Lithium in the Environment and in the Body

Authors: David, Katherine & Anja (Co-facilitators of the Cape Town Bipolar Support Group)
Email: feedback@philosophy.org.za
Published: November 2018 at http://www.bipolar.capetown/uploads/R06.pdf

Abstract: The purpose of this review is to provide a contextualised overview of Lithium in the environment and the body together with its physiological effects at various concentrations. It is hoped that the information presented here will allow policy makers at blood transfusion services at provincial and national levels to make evidence based decisions regarding the safety of blood products from donors who are taking lithium at therapeutic doses. We find that extemporaneous transfusions of blood from donors that are taking lithium at a therapeutic dose are neither toxic nor teratogenic and should therefore be allowed and even encouraged.

Introduction

Lithium is ubiquitous: it is present in varying concentrations[1] in the water we drink, in the sea, in the food that we eat and in the rocks and soil beneath our feet. Despite being an alkaline metal, lithium on our planet is only ever found in its ionic form as Li^+ or $Li^+_{(aq)}$. Because of lithium's concentration dependent effects on various biological functions it is essential that the concentration range should be specified when mentioning an effect.

At the one extreme, experimental animals raised on a diet deprived of lithium suffer from fertility problems, retarded development and reduced longevity. (Bowden, 2017) Although the exact mechanisms are not known, several authors conclude that lithium is probably an essential trace element in the diet. (Anke *et al*., 1991; Pickett & O'Dell, 1992; Schrauzer, 2002) At the other extreme, ingesting lithium in sufficient quantities to raise the concentration in the blood significantly higher than 1 $mmol.dm^{-3}$ is acutely toxic. (Jakobsson *et al*., 2017) This upper level however is not absolute *e.g.* elderly patients with impaired renal function may be more sensitive, while patients taking lithium as an acute therapy may have serum levels up to 1.5 $mmol.dm^{-3}$ (Bowden, 2017). In South Africa the upper most therapeutic level recommended is 1.2 $mmol.dm^{-3}$; however at 2.0 $mmol.dm^{-3}$ and higher lithium is undeniably toxic and may lead to seizures, permanent neurological damage, coma and death.

The levels of lithium in freshwater are highly variable depending on location. One survey (Ayotte *et al.,* 2011) found levels in well water at concentrations from less than 0.00014 $mmol.dm^{-3}$ to greater than 0.007 $mmol.dm^{-3}$. There is no consensus as to what is the optimum level of intake of lithium for populations or individuals; however sub-therapeutic levels of lithium may have a beneficial effect on mood disorders. (Jakobsson et al., 2017) Interestingly, several independent studies of different populations across the world have found an inverse statistical relation between the concentration of lithium in the drinking water and per capita suicide rates: the more lithium in the drinking water, the lower the suicide rate. (Schrauzer & Shrestha, 1990; Ohgami *et al*., 2009; Helbich *et al*. 2012; Giotakos *et al*., 2013; Blüml *et al*., 2013 and Kapusta *et al*. 2011). Another study by Giotakos *et al*.

[1] Concentrations in this review are always given in millimols per decilitre ($mmol.dm^{-3}$) equivalent to millimols per litre (mmol/L) in some publications or mEq/L in others, especially in American textbooks.

(2015) found an inverse correlation between the concentration lithium in the drinking water and homicide rates: the more lithium in the drinking water, the lower the rate of homicide. More generally, Zarse *et al*. (2011) conclude in the title to their study that "Low-dose lithium uptake promotes longevity in humans and metazoans." Their study was adjusted for age and morality from all causes, even when suicide was excluded. Of course, it would be wonderful at this point to declare water with a low concentration of lithium as an *elixir vitae*, however its effects appear to be more diverse. (See safety during pregnancy below.)

Safety of blood transfusion from a donor with a therapeutic serum level of lithium

The therapeutic serum levels of lithium used as an antimanic and/or mood stabiliser in South Africa range from 0.6 to 1.2 $mmol.dm^{-3}$. As a rule, patients in need of acute intervention are treated at a higher dose within this range and are titrated down to a lower maintenance dose once their condition stabilises. If a pint (450ml) of whole blood is drawn from such a patent, this same concentration of lithium will be present in the bag; however on the very rare occasion that a recipient reives a pint of whole blood from such a donor, the concentration of lithium in the recipient's blood will be diluted approximately ten-fold. Assuming that the recipient had 9 pints of blood and had 1 pint of lithium-containing whole blood transfused, that would leave the recipient with between 0.06 to 0.12 $mmol.dm^{-3}$ of lithium in his blood. This level is too low to have any therapeutic or toxic effect and will usually be cleared by the kidneys in a couple of days. The elimination half-life of lithium is about 18 to 24 hours. (Bowden, 2017)

