

Lithium and phosphorylation cell reactions

Lítio e reações celulares de fosfo/defosforilação

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Having read with great interest your excellent review of endocrine aspects of lithium treatments (1), I would like to contribute and share data extracted from our particular clinical experience, concerning to the effect of lithium on the thyroid gland and its mechanism of action. Being in complete agreement with your review about the relationship between lithium and alterations of the thyroid gland, we go further by stating that almost 100% of patients treated with lithium, in a dose-related manner, have decreased FT₄ levels compared with baseline values; although, in absolute terms, these values are within the normal range, coinciding our data about thyroid disorders with the results described in your article (goitrogenic potential of Lithium can be manifested in up to 50% of patients).

This dose-dependent decrease in FT₄ levels has allowed us to use it as Surrogate Biomarker, for patients treated with lithium salts. It is also useful to calculate the dosing regimens of the patients by adjusting the dose up to FT₄ values: 1.0-1.1 mcg/mL, its Clinical Surrogate Endpoint. If this level of FT₄ is achieved and TSH values rise above 4 mIU/mL, it should be valued starting treatment with 25-50 mcg of levothyroxine, as we have explained in Biomarker (2), as follows:

All the pharmacological activity of lithium salts is carried out by the insolubilization of intracellular inorganic phosphate salts by means of the formation of inorganic lithium phosphates. These phosphates have much lower solubility than their sodium salts (*e.g.*, the solubility of Li₃PO₄ in water is 0.03821 g/dL/20°C versus that of Na₃PO₄, which is 8.8 g/dL/25°C), leading to a decrease in the amount of intracellular inorganic soluble phosphates (P_i), and consequently causing a decrease in intracellular phosphate stored in organic compounds (P_o), and a slowdown in all metabolic reactions that involve exchange of inorganic phosphates, mainly those using ATP, but also those using other nucleotides with capacity for phosphate storage, as we know now, affecting, in a hierarchically manner, several intracellular pathways of activation and/or inhibition. Among others, those of GSK and inositol-phosphates are the first to be affected.

In the case of the thyroid gland, lithium salts cause a dose-dependent decrease in serum free thyroxine (FT₄) due to the very low solubility of inorganic lithium phosphates formed in the interior of target cells by action of lithium, which lead to a decrease in the intracellular pH and pH-dependent tyrosine iodination reaction, with consequent decrease in FT₄ levels, because the iodination of phenols is a direct reaction of iodine (I₂) with the phenolate ion, which is very sensitive to changes in pH, decreasing exponentially the rate of iodination when pH decreases.

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Due to lithium elimination by glomerular filtration, the population analysis conducted by Kernel's test has allowed us to detect two subpopulations related to serum creatinine and, therefore, with lithium clearance, caused by the presence of MDR1 polymorphisms, altering the aldosterone level and therefore the creatinine clearance, obtaining a equi-effective dose ratio (genotype: wild type/genotype: MDR1 polymorphic) in the range of 1.5-2.

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REFERENCES

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