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Ecopharmacology: A New Topic of Importance in Pharmacovigilance

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In 1999, >13 000 tonnes of antibacterials were used in the European Union (EU).[1] According to an estimate by Wise, 100 000 tonnes of antibacterials may be used annually.[2] It has been estimated that several 100 000 tonnes of pharmaceuticals are sold worldwide per year. After administration, most drugs are incompletely metabolised. For example, using data from Germany, an average excretion rate for antibacterials of 75% for the unchanged drug was calculated using amounts used and compound-specific excretion rates.[3] Active compounds are excreted into the environment through faeces and urine. Surplus drugs not taken by patients are often disposed of down the drain or with waste. Drugs from various groups, such as cytotoxic agents, antibacterials, analgesics, spasmolytics, sedatives, x-ray and MRI contrast media and disinfectants have been detected in the terrestrial and aquatic environment throughout the world.[4-6] This indicates that they are not fully eliminated, for example, by the treatment of effluent. The most important routes by which pharmaceuticals enter the environment are depicted in figure 1. Pharmaceuticals applied in veterinary medicine enter the environment mainly through manure and thereafter move into the soil from where they may trickle down into the ground water.

As for antibacterials, not only are the compounds themselves of interest but also the input and fate of resistant bacteria. Bacteria with resistance to most antibacterials have been detected in water and soil.[7] In a recent publication, it was suggested that resistant microbiota present in soil, in which resistance has occurred due to naturally produced antibacterials, are a major cause of antibacterial resistance in medical environments.[8] The significance of this to the problem of the input of antibacterials into the soil is not yet known. According to the European Parliament, the use of antibacterials for growth promotion in animals has been banned in the EU from 2006. The WHO has also advised that the use of antibacterials as growth promoters should be abandoned.[9] Prudent use of antibacterials in human medicine would not only decrease the risk of antibacterial resistance, but also help the environment. A reduction of up to 50% is supposed to be possible.[10]

Drugs are not only active within patients but also in the environment. Therefore, we are in favour of a risk assessment for pharmaceuticals that includes their environmental fate and their potential impact on organisms in the environment and on the ecosystems that these organisms live in. A risk assessment has been obligatory for newly licensed compounds used as veterinary pharmaceuticals since 1998. The Directive 2004/27/EC of the European Parliament and of the Council of the European Union requires drug companies to submit an environmental risk assessment as part of a marketing authorisation application:

"Article 8 (3):

(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged;

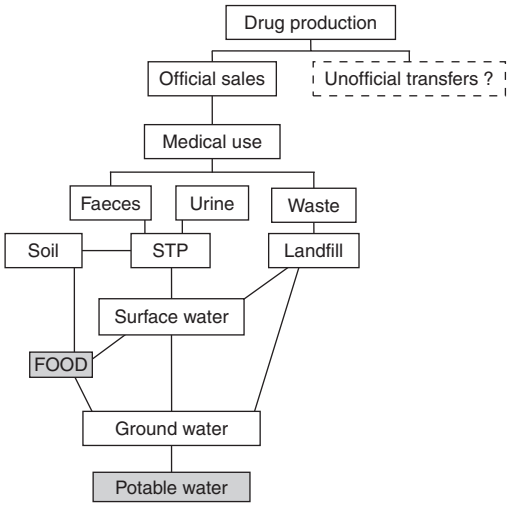

Fig. 1. A schematic diagram of the main routes by which pharmaceuticals are emitted into the environment. Ingestion of pharmaceuticals in food is possible if the water used for irrigation contains pharmaceuticals or if sewage sludge containing pharmaceuticals from sewage treatment (e.g. strongly sorbing compounds such as quinolones and tetracyclines or cytotoxic compounds, such as mitoxantrone or epirubicin) contaminates the soil in which the food is grown. Input of pharmaceuticals into soil is also possible via manure because of the application of drugs in veterinary medicine and for the promotion of growth in livestock. **STP** = sewage treatment plant.

(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment".

This new legislation shows how important ecopharmacology may become in the future. The legislation applies for single compounds only. It does not apply to compounds and products licensed before the legislation became effective and these compounds and products form the vast majority. As a result, we have little or no data assessing their fate and effects in the environment. The legislation is also not applicable for mixtures; therefore, we also have to keep in mind the precautionary principle and its application within the context of ecopharmacology.

An interesting approach was carried out by the Swedish government; it asked for an official report from the Swedish Medical Products Agency on the environmental effects of drugs. Twenty-seven drugs were studied in an environmental hazard and risk assessment.[11,12] The fate and effects can be described in terms of ecopharmacology instead of pharmacology. However, there are some important differences between pharmacology and ecopharmacology (table I). Ecopharmacology concerns the 'life' of drugs within the environment (ecosystem), with all their consequences in humans and other organisms in the environment.

In the 20th century, >100 000 chemicals were introduced into the market that are used in everyday life. This was 'blindly' carried out without considering the direct and indirect consequences on the environment and for human health. There are about 4000 drugs used, each with properties that make them interesting from an environmental point of view. The 'drug issue' is of great interest to people working in pharmacovigilance. When medicines are used or misused there can be serious and damaging consequences to our global environment and ecosystem. As always, more rational drug use could be very helpful for the patient and for the ecosystem. Drugs can pollute our environment, water, animals, soil and plant life, and can also have ongoing effects in humans, causing adverse effects (considering also the effects related to unwanted and unknowing consumption of unnecessary drugs), compromising human responses to medicines and contributing to drug resistance.

Table I. Pharmacology and ecopharmacology: a comparison (reproduced from Kümmerer,[6] with permission)

Issue	Pharmacology (humans)	Ecopharmacology (environment)
Number of compounds administered	One or only a few compounds at the same time	An unknown cocktail of different compounds
Desirable physico-chemical properties	Stable	Readily (bio)degradable
Administration	Targeted, on demand, controlled	Diffuse i.e. emissions from medical care units and the community
Wanted effects/ adverse effects	Active, wanted effects, adverse effects	Wanted effects in target organism are often the most important adverse effects in the environment
Metabolism/ biotransformation/ affected organisms	One type of organism	Various types organisms at different trophic levels

This widespread contamination should be taken into consideration because of its potential risk to humans. Therefore, this contamination should also be a concern for those working in pharmacovigilance. For example, resistance and the selection of resistant bacteria in the environment is a very important topic of discussion between scientists.[13] In general, environmental concentrations of drugs are well below therapeutic levels. In the environment, several drugs are present at the same time and in the same place (table I). Therefore, drug interactions are possible and may result in enhanced toxicity, which has already been demonstrated in algae for NSAIDs, such as diclofenac, ibuprofen, naproxen and aspirin (acetylsalicylic acid),[14] and antibacterials.[15] We do not know the significance in humans of interactions between multiple drugs at low concentrations if they are ingested in the drinking water over the whole lifespan, therefore we must think and act on a precautionary basis.

We should consider special populations like infants and children, the elderly, pregnant women and patients with diseases such as nephropathy and hepatitis, which are conditions that interfere with drug effects. Moreover, type B adverse reactions are dose/concentration independent and some substances like hormones are very active compounds such that even low-level environmental concentrations may cause damage. Hormones, and the so-called endocrine-disrupting chemicals, are known to be active against organisms in the environment at very low levels (<1 ng/L), causing effects in individuals and on a population level. The concept of ecopharmacology and the relevance of pharmaceuticals in the environment should be integrated into the curricula of medical doctors and pharmacists to address and solve the issues described here.

There is a lot concerning this topic that we need think about and a lot that we need to do. It is a situation which affects us all but about which we know very little.

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