More typically, a bag of donated whole blood will be separated into its components: red blood cells, platelets and plasma. Assuming that a bag of whole blood containing a therapeutic dose of lithium is separated out in this way, the physical quantity of lithium in the bag will be divided roughly in half between the plasma and the red blood cells. The amount present in the platelet fraction will be negligibly small. Red blood cells also exhibit an efflux of lithium that is dependent on the movement of sodium ions. (Canessa, M. *et al.*, 1980) The ratio of intracellular to extracellular concentrations of lithium in red blood cells is approximately one half as measured by Mendels & Frazer (1973). This represents a further 50% dilution of lithium in the red blood cell fraction of separated blood.

Safety during pregnancy

Lithium was formerly classed by the FDA as a Category D Drug *i.e.* A drug with a known teratogenic risk to a foetus, based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Since 2015 the former A, B, C, D, X categories were gradually phased out, replaced with narrative sections and subsections, such as

Pregnancy (includes Labor and Delivery):

- Pregnancy Exposure Registry
- Risk Summary
- Clinical Considerations
- Data

Lactation (includes Nursing Mothers)

- Risk Summary
- Clinical Considerations
- Data

(See FDA Pregnancy Categories)

In assessing the safety of lithium during pregnancy therefore, individual subsections should be considered rather than trying to force it into one or another former category. Epidemiological studies by Harari *et al*. (2015a,b) have found a positive correlation between exposure to lithium during pregnancy via drinking water and reduced thyroid function as well as and reduced birth weight. In the former case the median concentration of lithium in the blood was 0.0036 $mmol.dm^{-3}$ with a range of 0.000027 - 0.021 $mmol.dm^{-3}$. This is several orders of magnitude below the therapeutic dose of lithium; however it is not known whether another confounding factor was at work in these studies or whether some other substance in the water might be causally implicated. Rather than cautioning expectant mothers against drinking the available water the authors conclude that "Further studies are, however, necessary to confirm these findings and to understand the mechanisms involved." Harari *et al*. (2015b) One obvious difference between the women in these studies and a potential recipient of transfused blood containing a sub-therapeutic concentration of lithium is that of chronicity. The women in the study were exposed to low concentrations of lithium in their drinking water day in and day out for the entire duration of their pregnancy (and lactation) whereas a receipt of transfused blood containing a sub-therapeutic concentration of lithium would be a once off (extemporaneous) affair.

The deciding question for an ethics committees is whether lithium is a teratogen and more importantly, at what dose. A review by Giles & Bannigan (2006) of the effects of lithium at therapeutic doses on the outcome of human pregnancy concluded that "lithium is a "weak" teratogen in humans." Animal studies at comparable serum levels however did not evince any abnormalities. Nevertheless, as we have seen in the discussion above, a recipient of a blood product from a donor taking lithium at a therapeutic dose can expect to receive only on tenth to one twentieth of the given amount of lithium, which would soon be cleared from the circulation by the kidneys and again this would be a once off event.

Yacobi & Ornoy (2008) undertook a meta-study of all case reports as well as retrospective and prospective studies claiming to have found a possible teratogenic link to lithium exposure. The authors found 24 case reports, of which six infants had congenital anomalies, five having cardiac anomalies, one of them being Ebstein's anomaly (a congenital tricuspid valve defect). In the retrospective studies, of 225 registered cases there were 25 anomalies, 18 of which were cardiac and of those six had the Ebstein's anomaly. Another retrospective study of 59 cases found 7 anomalies, 4 of which were cardiac. None of the prospective studies of 296 live births found any increase in the rate of congenital anomalies, although two did have the Ebstein's anomaly. All of the case control studies for the Ebstein's anomaly were negative. Among 222 infants with Ebstein's anomaly, 44 of which with tricuspid atresia (missing or abnormally developed tricuspid valve), none of their mothers were taking lithium during pregnancy. The authors therefore conclude that,

"Considering the serious limitations of the retrospective and case control studies that are also retrospective, lithium does not seem to be a significant teratogen, and hence should be given, if indicated, in pregnancy." Hence if lithium is safe as a drug, where indicated, during pregnancy, receiving a transfusion of at least a ten-fold diluted dose of the same is probably even safer.

