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Ketamine and the metabolite norketamine: Persistence and phototransformation toxicity in hospital wastewater and surface water

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ABSTRACT

Ketamine has been increasingly used both recreationally and medicinally around the world. Although the metabolic pathways to form its metabolite norketamine have been carefully investigated in humans and animals, knowledge of their environmental occurrence and fate is limited. In this study, we investigated the occurrence of ketamine and norketamine in 20 natural bodies of water, effluents from 13 hospitals, two wastewater treatment plants and one water supply plant. Ketamine was found at concentrations as high as 10 μg/L. Ketamine and norketamine were consistently found in similar concentrations (ketamine/norketamine ratio: 0.3–4.6) in the collected water samples, and this ratio similar to that found in urine samples. Dark incubation experiments have shown that ketamine is not susceptible to microbial degradation or hydrolysis. Phototransformation was demonstrated to significantly reduce the concentration of ketamine and norketamine in river waters ($t_{1/2}$ = 12.6 ± 0.4 and 10.1 ± 0.4 h, respectively) and resulted in byproducts that are similar to human metabolites. Both direct and indirect photolysis led to the N-demethylation of ketamine to form norketamine and other byproducts, including hydroxy-norketamine (HNK), dehydronorketamine (DNK), hydroxy-ketamine (HK) and isomer forms of ketamine and norketamine. Irradiated solutions exhibited higher toxicity (via the Microtox® test). Although a final risk assessment could not be made due to a lack of studies on the chronic effects on aquatic organisms, the high and persistent environmental occurrences of ketamine and norketamine as well as the increasingly acute toxicity of the photo byproducts demonstrate the importance of including metabolites in evaluation of the overall risk of ketamine.

1. Introduction

The use of strong analgesic and anesthetic medications is widespread among the general population, for whom these drugs can provide pain relief as well as a "high" at supra-clinical doses. Because of the potential for abuse, access to and use of these substances are carefully controlled. However, these medications may enter water sources through wastewater, thereby becoming contaminants that pose an

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unknown risk to aquatic life as well as to humans via drinking water. The environmental occurrence of ketamine can be attributed to two major sources: (1) abuse by individuals (ketamine is one of the most widely used club drugs) and (2) use as a general anesthetic and short-acting analgesic in veterinary, clinical and pediatric practices. The popularity of ketamine has increased within the adolescent drug culture in Taiwan as well as around the world, especially in southeast Asia and other regions in Asia (Cheung, 2010; Lian et al., 2005; Liu et al., 2005; Noorzurani et al., 2010). In addition, ketamine has been increasingly used for complex pain management (Smith, 2010) in the past decade and is also recently being considered for the treatment of major depressive disorder (Li et al., 2011). Ketamine generates effects similar to those produced by phencyclidine with visual effects of lysergide (Cheng et al., 2007; Moore et al., 2001). Recent studies have associated urinary tract dysfunction with the prolonged exposure and use of ketamine.

Ketamine is not completely metabolized in humans and other organisms. The typical urine excretion products are the parent compound and three metabolites: norketamine (NK), hydroxy-norketamine (HNK) and dehydronorketamine (DNK) (Adams et al., 1981; Chang and Glazko, 1974; Moore et al., 2001; Wang et al., 2005; Wieber et al., 1975). Norketamine, which has one-third to one-half the potency of ketamine, has been reported to be the major metabolite (Baselt and Cravey, 1982; Chang and Glazko, 1974; Kim et al., 2008; Mozayani, 2002; Savchuk et al., 1998; Tanaka et al., 2005; Woolf and Adams, 1987). In a study where microsomal preparations from rat livers were used, Adams et al. (1981) confirmed that N-demethylation of ketamine is the first major step of biotransformation; the NK produced accounts for 26% of the dose, and HNK isomers together accounted for another 5%. Other studies showed that approximately 2% of the parent compound, 2% of NK and 16% of DNK were excreted via urine in 72 h (Chang and Glazko, 1974; Wieber et al., 1975). However, researchers are still debating whether DNK is a true metabolite or an analytical artifact (Stenberg and Idvall, 1981; Wang et al., 2005; White et al., 1982). Moore et al. (2001) showed that 33 cases of human positive urine samples contained very similar concentrations of ketamine and NK, with a mean ketamine/NK ratio of 0.74 (range: 0.13–2.55).

