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Fate of carbamazepine, its metabolites, and lamotrigine in soils irrigated with reclaimed wastewater: Sorption, leaching and plant uptake

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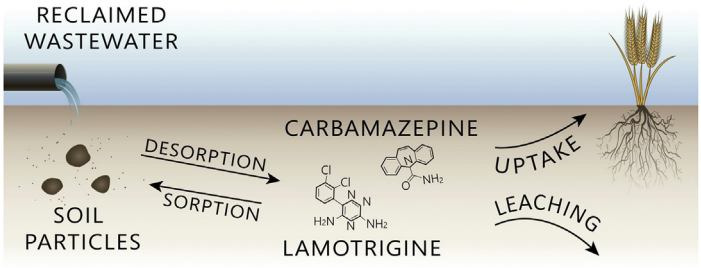
HIGHLIGHTS

- Carry-over of carbamazepine was shown in rain-fed wheat.
- Adsorbed carbamazepine is readily available for plant uptake.
- Lamotrigine and carbamazepine tend to accumulate in the top soil layer.
- Sorption of the studied pharmaceuticals is reversible and non-competitive.

GRAPHICAL ABSTRACT



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ABSTRACT

Irrigation with reclaimed wastewater may result in the ubiquitous presence of pharmaceutical compounds (PCs) and their metabolites in the agroecosystem. In this study, we focused on two highly persistent anticonvulsant drugs, lamotrigine and carbamazepine and two of its metabolites (EP-CBZ and DiOH-CBZ), aiming to elucidate their behavior in agricultural ecosystem using batch and lysimeter experiments. Sorption of the studied compounds by soils was found to be governed mainly by the soil organic matter level. Sorption affinity of compounds to soils followed the order lamotrigine > carbamazepine > EP-CBZ > DiOH-CBZ. Sorption was reversible, and no competition between sorbates in bi-solute systems was observed. The results of the lysimeter studies were in accordance with batch experiment findings, demonstrating accumulation of lamotrigine and carbamazepine in top soil layers enriched with organic matter. Detection of carbamazepine and one of its metabolites in rain-fed wheat previously irrigated with reclaimed wastewater, indicates reversibility of their sorption, resulting in their potential leaching and their availability for plant uptake. This study demonstrates the long-term implication of introduction of PCs to the agroecosystem.

1. Introduction

Numerous pharmaceutical compounds (PCs) and their metabolites have been detected in wastewater effluents due to their

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incomplete removal by conventional treatment technologies (Andreozzi et al., 2003; Metcalfe et al., 2003). Environmental discharge and irrigation with reclaimed wastewater have resulted in the ubiquitous presence of PCs in soil, surface water and groundwater (Benotti et al., 2009; Kinney et al., 2006). Moreover, some PCs can be taken up by crops (Herklotz et al., 2010; Shenker et al., 2011; Wu et al., 2014). Hence, the presence of PCs and their metabolites in the environment has raised concern due to the potential ecological and health risks associated with exposure to these pollutants (Cunningham et al., 2010; Kostich et al., 2014).

Carbamazepine and lamotrigine have similar pharmacological activity (i.e., both are extensively used for the treatment of epilepsy, bipolar disorder and other psychotherapy applications); however, they have distinct chemical structures and properties that can affect their environmental behavior. Carbamazepine is among the most frequently detected PCs in wastewater effluents at relatively high concentrations of about 1 μg L^{-1} (Clara et al., 2004; Verlicchi et al., 2012). Approximately 25–30% of the orally administered dose of carbamazepine is excreted unchanged from the human body while absorbed carbamazepine goes through excessive metabolism (Paltiel et al., 2016; Zhang et al., 2008). 10,11-epoxycarbamazepine (EP-CBZ) is a therapeutically active metabolite, which is excreted from the body at approximately 2% of the orally administered dose, and is therefore detected in reclaimed wastewater in concentration range of 50–120 ng L^{-1} (Bahlmann et al., 2014; Bueno et al., 2012). 10,11-dihydro-10,11-*trans*-dihydroxycarbamazepine (DiOH-CBZ), which is not therapeutically active, is the most common carbamazepine metabolite found in urine (30% of the oral dosage). DiOH-CBZ is the predominant metabolite detected in reclaimed wastewater in concentrations equal to or higher than the parent compound (Leclercq et al., 2009; Miao et al., 2005). Lamotrigine is a relatively new drug that was recently detected for the first time in wastewater, surface water and drinking water (Ferrer and Thurman, 2010). In environmental samples, lamotrigine (at concentrations of up to 1 μg L^{-1}) was accompanied with its primary metabolite, lamotrigine-2-*N*-glucuronide (Ferrer and Thurman, 2012; Writer et al., 2013b; Zonja et al., 2015). This metabolite, though pharmacologically inactive, can undergo deconjugation in water to form the parent compound (Ferrer and Thurman, 2010).

