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Predictors of urinary antibiotics in children of Shanghai and health risk assessment

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ABSTRACT

Background: An extensive exposure to antibiotics has been confirmed in children, but the predictors and potential health risk remain unclear.
Objective: To investigate the predictors of antibiotics in urine and potential health risk in children of Shanghai.
Methods: We selected 284 school children aged 8–11 years from a central area of Shanghai, China, in 2017. Ultra-performance liquid chromatography coupled with high-resolution mass spectrometry was used to measure 20 antibiotics, including four human antibiotics (HAs), six veterinary antibiotics (VAs), 10 human/veterinary antibiotics (H/VAs), and three metabolites in first morning urine. Logistic regression model was used to examine the associations of 17 variables related to demographic and socioeconomic factors, recent antibiotic use, drinking water intake, food consumption, and anthropometric measurements with the detection frequency of HAs, VAs, or H/VAs in urine. After daily intake was estimated, health risk was assessed for VAs and H/VAs by using hazard quotient (HQ) and hazard index (HI) based on microbiological or toxicological effects.
Results: The detection frequencies of 20 antibiotics and three metabolites ranged from 0 to 27.8% with an overall detection frequency being 56.0%. The detection frequency of HAs increased with age and screen time at weekend. Sex, age, family income and screen time were positively associated with the detection frequencies of VAs and H/VAs. Children reporting antibiotic use in the past three months had a higher detection frequency of HAs. Children with a higher consumption frequency of dairy products had a higher detection frequency of VAs + H/VAs, but a lower detection frequency of HAs. An increased overall detection frequency of all antibiotics was seen in children with higher consumption frequencies of aquatic products, livestock and poultry meat, or milk and dairy products. HQ > 1 was only found for ciprofloxacin (5.6%) and ofloxacin (0.4%) based on microbiological effect. HI > 1 was found in 6.0% of children for microbiological effect and none was found for toxicological effect.
Conclusions: Predictors for antibiotics in urine for children included sex, age, family income, screen time, clinical use, and animal-derived food consumption. There was potential health risk for children with exposure to antibiotics.

1. Introduction

Increasing evidence has indicated that the adverse effects of exposure to antibiotic are extended from common side effects to immune and metabolic diseases related to human microbiome (Thomas et al., 2017). Inappropriate use of antibiotics in animal husbandry and aquaculture industry have resulted in extensive residues of antibiotics in animal-derived food, such as pork (Yamaguchi et al., 2015), aquatic products (Uchida et al., 2016), and dairy products (Zheng et al., 2013). According to the pharmacokinetics, a considerable proportion (30–90%) of antibiotics consumed in animals and human can be excreted into waste stream in unchanged species or active metabolites by urine or feces and result in contamination of aquatic environment (Carvalho and Santos, 2016). A part of antibiotics consumed by human

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and animals can enter into human body again through the residues in food and in aquatic environment and pose a potential health risk (Zhang et al., 2015). The use (consumption) of antibiotics, however, is often monitored via questionnaire survey and prescription examination, which provides no information about the exposure of human to antibiotics from their residues in food and aquatic environment (Wang et al., 2014a). Biomonitoring of antibiotics in urine can measure the total exposure of human to antibiotics from clinical use as well as antibiotic residues in food and aquatic environment (Wang et al., 2014a).

Several population-based studies have measured antibiotics or their metabolites in urine (Ji et al., 2010; Li et al., 2017; Wang et al., 2015; Wang et al., 2016a; Wang et al., 2017a). A study conducted in Korean population reported that trimethoprim, enrofloxacin, ciprofloxacin, and roxithromycin were detected in 30–65% of urine samples (Ji et al., 2010). In two previous studies conducted in China, about 20 antibiotics in urine were measured and overall detected in 78.4% of children and 41.6% of pregnant women (Wang et al., 2015; Wang et al., 2017a). These studies have demonstrated an extensive exposure to antibiotics in human and raised a concern about its potential health risks. In the present study, we investigated the predictors of exposure to antibiotics and conducted a health risk assessment among 284 school children from Shanghai.

2. Materials and methods

2.1. Study population

In cooperation with the local Centers for Disease Control and Prevention, one study site had been previously established in Changning District in downtown Shanghai to explore the effects of environmental pollutants on children's health since 2013 (Wang et al., 2015). The current study was conducted in September 2017 and Changning District was roughly divided into five geographical areas (east, west, south, north, and centre). After one neighborhood was randomly selected in each area, one primary school was randomly selected from each selected neighborhood. Based on medical records, 284 healthy children aged 8–11 years (143 boys and 141 girls) were selected from second, third, and fourth grades of five primary schools. After their parents or guardians signed a written informed consent form, children were asked to provide first morning urine and to complete a brief questionnaire survey consisting of 38 items on demographic and socio-economic characteristics, smoking, antibiotic clinical use in the past three months, physical activity, consumption of drinking water and common food with the help of their parents or guardians. Anthropometric measurements were performed by trained technicians during a routine physical examination. All children provided their urine samples and completed anthropometric measurements, but only 220 out of 284 children completed the questionnaire survey. The study was reviewed and approved by the Institutional Review Board of Fudan University.

