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Urinary reference ranges and exposure profile for lithium among an Italian paediatric population

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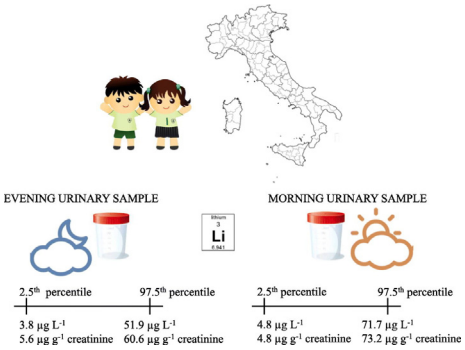
HIGHLIGHTS

- Urinary Li reference range of Italian children is 3.8–51.9 μg L^{-1} for evening samples.
- Urinary Li reference range of Italian children is 4.8–71.7 μg L^{-1} for morning samples.
- Age and urinary Li levels are inversely correlated in evening and morning samples.
- Urinary creatinine and Li levels are directly related in evening and morning samples.

GRAPHICAL ABSTRACT



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ABSTRACT

The aims of the present study were to establish reference values useful in monitoring Lithium (Li) treatment and to trace environmental Li exposure profiles in paediatric age.
A cross-sectional study was conducted on a group of healthy Italian children aged 5–11. Data on possible predictors were assessed through a questionnaire, and Li levels in morning and evening urinary samples were determined by ICP-MS technique.
The reference intervals for the evening and morning samples were respectively 3.8–51.9 μg L^{-1} or 5.6–60.6 μg g^{-1} creatinine and 4.8–71.7 μg L^{-1} or 4.8–73.2 μg g^{-1} creatinine. Urinary Li levels showed a significantly inverse correlation with age and a positive correlation with urinary creatinine in both the evening and morning samples. No other studied variables influenced Li urinary excretion.
These results, obtained using a readily available matrix as urine, can be useful for both environmental research and Li treatment monitoring.

1. Introduction

Lithium (Li) is an alkaline metal that has played an interesting role in human health. Indeed, Li salts have been successfully used for more than 2000 years in the treatment of certain psychiatric disorders, such

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as bipolar disorder and certain forms of mania and depression (Johnson and Amdisen, 1983). Moreover, in recent decades, the use of Li in industrial activities has gradually increased, in particular for producing rechargeable batteries, steel and ceramics (Tkatcheva et al., 2015). Thus, Li environmental levels and Li exposure of individuals and communities have been growing over the years.

Li toxicity has been extensively studied from a pharmacological point of view. Several adverse health effects have been evidenced, both for acute poisoning and chronic exposure. In particular, accidental or intentional intake of an excessive dose of Li may cause a broad range of effects, from nausea and vomiting to coarse tremors, lethargy and coma. Long-term therapeutic treatments can determine chronic effects affecting the gastrointestinal, central nervous, renal, endocrine, cardiovascular and other body systems (Malhi et al., 2012; Oruch et al., 2014). These adverse effects are primarily due to the narrow therapeutic index of Li. Indeed, Li requires a very close monitoring of serum concentrations to ensure levels are within the therapeutic range and minimize treatment-related risks (Kirkham et al., 2013). Moreover, occupational or environmental exposure to excessive amounts of Li has been linked to possible threats to human health, even though a review on this issue reported that, overall, the human and environmental toxicity of Li is low (Aral and Vecchio-Sadus, 2008). However, Li concentrations in the environmental matrices range widely worldwide: Li has been found in considerable amounts in natural salt brines, and in salted lakes, its levels range from 20 mg L^{-1} in the Dead Sea to 1500 mg L^{-1} in Salar de Atacama, Chile (Dolara, 2014). Li intake among general population may occur mainly through food, drinking water and air. In particular, Li concentrations in food were found in the range 5 μg Kg^{-1} (oil and fat) - 30–40 μg Kg^{-1} (fishery products vegetables and spices) (Noël et al., 2012), in Italian tap water from 0.11 to 60.8 μg L^{-1} (Pompili et al., 2015), in urban air from 0.10 to 0.50 ng m^{-3} (Canepari et al., 2014; Minguillón et al., 2012). Additionally, Li batteries are considered a relevant anthropogenic source of Li. Their use and disposal determine the increase of environmental levels of this element and, consequently, the exposure of general population (Aral and Vecchio-Sadus, 2008).

Although Li shows potential toxic effects, its presence in the environment is not regulated; consequently, it does not undergo to routinely monitoring (Tkatcheva et al., 2015). Thus, environmental data on Li contamination are still not sufficient for an appropriate assessment of the risk for environmental and human health.

