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A Negative Association Between Lithium in Drinking Water and the Incidences of Homicides, in Greece

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Abstract The purpose of the present study was to evaluate the association between lithium levels in the public water supply and incidences of homicide in Greece. A total of 149 samples of drinking water were collected from 34 out of 52 prefectures, and data for homicides were taken from *National Statistic Service of Greece* (Hellenic Statistical Authority - EL.STAT). The average lithium level was 11.10 μg/l (SD=21.16). The results indicate that there is a tendency for lower mean number of homicides in the prefectures with high levels of lithium in drinking water (R^2=0.054, β=−0.38, p=.004). Considering the results of our previous study, which showed an inverse association between the lithium levels in drinking water and the incidence of suicide, homicide, rape, and drug abuse, we suggest that natural lithium level intake may influence impulsiveness, a factor that mediate to the manifestation of both suicidality and aggressiveness.

Keywords Trace element · Lithium · Drinking water · Homicide · Impulsivity · Mood disorders · Molecular pathway · Neurotoxins

Introduction

Lithium is widely used in pharmacological doses for the treatment of bipolar disorder and helps in the prevention of suicidal behavior as well as the reduction of impulsive aggression in patients with mood disorders [1–4]. An ecological study of Schrauzer and Shrestha [5] has shown an inverse association between the lithium levels in drinking water and the incidence rates of suicide, homicide, and rape. The purpose of the present study was to evaluate the association between lithium levels in the public water supply and homicide rates in Greece and

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present it in the context of our current knowledge on the effects of lithium intake.

Method

A total of 149 samples of drinking water were collected during 2012 from 34 out of the 51 prefectures of Greece. A team of researchers undertook the collection of drinking water from both rural and urban areas of these prefectures. Lithium levels were analyzed by inductively coupled plasma mass spectrometry (ICP-MS) [6]. Data for homicides, from 34 prefectures of Greece, were taken from the *National Statistic Service of Greece* (Hellenic Statistical Authority - EL.STAT) for the period of 2007–2011. The index of homicides was the mean of homicides per prefecture in Greece. Analyses were performed with the IBM Statistical Package for Social Sciences 20.

Results

The average lithium level, as evidenced by the raw values for the 34 prefectures of Greece, was 11.10 μg/l (SD=21.16). Four regressions (linear, exponential, inverse, linear weighted for prefecture population) were performed between lithium levels in drinking water as independent variable and mean number of homicides for the period of 2007–2011 as dependent variable (see Table 1 and Fig. 1). Table 1 displays the correlation between the variables, the standardized regression coefficients (β), the R, R^2 and the adjusted R^2. R for regression was significantly different from zero in the case of linear (F(1, 147)=8.338, p=.004) and exponential regression (F(1,147)= 6.327, p=.013), and 95 % confidence limits were calculated. Linear regression interprets the largest proportion of variance explained relative to the exponential and inverse regression analyses. However, the coefficient β of inverse regression analysis is shown to be higher than all other regressions. A negative correlation was observed between lithium levels in drinking water and homicides even after controlling for population per prefecture. R for regression, after weighted for prefecture population, was not significantly different from zero (F(1,147)=2.399, p=.124), but nevertheless, still a negative tendency was observed between lithium levels and homicide (see Table 1).

Discussion

A systematic tendency was observed in Greece for the negative association between homicides and lithium levels. When a linear regression analysis weighted by population was conducted, the results did not find a robust relationship between these two variables. After controlling for population, a negative association between our variables was also observed, but the proportion of the variance explained fell from 4.7 to 0.9 %.

Lithium, as a natural trace element, is washed out by rain from rocks and from the soil, dissolving in ground water and reaching the food chain via drinking water. In some regions, its concentrations may reach up to 5.2 mg/l, corresponding to a natural daily intake of lithium of up to 10 mg/l [7]. The biochemical mechanisms of action of lithium are considered to be connected with the functions of several enzymes, hormones, and vitamins, as well as with growth and transforming factors [8].

In animals, lithium upregulates neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor, neurotrophin-3 (NT3), as well as receptors to these growth factors in the brain. Lithium has been reported to be beneficial in animal models of brain injury, stroke, amyotrophic lateral sclerosis, spinal cord injury, and Alzheimer's, Huntington's, and Parkinson's diseases. It stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum, and forebrain. Lithium also remarkably protects neurons against glutamate, seizures, and apoptosis due to a wide variety of neurotoxins [9].

In humans, lithium treatment has been associated with humoral and structural evidence of neuroprotection, such as increased expression of antiapoptotic genes, inhibition of cellular oxidative stress, synthesis of brain-derived neurotrophic factor

Table 1 Four regression analyses of levels of lithium in drinking water on the mean number of homicides for years 2007–2009 per prefecture

	Predictor	Correlation homicides	β	R	R^2	Adjusted R^2
Linear	Lithium in drinking water	−.232**	−.038**	.232	.054	.047
Inverse	Lithium in drinking water	−.102	−.249	.102	.010	.004
Exponential	Lithium in drinking water	−.041*	−.007*	.203	.041	.035
Linear weighted by population per prefecture	Lithium in drinking water	−.200*[a]	−.127	.127	.016	,009

Dependent variable: mean prefecture number of homicides (period 2007–2011), (method enter)