2.2. Selection of antibiotics

In this study, based on the usage amount or detection frequency in urine or aquatic environment in previous studies (Li et al., 2017; Liu and Wong, 2013; Wang et al., 2017a; Zhang et al., 2015), 20 common antibiotics and three metabolites (acetylated species of sulfamethazine, sulfamethoxazole, and sulfadiazine) were selected from five antibiotic categories (three macrolides, four tetracyclines, six fluoroquinolones, seven sulfonamides, and three phenicols) (Table 1). According to the hierarchical management catalog of clinical antibiotics issued by the Shanghai Health Bureau (2012) (SMCHFP, 2012), the first batch catalog of veterinary prescription drugs issued by the Ministry of Agriculture of China (MOA) (2013) (MOA, 2013), and the catalog of drug feed additives issued by MOA (2017) (MOA, 2017), these antibiotics were classified into three categories by the use object: human antibiotics (HAs), veterinary antibiotics (VAs), and human/veterinary antibiotics (H/VAs). HAs and VAs are exclusively used in human and animals, respectively, and H/VAs are shared by human and animals. There were four HAs, six VAs, 10H/VAs, and three metabolites of H/VAs in the current study (Table 1). Ciprofloxacin in urine can be metabolized not only from enrofloxacin (Davis et al., 2007), but also from ingesting the contaminated food by ciprofloxacin or its clinical use. Because the detection frequency of ciprofloxacin (11.3%) was much higher than that of enrofloxacin (0.4%) (Table 1), ciprofloxacin was unlikely to be the metabolite of enrofloxacin. Therefore, the subsequent estimation of daily exposure dose and health risk assessment of ciprofloxacin were based on itself.

2.3. Analysis of antibiotics

First morning urine samples were collected in polypropylene centrifuge tube by children themselves using a 20 mL polypropylene urine cup, and were transported to the laboratory in an ice chest and frozen at −80 °C in 12 h until analysis. Urinary creatinine was determined on the Architect C8000 biochemical analyzer (Abbott Laboratories, Abbott Park, IL) following the method provided by the manufacturer. Total concentrations of antibiotics (free and conjugated) were determined by the isotope dilution ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (UPLC-Q/TOF MS) following the method established by our lab previously (Wang et al., 2014a). Briefly, after an aliquot (1.0 mL) of urine was spiked with isotope-labeled internal standards and hydrolyzed by β-glucuronidase, the mixture was purified by the OASIS HLB 96-well solid-phase extraction plate and evaporated to dryness with weak nitrogen flow. After the residues were redissolved in 30% methanol water solution, the mixture was analyzed by UPLC-Q/TOF MS. Among 96 wells of solid phase extraction plate, 92 wells were used for 92 real urine samples, two wells were used for two parallel solvent blank samples, and two wells were used for two parallel spiked urine samples at 40 ng/mL of all antibiotics. One urine sample was randomly selected from each batch to make the spiked urine sample. Solvent blank and spiked urine samples were analyzed together with urine samples and used to monitor the background interference, precision, and accuracy during the whole analytical process. Antibiotics in urine were determined by the isotope internal calibration curve consisting of eight concentration levels between 0.05 ng/mL–100 ng/mL and the isotope internal calibration curve was made for each batch of urine samples. The limit of detection, defined as a signal-to-noise ratio of 3, ranged from 0.04 to 1.87 ng/mL. No background interference was observed for antibiotics. The recoveries of 20 antibiotics and three metabolites in spiked urine samples ranged from 72.6 to 122.8% with the relative standard deviations varying between 8.9 and 15.3%.

2.4. Daily exposure dose

Antibiotic daily exposure doses were estimated by the formula frequently used to estimate the daily exposure doses of other environmental pollutants (Soeborg et al., 2014; Wang et al., 2014b): $DED = C_a \times M_c \times 100/(C_c \times M_b \times P)$ (DED: daily exposure dose, μg/kg/day; C_a: antibiotic concentration in urine, μg/L; C_c: creatinine concentration in urine, mmol/L; M_c: daily output of creatinine in urine, mmol/day; M_b: body weight, kg; P: Antibiotic excretion proportion in urine as unchanged and glucuronide-conjugated forms). The daily output of creatinine in urine was predicted by a height-based linear regression equation derived from 454 healthy children aged 3–18 years with a determination coefficient of 0.87: Common log-transformed $M_c = 0.0102 \times H - 0.6854$ (H: body height, cm) (Remer et al., 2002). Due to the lack of human pharmacokinetic data, the excretion proportions of enrofloxacin and florfenicol in urine were derived from animal pharmacokinetic studies and the excretion proportions of other antibiotics were derived from human pharmacokinetic data (Table S1) (Wang et al., 2017a).