Even though numerous reports have identified ketamine in urine samples and its metabolic pathways to form norketamine have been carefully investigated in humans and animals, knowledge related to the environmental occurrence and fate of ketamine and norketamine is very limited. Currently, only ketamine's occurrence in natural and wastewaters has been reported. In our previous study (Lin et al., 2010), we identified ketamine at concentration as high as 206 ng/L in hospital wastewaters and reported ketamine's persistence through wastewater treatment plants (WWTPs), which resulted the occurrence of ketamine in several surface waters in Taiwan at concentrations as high as 341 ng/L Bijlsma et al. (2012) showed that ketamine was consistently found to exist at slightly higher concentrations (<10–88 ng/L) in the effluents compared to its concentrations in influents in five sewage treatment plants (STPs). Huerta-Fontela et al. (2008) and van der Aa et al. (2013) have also observed ketamine to occur at concentrations of 5–50 ng/L and 2–28 ng/L in Spanish and Dutch wastewater treatment plants, respectively. Whereas its major metabolite, norketamine, has not been investigated, and the fates of both ketamine and norketamine in water systems are currently unknown.

After released into the receiving waters, ketamine and norketamine are subjected to environmental processes such as biodegradation/transformation, sorption and other chemical degradative processes that may contribute to their reduction and elimination. Photolysis has been reported to significantly reduce the predicted environmental concentrations (based on consumption/usage rate) of many recalcitrant drugs (Lam et al., 2005; Lin and Reinhard, 2005; Lin et al., 2013; Wammer et al., 2013; Wang and Lin, 2012) through both direct and indirect photolysis. In addition to the well-known photosensitizers, such as dissolved organic matter, nitrates and nitrites, the presence of bicarbonate has also been recently noted to greatly enhance the photolysis rates of *N*,*N*-dimethylaniline, cephalosporin antibiotics and 5-fluorouracil (Huang and Mabury, 2000; Lin et al., 2013; Wang and Lin, 2012).

Taipei and its suburbs comprise a densely populated area with more than 6.4 million inhabitants and more than 80 district hospitals and medical centers. In this district, waste streams that contain large quantities of medications discarded by hospitals significantly impact their receiving surface waters. Hospitals and patients around the globe consume similar drugs and excrete them or their metabolites into wastewater that may become drinking or surface water. Because ketamine originates from human usage and is not eliminated through current wastewater treatment processes, it is important to understand how its fate, transport and associated risks impact environmental and human health. To our knowledge, this is the first study on the photolysis of ketamine and the first work to investigate the occurrence and fate of ketamine's major metabolite, norketamine, in the natural water environment. The phototransformation pathway of ketamine is proposed, and the toxicities of the byproducts are evaluated.

2. Materials and methods

2.1. Chemicals and standards

LC-grade methanol was purchased from Mallinckrodt Baker (Phillipsburg, PA, USA). ACS-grade formic acid was obtained from Riedel-deHaën (Seelze, Germany). Ketamine hydrochloride (100%), ketamine-d_4 hydrochloride, 2-chlorotoluene (99%), 2-aminocyclohexanone (≥99%), 2-phenylcyclohexanone (98%), sodium bicarbonate, sodium nitrate, sodium hydroxide and sulfuric acid were purchased from Sigma–Aldrich (St. Louis, MO, USA). Norketamine hydrochloride (100%) was purchased from Tocris Bioscience (Bristol, UK). Cyclohexanone (≥99%) was purchased from Alfa Aesar® (MA, USA). Sodium azide was purchased from Nacalai Tesque (Kyoto, Japan). Suwannee River Fulvic Acid standard (FA) (1S101F) was obtained from the International Humic Substance Society (IHSS, St. Paul, MN, USA). Individual stock standard solutions were prepared on a weight basis in DI water. These solutions were stored in amber glass bottles at 4 °C for a maximum of 30 days.