*p<.05; **p<.01

[a] Partial correlation controlling for prefecture population

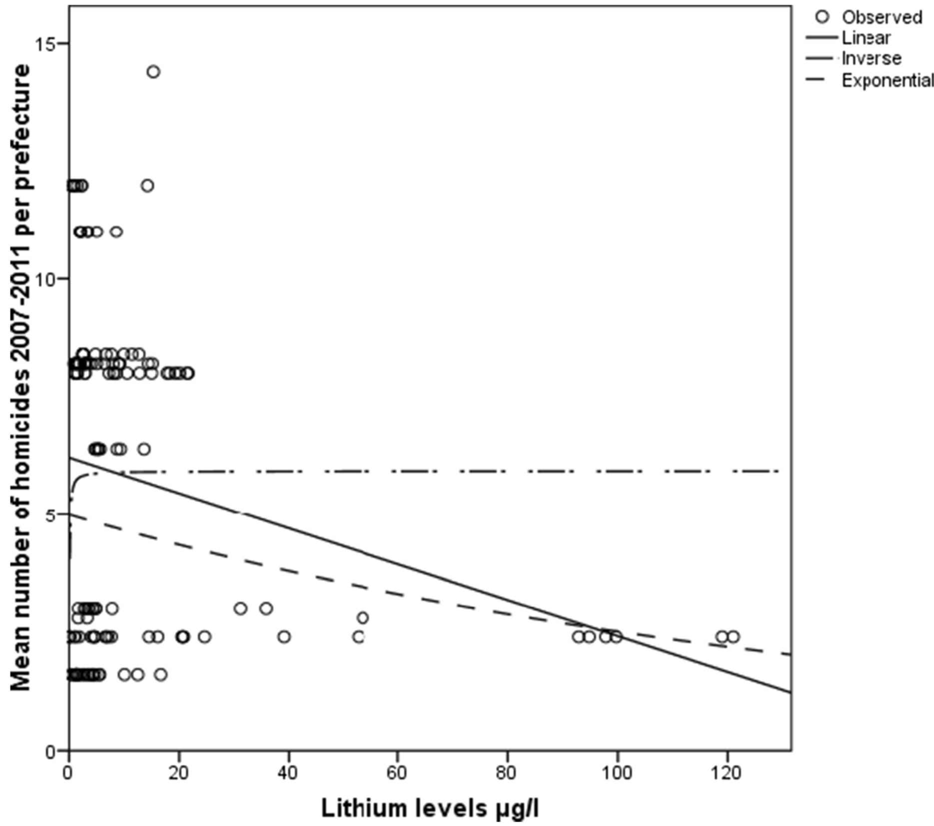

Fig. 1 Scatterplot between the mean number of homicides for 2007–2011 per prefecture and lithium levels in microgram per liter

(BDNF), cortical thickening, increased grey matter density, and hippocampal enlargement. Such a wide range of intracellular responses may be secondary to two key effects, that is, the inhibition of glycogen synthase kinase-3 beta (GSK3β) and inositol monophosphatase (IMP) by lithium [10]. Lithium acts through multiple pathways to inhibit GSK3 beta. This enzyme phosphorylates and inhibits nuclear factors that turn on cell growth and protection programs, including the nuclear factor of activated T cells (NFAT) and WNT/beta-catenin [9].

Lithium salts have a well-established role in the treatment of major affective disorders. Neuroimaging studies in humans have demonstrated that chronic use is associated with cortical thickening, higher volume of the hippocampus and amygdala, and neuronal viability in bipolar patients on lithium treatment. Chronic lithium intake is associated with a reduced risk of Alzheimer's disease in subjects with bipolar disorder, while chronic lithium treatment at subtherapeutic doses can reduce cerebral spinal fluid phosphorylated tau protein [11]. Therefore, lithium treatment may yield disease-modifying effects in AD, both by the specific modification of its pathophysiology via inhibition of overactive GSK3β and by the unspecific provision of neurotrophic and neuroprotective support [10]. Additionally, recent in vivo and in vitro studies indicate that lithium is able to ameliorate ethanol-induced neuroapoptosis. Lithium is an inhibitor of GSK3 which has recently been identified as a mediator of ethanol neurotoxicity [12].

There is increasing evidence from ecological studies that lithium levels in drinking water are inversely associated with suicide mortality [13–16], while some studies have shown that lithium is effective on the treatment of aggression and impulsivity, even as a low-dose supplementation [4, 17, 18]. The present study showed an inverse association between the lithium levels in drinking water and the incidence of homicides. These results are in accordance with that of the abovementioned ecological study of Schrauzer and Shrestha [5], which showed an inverse association between the lithium levels in drinking water and the incidence rates of suicide, homicide, and rape. The present study is an extension of a previous study that showed an inverse association between the lithium levels in drinking water and the incidence of suicide in Greece [16]. We suggest that intake of natural lithium levels may influence impulsiveness levels, which is a factor that mediate the manifestation of both suicidality and aggressiveness. Evidence from both basic and clinical researchers supports that lithium may decrease impulsivity. Based on findings that lithium inhibits both GSK3 isoenzymes, Jiménez et al. [19] analyzed the potential impact of genetic variants located at the GSK3α and β genes on impulsivity levels. They found that genetic variability at GSK3β gene was associated with increased impulsivity in bipolar patients. Furthermore, a recent meta-analysis

[20] in 48 randomized control trials comparing lithium with placebo or active drugs in a long-term treatment for mood disorders found that lithium is an effective treatment for reducing the risk of suicide in people with mood disorders, and the authors suggested that impulsivity might be a mechanism mediating the antisuicidal effect. Finally, the present results pose the question of whether the prospect of adding lithium to drinking water is realistic, weighing the benefits and potential risks [21–24].

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