reused (irrigation or domestic uses) (3b); overflow of untreated sewage from storm events and system failures directly to surface waters (3b)
4. Transfer of sewage sludge to land (e.g., soil amendment/fertilization); "straight-piping" from homes (untreated sewage discharged directly to surface waters); release from agriculture: spray drift from tree crops (e.g., antibiotics); dung use from medicated domestic animals (e.g., feed) – CAFOs
5. Direct release to open waters via washing/bathing/swimming
6. Discharge of regulated/controlled industrial manufacturing waste streams; disposal/release from clandestine drug labs and illicit drug usage
7. Disposal to landfills via domestic refuse, medical wastes and other hazardous wastes; leaching from defective (poorly engineered) landfills and cemeteries

8. Release to open waters from aquaculture (medicated feed and resulting excreta); future potential for release from molecular farming (production of therapeutics in crops)
9. Release of drugs that serve double duty as pest control agents: examples: certain antibiotics used for orchard pathogens; warfarin (anticoagulant) – rat poison; acetaminophen (analgesic) – brown tree snake control; caffeine (stimulant) – *coqui* frog control
10. Ultimate environmental transport and fate of PPCPs. Most PPCPs are eventually transported from terrestrial domain to aqueous domain where they undergo different transformations: photo-transformation (both direct and indirect reactions via UV light); physicochemical alteration, degradation, and ultimate mineralization; volatilization (mainly certain anesthetics, fragrances); some uptake by plants; respirable particulates containing sorbed drugs (e.g., medicated-feed dusts)

All the main routes can be considered the same from country to country, region to region with the prevalence of one or another. However, there can be found apparent differences in amounts and kinds of PPCPs occurring in the environment of different states. These depend on the peculiarities of their production, marketing, usage and disposal techniques.

Thus, among the most prescribed and used pharmaceuticals in the Eastern European (including former USSR states) are those not that widely represented or even prohibited in the USA and Western European countries. These are arbidol hydrochloride (1-methyl-2-(phenylthio)methyl)-3-carbethoxy-4-((dimethyl-amino)methyl)-5-hydroxy-6-bromindole hydrochloride (**1**), drotaverine hydrochloride ((1*Z*)-1-[3,4-dietoxyphenyl)methylidene]-6,7-diethoxy-3,4-dihydro-2*H*-isoquinoline hydrochloride (**2**), metamizole sodium (sodium [(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)methylamino] methanesulfonate) (**3**), phenylpiracetam (2-(4-phenyl-2-oxopyrrolidin-1-yl)acetamide) (**4**), rimantadine hydrochloride (1-(1-adamantyl)ethanamine hydrochloride (**5**) (Fig. 2.2).

Arbidol hydrochloride (**1**) (arbidol) and rimantadine hydrochloride (**5**) (rimantadine) are very popular anti-flu drugs that can be often bought without any prescription needed.

Arbidol pharmacokinetics supposes that large amounts of drug are passing organism without any changes. Bioavalability of the drug after oral administration is about 100%. About 40% of oral dose is excreted as unchanged form, the rest is composed of about 17 different metabolites. The biotransformation of arbidol leads to the loss of dimethylaminomethyl substituent in position 4 and sulfooxidation with formation of N-demethylarbidol, N-demethylsulfonylarbidol, sulfonylarbidol, sulfinylarbidol and N-demethylsulfinylarbidol. During the 2nd phase of the metabolism, conjugation at hydroxyl group occurs with formation of glucuronides and sulfates. The major arbidol metabolites are glucuronide arbidol and glucuronide sulfinylarbidol [8, 9].

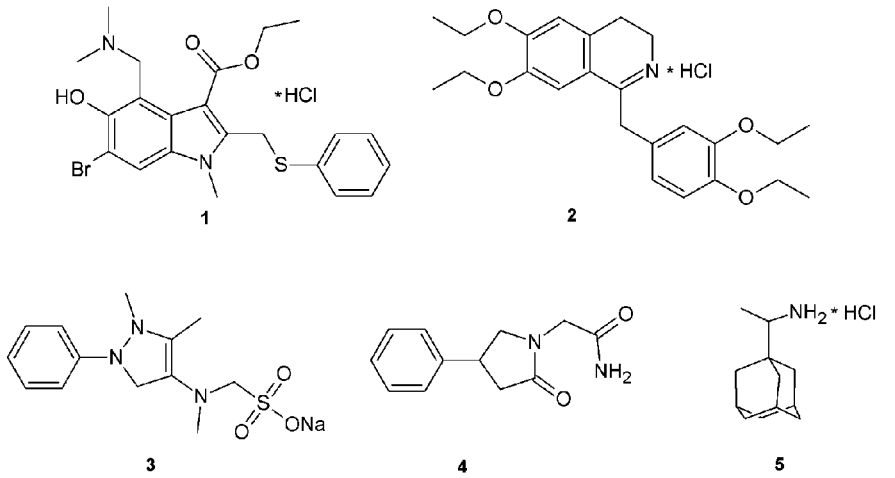

Fig. 2.2. Chemical structures of arbidol hydrochloride (**1**), drotaverine hydrochloride (**2**), metamizole sodium (**3**), phenylpiracetam (**4**), rimantadine hydrochloride (**5**).

Rimantadine (**5**) is metabolized in liver in a higher percentage than arbidol, with only 15–20% of the administrated dose being excreted as initial drug. The main rimantaidne metabolites are 2-, 3-, and 4-hydroxyrimantadine. From these, 2-hydroxyrimantaidne shows the same level of antiviral activity as rimantadine, while 3- and 4-hydroxyderivatives posses a lower anti-flu activity [10].