In this research field, human biomonitoring studies are needed both for establishing specific reference values useful in monitoring Li treatment and for tracing Li exposure profiles of the general population, particularly in paediatric populations. Indeed, specific reference values and risk evaluation processes for most assessed chemical substances does not exist for the paediatric population. Because the studies performed on the general population almost always concerns adults only, research conducted on children is still insufficient compared to the need for scientific evidence. Regarding children's exposure to environmental Li, the Task Force of the World Health Organization for children's environmental health stated several years ago that children are not little adults, but they must be considered unique individuals because of differences in the contaminants intake, body metabolization and susceptibility to the adverse effects resulting from pollutants exposure (Anderson et al., 2000). Moreover, although Li does not represent the first-choice treatment in children, it has been successfully used for the treatment of psychiatric disorders at the paediatric age, and it has turned out to be effective and well tolerated (Findling et al., 2011). However, because of the narrow therapeutic range, it is necessary to monitor carefully and frequently the therapy by assessing Li concentrations in biological fluids. Typically, blood Li levels are used for this purpose even if it has been highlighted that more than 90% of the Li present in the human body is eliminated via the kidneys and the serum Li half-life is less than 24 h. Urine, therefore, seems to be a more suitable matrix for monitoring Li exposure (Usuda et al., 2007). Additionally, it is more difficult to obtain blood than urine samples, particularly in a paediatric patient; consequently, the urinary Li concentrations could be a suitable alternative to blood levels.

The aims of the present study were a) to establish the reference values of urinary Li in a large group of healthy Italian children, b) to trace the exposure profile of children to environmental Li, and c) to assess the contribution of certain potential interfering/confounding factors, such as gender, age, body mass index (BMI), urbanization degree of residence area, environmental tobacco smoke (ETS) exposure and educational level of parents to the urinary excretion of Li.

2. Methods

2.1. Study population and design

A cross-sectional study was proposed to the parents of 619 healthy Italian children, aged between 5 and 11 years, attending individual primary school districts and living in two areas of Italy (Latium Region) characterized by two degrees of urbanization: a highly urban and a rural area. Details on the selected areas and the enrolment of school children were previously reported (Andreoli et al., 2012; Protano et al., 2010, 2012a, 2012b, 2012c, 2014). Briefly, the research project was described to all children and their families. Then, all the material useful to participate in the study (questionnaire, informed consent for parents and children aged nine or over, and containers for urine sampling) was delivered to children. The families that decided to participate returned to school with the self-administered questionnaire, other documents, and the urine samples on a previously agreed date. The questionnaire was elaborated "ad hoc" to obtain information about the children (gender, age, weight, height, ETS exposure status, use of medicines, special diet, parents' educational level, and the activities taken place during the sampling day). Details on the validation of the questionnaire are provided in Protano et al. (2017).

The research protocol, together with the questionnaire and the informed consent forms, was approved by the Ethical Committee of the teaching hospital Policlinico Umberto I of Rome, Italy (Protocol n. 2894/12.09.2013).

2.2. Sample collection and analytical determinations

Two spot urine samples for each participant were collected in a metal-free polyethylene high-density bottle during two consecutive weekdays; the first sample was collected in the evening of the first day (the last emiction before going to sleep) and the second in the early morning of the day after (the first emiction after waking up). Samples were immediately refrigerated and kept at 4 °C until the delivery to the laboratory, where each sample was subdivided in aliquots and frozen at −20 °C until the time of analyses.

The analytical procedure for the determination of Li in urine is described in detail in Protano et al. (2016) with certain modifications reported here. Briefly, the sample was thawed at room temperature and 1 mL was diluted to 10 mL with 1% (v/v) HNO_3 (67% nitric acid, Promochem, LGC Standards GmbH, Wesel, Germany, diluting with deionized water, produced by a deionizator Elga Lab Water Purelab Plus) in metal-free polyethylene tubes. This procedure allowed a significant reduction of the treatment time and sample manipulation with respect to microwave-assisted acid digestion, yet remained reliable and readily applicable to routine analysis (Protano et al., 2016).

The acidified solution was spiked with 100 μL of Yttrium 1 mg L^{-1} (internal standard); this internal standard was prepared by properly diluting a standard solution (1000 ± 2 mg L^{-1}; Panreac Química, Barcelona, Spain) with 1% HNO_3. Each solution was filtered through a syringe filter (cellulose nitrate membranes, 0.45 μM pore size, GVS Filter Technology, Indianapolis, USA), taking care to discard the first 5 mL of the solution, and placing in a new tube approximately 2.5 mL of the remaining solution. All filters were previously washed with 1% HNO_3 to reduce blank values.