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Transformation of atenolol, metoprolol, and carbamazepine in soils: The identification, quantification, and stability of the transformation products and further implications for the environment☆

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ABSTRACT

Pharmaceuticals are a large group of substances that have been recognized as environmental contaminants in recent years. Research on the pharmaceutical fate in soils is currently limited or missing. In this study, three pharmaceuticals (atenolol (ATE), carbamazepine (CAR), and metoprolol (MET)) were introduced to soils and exposed for 61 day under aerobic conditions. Thirteen different soils were used in the study to increase the understanding of pharmaceutical behaviour in the soil matrix. Ten metabolites were detected and tentatively identified. Some of them, such as atenolol acid (AAC), carbamazepine 10,11-epoxide (EPC), 10,11-dihydrocarbamazepine (DHC), *trans*-10,11-Dihydro-10,11-dihydroxy carbamazepine (RTC), and metoprolol acid (MAC), were consequently confirmed using commercial reference standards. It was concluded that the aerobic conditions of the experiment determined the pharmaceutical degradation pathway of studied compounds in the soils. The different amounts/rates and degradation of the transformation products can be attributed to differences in the soil properties. ATE degraded relatively quickly compared with CAR, whereas MET degradation in the soils was unclear. The persistence of CAR and its metabolites, in combination with low CAR sorption, enable the transportation of CAR and its metabolites within soils and into the ground water. Thus, CAR may cause adverse effects on the environment and humans.

1. Introduction

Pharmaceuticals are a widely used group of compounds that are present in various environmental compartments. Due to their high consumption and possible harmful effect on ecosystems, pharmaceuticals have been identified as “emerging organic contaminants” (Brodin et al., 2013; Li, 2014). ATE is used as the treatment of cardiovascular disorders (Wadworth et al., 1991) and may be used as adrenergic beta-antagonists, anti-arrhythmia, and antihypertensive agents. Currently, ATE is also used for infantile hemangioma treatment (Abarzúa-Araya et al., 2014). MET is related to the same group of pharmaceuticals as ATE. Recently, MET replaced ATE in clinical practice for the treatment of hypertension (van den Born et al., 2005). MET has been frequently used for ventricular arrhythmia (Gao et al., 1997), severe heart failure (Goldstein et al., 2001), etc. CAR has been shown to be effective as an analgesic, non-narcotic, and anticonvulsant drug. CAR has been used to treat certain psychiatric disorders, such as schizophrenia (Leucht et al., 2002), epilepsy (Shakespeare and Simeon, 1998), bipolar mood disorders (Zhang et al., 2007), and other illnesses, such as fibromyalgia (Wiffen et al., 2014), acute and chronic pain (Wiffen et al., 2005), and aggression (Yatham and McHale, 1988). Additionally, MET and CAR have been included as generic medications in the World Health Organization's List of Essential Medicines (Organization, October 2013).

It has been reported that CAR exhibits a low removal efficiency, and in some cases, even a negative removal efficiency (Collado et al., 2014) with no seasonal variation (Golovko et al., 2014b) in concentration, whereas the behaviour of MET and ATE are more complicated. The MET removal efficiency has been

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reported as medium (Collado et al., 2014) or low (Kasprzyk-Hordern et al., 2009). ATE exhibits a low removal efficiency of 10% during winter and 50% in summer (Golovko et al., 2014a), but a high (>70%) removal efficiency has been documented in some cases (Collado et al., 2014; Kasprzyk-Hordern et al., 2009). All of the mentioned pharmaceuticals constantly enter the environment via WWTPs. This led to their frequent detection in surface water (Collado et al., 2014; Grabicova et al., 2015; Li, 2014), which may be used for irrigation of agricultural fields. Agriculture field fertilization with sewage sludge may be another possible way of environmental contamination (Poulsen et al., 2013) (in the case of soil and ground water). It has been also exhibited that CAR and MET were persistent in soils when introduced via treated wastewater and that the pre-exposure of the soils to pharmaceuticals via irrigation did not enhance their biodegradation (Grossberger et al., 2014).

Several studies have describe stability of selected compounds under different conditions, such as solar-simulator irradiation (Neamtu et al., 2014), photocatalytic ozonation (Rey et al., 2012), the direct UV photolysis (Calza et al., 2013), indirect photolysis in the presence of fulvic acids (Chen et al., 2012), and UV/H_2O_2 oxidation (Shu et al., 2013) etc. To conclude, CAR photodegradation was slow, compound was shown to be relatively persistent towards direct photolysis, while ATE and MET had a moderate photostability.

The fate of these compounds in soil has not been sufficiently studied. No information on the ATE and MET transformation in soil is available. A few studies have focused on CAR degradation in soils (Li et al., 2013; Monteiro and Boxall, 2009; Salvia et al., 2014; Yu et al., 2013). Those studies included small amounts of soils and biosoils (5 is max), and primarily focused on specific issues, such as the degradation in soil columns (Salvia et al., 2014), the impact of sterilization on dissipation (Yu et al., 2013), etc.