Drotaverine hydrochloride (**2**) is a chemical analogue of papaverine that is frequently used as antispasmodic drug. The main mechanism of its pharmacological action is based on selective inhibition of phosphodiesterase 4. The oral bioavalability of drotaverine ranges form 25% to 91% [11]. Drotaverine undergoes hepatic biotransformations that include mainly oxidation with formation of monophenolic metabolites and their consequent conjugation with glucuronic acid. Its metabolites are excreted with urine at the level of about 20–25% and with faeces at about 60–65% of the administered dose [12].

Metamizole sodium (**3**) (metamizole) is a NSAID, commonly used as painkiller and antipyretic. It has been prohibited in the US and many European countries as of risk of agranulocytosis it can cause, but it is still in a wide use as an over-the-counter medicine in many countries including Brazil, Bulgaria, India, Romania, Russia, Spain, Turkey and Mexico.

After oral or intravenous administration metamizole undergoes rapid metabolism with formation of 4-methylaminoantipyrine that is further transformed in 4-formylaminoantipyrine (FAA) and 4-aminoantipyrine (AA), which is acetylated to 4-acetylaminoantipyrine (AAA). These 4 major metabolites account ~60 % of the administered dose excreted from the organism [13, 14].

The occurrence and fate of metamizole metabolites were studied in investigations of sewage effluents from a military hospital, municipal sewers and a sewage

treatment plant (STP) in Berlin, Germany [15]. This study showed that during the sewage treatment an average decrease of AA/AAA was 26% of the loads, whereas no changes were observed for FAA. The measured concentrations of metamizole residues in the STP effluents were up to 7 μg/l.

Phenylpiracetam (carphedon) is a derivative of a well-known nootropic drug piracetam. Recently, it has become an often prescribed general stimulant and nootropic medicine in Russia. Phenylpiracetame does not undergo any biotransformations in humane organism. Approximately 40% of the drug administered is excreted with urine and about 60% with bile and transpiration [16].

Another particularity concerning the PPCPs in the Eastern European countries is their use in uncontrolled and imprudent manner. A greater concern represents abusive self-medication and inappropriate disposal of high active drugs like antibiotics and antipsychotic drugs. Thus, the study performed in Russia showed that antibiotics were widely stocked among the general population. The most common preparations in home medicine cabinets were trimethoprim-sulfamethoxazole (46.3%), ampicillin (45.1%), chloramphenicol (32.7%), erythromycin (25.5%), and tetracycline (21.8%). The major indications for automedication with antibiotics were acute viral respiratory infections (12.3% of total indications), cough (11.8%), intestinal disorders (11.3%), fever (9%), and sore throat (6.8%) [17]. Similar results of antibiotic misuse were obtained for Poland [18].

Very often, antibiotics are incorrectly prescribed by doctors. A study assessing prescribers' indications for drugs in childhood showed that incorrect antibiotic indications accounted from 24.1% of the total antibiotics prescribed in Tenerife (Spain) to 67.4% in Slovakia. Incorrect indication of first-choice antibiotics prescribed in acute otitis media and tonsillitis ranged from 28.9% of total antibiotics use in Russia to 75.4% in Tenerife (Spain) [19].

Besides, the increase in misuse of prescription drugs is rapidly increasing, and according to some studies, may soon exceed that of illicit narcotics. According the studies performed in 2001–2005 the global consumption buprenorphine, an analgesic prescribed for substitution treatment of drug dependency, more than tripled from 420 million daily doses to 1.5 billion daily doses. Illicit preparations of buprenorphine have been found to be misused in Iran, Pakistan, the United Arab Emirates, the Czech Republic, Finland, Georgia, and Mauritius, among other countries. The same study showed that misuse of fentanyl through pharmacy theft, fraudulent prescriptions, and illicit distribution by patients, doctors, and pharmacists is also a growing problem in North America, Europe and Russia, where it is sold by traffickers as an imitation of illicit drugs such as heroin.

The misuse of prescription drugs is exacerbated by the higher volumes of drugs in the unregulated market and the rapid growth of internet pharmacies, which in some countries are not subject to national drug control regulations. And, despite the closure of thousands of illegal internet pharmacies, there is an increasing number of such internet sites selling medicines containing opioids and stimulants without prescription [20].

Other major problems are pharmaceutical waste management schemes and treatment technologies implemented in the Eastern European countries. Though, many countries from the region have a very good legislation in the field, it is not being implemented. A good study in this field has been performed by Croatian researchers [21, 22]. It disclosed the evidence of improper practices from the point of waste production to final disposal, while landfilling appeared to be the main route of pharmaceutical waste disposal in Croatia. Moreover, information on quantities, type and flow of medical waste were found to be inadequate. A similar situation can be found in other Eastern European countries too [23, 24].

Still, a very small number of studies were performed in the field of PPCPs in the Eastern European environment. Most of them detected the presence of certain groups of PPCPs in the STPs effluents and rivers: caffeine, galaxolide, carbamazepine and triclosan in the Somes river, Romania [25, 26]; anthropogenic gadolinium and estrogens in hydrologic basin of Prague, Czech Republic [27, 28]; ibuprofen, naproxen, ketoprofen, diclofenac, bezafibrate and clofibric acid in the Warta River, Poland [29] and other common anti-bacterial, anti-convulsant, anti-hallucinatory, anti-inflammatory, and analgesic formulations in the rivers of the South Poland [30] in the range of 1–10 ng/l.

3. Conclusion

The region of the Eastern European (including the former USSR states) can be characterized as a rapidly growing pharmaceutical market with very popular indigenous drugs and not that well established rules and culture of medicinal consumption. Besides, the local practices of pharmaceutical waste release and disposal as well as practices of untreated sewage release and poor technologies of its treatment are of big concern. Thus, there is a need of research and information in the field of PPCPs in the environment in these states considering all the local specifics and practices.

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