While carbamazepine interactions with soils have been extensively studied, little is known about the behavior of its two main metabolites (EP-CBZ and DiOH-CBZ). For both metabolites, weaker sorption as compared to carbamazepine was observed (Fenet et al., 2012; Stein et al., 2008), and the higher mobility of metabolites was explained by their lower hydrophobicity as compared to the parent compound. The data on lamotrigine behavior in soils is scarce. Greater in-stream attenuation and higher retardation factor were observed for lamotrigine as compared to other PCs commonly detected in soil (Borgman and Chefetz, 2013; Writer et al., 2013a), suggesting that lamotrigine has certain potential for sorption in soils. In this study we aimed to investigate the environmental fate of these compounds by elucidating their sorption-desorption behavior in soils, and to estimate their mobility and bio-availability for plant uptake under field conditions by performing lysimetric studies.

2. Material and methods

2.1. Pharmaceuticals

Lamotrigine (>99%), carbamazepine and 10,11-epoxycarbamazepine (>98%) were purchased from Sigma-Aldrich (Rehovot, Israel). 10,11-dihydro-10,11-*trans*-dihydroxycarbamazepine (>97%) and the labeled internal standards carbamazepine-13C,d2, 10,11-epoxycarbamazepine-d2 and lamotrigine-13C3 were purchased from Toronto Research Chemicals (Toronto, Canada). Chemical structures and selected physico-chemical properties of studied compounds are presented in Table 1.

2.2. Soils

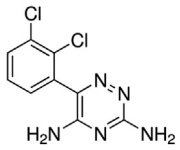
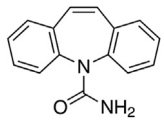
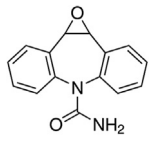
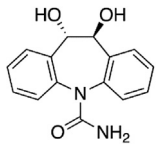
To examine the effect of soil properties on the behavior of the studied PCs and their metabolites, representative agricultural soils of different clay and organic matter content were collected from three locations in the northwest Negev region of Israel (Nir Oz, Ein Hashlosha and Sa'ad). These loessial Arid soils were used both for laboratory batch experiments and lysimeter studies. Selected soil properties are presented in Table 2.

2.3. Batch experiments

2.3.1. Sorption-desorption experiments

Sorption and desorption of lamotrigine, carbamazepine, EP-CBZ and DiOH-CBZ by each of the three soils were studied separately using batch-equilibrium technique. Details of the experimental setup are shown in the Supporting Information. In short, six initial concentrations of the analytes in the range of 0.05–5 mg L^{-1} were introduced to the soils. Application of these concentrations (which are above the environmentally relevant amounts) enabled comprehensive observation of the analytes' sorption behavior. Soil:solution ratio was 1:5 (w/v) for lamotrigine and 1:1 (w/v) for carbamazepine and its metabolites. Tubes (samples and blanks) were agitated in the dark, at 25 °C, for 7 days to reach sorption equilibrium (based on preliminary kinetics experiments). Then the tubes were centrifuged (10,000 *g*, 10 min), the supernatants were filtered (0.45 μm PTFE), and concentrations of all compounds were measured using HPLC. For desorption, 50% of the supernatant

Table 1
Chemical structures and physico-chemical properties of the investigated compounds.

	Structure	log K_{ow}[a]	pK_a
Lamotrigine		1.93	5.7[b]
Carbamazepine		2.77	pK_{a1} = −0.5[c] pK_{a2} = 14.4
10,11-epoxycarbamazepine (EP-CBZ)		1.97	pK_{a1} = −0.9[c] pK_{a2} = 14.8
10,11-dihydro-*trans*-10, 11-dihydroxycarbamazepine (DiOH-CBZ)		0.81	pK_{a1} = −1.5[c] pK_{a2} = 11.7 pK_{a3} = 12.3 pK_{a4} = 14.0

[a] Calculated using MarvinSketch software (http://www.chemaxon.com).
[b] Young et al. (2014).
[c] Calculated via density functional theory at the SMD/M05-2X/6-311++G(d,p) level of theory.