Those compounds were quite well studied in the different kind of sludge. A few research were focused on sorption coefficient determination, such as distribution coefficients for linear (K_d) isotherms. Thus, it has been shown that ATE has 4.6×10^2 l kg^{-1} values for K_d in a primary sludge, while 1.6×10^3 L kg^{-1} for secondary sludge long sludge age (Horsing et al., 2011) and average value of 0.038 L g^{-1} in wastewater sludge for another study (Maurer et al., 2007). The solid-water distribution coefficient (Kd) has also been obtained for CAR in mesophilic (35.4 L kg^{-1}) (Carballa et al., 2008), thermophilic (20.2 L kg^{-1}) (Carballa et al., 2008), and secondary (1.2 L kg^{-1}) (Ternes et al., 2004) sludge. An average K_d value of 0.001 L g^{-1} has been found for MET in wastewater sludge (Maurer et al., 2007). According to literature data, adsorption of studied compounds was hardly depended on type of matrix, which was investigated. Several studies have reported the harmful effect of these compounds on aquatic organisms during different developmental stages (Almeida et al., 2014; Contardo-Jara et al., 2010; Kim et al., 2007; Lamichhane et al., 2013; Steinbach et al., 2014; Triebskorn et al., 2007). There is no information available on the effects of these pharmaceuticals on organisms living in soils. During various degradation processes, pharmaceuticals form different metabolites and degradation products (Abramovic et al., 2011; Rubirola et al., 2014; Salgado et al., 2013; Tay et al., 2011). The impact of these compounds on the environment is still not known (Kim et al., 2007; Triebskorn et al., 2007).

The first step to studying the influence of various substances (i.e., pharmaceuticals and their metabolites) on soil organisms is their identification and behaviour in a soil environment. To our knowledge, there is only one published study on the degradation of CAR and its metabolite identification in soils (Li et al., 2013). According to the study, two loam and clay soils were exposed for 120 days and five metabolites were formed: 10,11-dihydro-10-hydroxycarbamazepine, carbamazepine-10,11-epoxide, acridone-N-carbaldehyde, 4-aldehyde-9-acridone, and acridine (Li et al., 2013).

Our study investigates the possible formation of degradation products from the selected compounds and their stability in a soil matrix. Thirteen different soil types, which represent different regions of the Czech Republic, were selected to determine the pharmaceutical degradation in soils under near natural conditions. To our knowledge, no other studies on pharmaceuticals and their metabolite fates in many different soil types have been reported to date.

2. Materials and methods

2.1. Chemicals

ATE, CAR, and metoprolol tartrate salt were purchased from Sigma-Aldrich (Steinheim, Czech Republic). An isotope-labelled internal standard (IS) of CAR (D10) was acquired from CDN Isotopes (Pointe-Claire, Quebec, Canada), whereas ATE (D6) and metoprolol hydrochloride (D7) were purchased from Alsachim (Strasbourg, France). Metabolite standards of AAC,MAC, EPC, OXC, DHC, and RTC were purchased from Labicom (Olomouc, Czech Republic). A stock solution of each pharmaceutical was prepared in methanol at a concentration of 1 mg mL^{-1}. A spiking mixture of each was prepared by diluting the stock solution with methanol to a final concentration of 1 μg ml^{-1}. All stock and spiking solutions were stored at −20 °C. The LC-MS grade acetonitrile (LiChrosolv Hypergrade) was obtained from Merck (Darmstadt, Germany). Formic acid was used to acidify the mobile phases and was purchased from Labicom (Olomouc, Czech Republic). The ultrapure water was prepared via an Aqua-MAX-Ultra System (Younglin, Kyounggi-do, Korea).

2.2. Instrumentation

An Accela 1250 LC pump (Thermo Fisher Scientific, San Jose, CA, USA) coupled with a hybrid quadrupole/orbital trap Q-Exactive mass spectrometer (Thermo Fisher Scientific) and a HTS XT-CTC autosampler (CTC Analytics AG, Zwingen, Switzerland) were used to separate and detect target analytes. An analytical Hypersil Gold column (50-mm length, 2.1 mm i.d, 3-μm particles; Thermo Fisher Scientific) preceded the same phase pre-column (10-mm length, 2.1 mm i.d., and 3-μm particles) and the Cogent Bidentate C18 column (50 mm × 2.1 mm i.d., 4-μm particle size from MicroSolv Technology Corporation Eatontown, NJ, USA), which were used for the chromatographic separation of the target analytes. The soil samples were extracted using an ultrasonic bath (DT 255, Bandelin electronic, Sonorex digitec, Berlin, Germany).

2.3. Sample collection and experimental set-up

Thirteen different soil types, including Stagnic Chernozem Siltic developed on marlite (X), Haplic Chernozem on loess A (I), Haplic Chernozem on loess B (D), Chernozem Arenic on gravely sand (L), Greyic Phaeozem on loess (C), Haplic Luvisol on loess (S), Haplic Cambisol on orthogneiss A (H), Haplic Cambisol on syenite B (P), Haplic Cambisol on quartzite C (J), Dystric Cambisol on paragneiss (W), Arenosol Epieutric on sand (E), loess (U), and sand (Q), were collected from several locations in Czech Republic. These soils were described in detail previously (Kodesova et al., 2015). Samples were collected from the surface horizon (0–25 cm), except loess and sand, which were taken from the subsurface (50–80 cm). The soils were then air-dried, ground, and sieved through a 2 mm sieve. The

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