Pragmatics Considerations

Our environment is already awash with lithium at micromole levels of concentration. Furthermore as Harari *et al*. (2015b) point out, certain brands of bottled water contain lithium with elevated concentrations similar to the highest levels detected in their study, and they are on the increase. Perhaps manufactures are responding to a perceived demand for mineral water with a higher concentration of lithium; however more likely they are driving this demand by marketing their product as more salubrious. If the blood transfusion services were to be consistent by placing a blanket-ban on blood with elevated levels of lithium, these consumers should be excluded from donating.

Finally, there is the question of what to do about donations of blood containing therapeutic levels of lithium that the blood transfusion services are unaware of. Mary and John are real donors know to the authors; however their names have been changed to protect their identities. Both Mary and John have O negative blood. Mary has disclosed to her branch that she is taking lithium but has been urged by the personnel there to donate anyway. John has not disclosed that he is taking lithium but feels duty-bound to donate his blood because he has been told that it is given to babies and is in dire supply. We do not know how many such cases there are and testing every pint for the presence of lithium would be prohibitively expensive. Those taking lithium however already know the concentration of lithium in their own blood as this is checked at least every 6 months to verify that it is at a safe but efficacious level.

Conclusion

There is no conclusive empirical research that lithium at a ten or twenty-fold less than therapeutic dose, given as a single donation at a time, is either toxic or teratogenic. May of the older studies that have claimed that lithium is teratogenic have failed to take into account the base rate of deformations in the general population or have failed to take account of other medication patients may have been taking. Others that have demonstrated a teratogenic effect have done so at concentrations exceeding the safe, therapeutic limit in human patients. Therefore placing a blanket-ban on donations from patients taking lithium is unfounded when adhering to an evidence based approach. Donations of blood from such persons should therefore be allowed and even encouraged if they are deemed safe in all other respects.

References:

ANKE M. *et al.* (1991) The biological importance of lithium. *Lithium Biol Med* 149–167

AYOTTE, J. *et al.* (2011) *Trace elements and radon in groundwater across the United States, 1992–2003*. US Department of the Interior, US Geological Survey

BLÜML, V. *et al*. (2013) Lithium in the public water supply and suicide mortality in Texas. *J Psychiatr Res* **47**(3):407–411

BOWDEN, C. (2017) Lithium. **In** Kaplan and Sadock's Comprehensive Textbook of Psychiatry. (10th Ed.) Sadock, B., Sadock, V. & Ruiz, P. Eds. p. 3088 - 3101: Wolters Kluwer Health

CANESSA, M. *et al.* (1980) Increased sodium-lithium countertransport in red cells of patients with essential hypertension. N Engl J Med **302**(14):772–776

FDA Pregnancy Categories - FDA Pregnancy Risk Information: An Update. https://www.drugs.com/pregnancy-categories.html (accessed 10 November 2018)

GILES J. & BANNIGAN J. (2006) Teratogenic and developmental effects of lithium. *Curr Pharm Des*. **12**(12):1531-41.

GIOTAKOS, O. *et al*. (2013) Lithium in the public water supply and suicide mortality in Greece. *Biol Trace Elem Res* **156**(1–3):376–379

GIOTAKOS, O. *et al*. (2015) A negative association between lithium in drinking water and the incidences of homicides, in Greece. *Biol Trace Elem Res* **164**(2):165–168

HARARI F. *et al.* (2015a) Exposure to lithium and cesium through drinking water and thyroid function during pregnancy: a prospective cohort study. *Thyroid* **25**(11):1199-208

HARARI F. *et al.* (2015b) Environmental exposure to lithium during pregnancy and fetal size: a longitudinal study in the Argentinean Andes. *Environ Int* **77**:48–54

HELBICH, M. *et al*. (2012) Geospatial examination of lithium in drinking water and suicide mortality. *Int J Health Geogr* 13 June:11-19

JAKOBSSON, E. *et al.* (2017) Towards a Unified Understanding of Lithium Action in Basic Biology and its Significance for Applied Biology. *J Membrane Biol* **250**: 587–604

KAPUSTA, N. *et al*. (2011) Lithium in drinking water and suicide mortality. *Brit J Psychiatr* **198**(5):346–350

MENDELS, J. & FRAZER, A. (1973) Intracellular lithium concentration and clinical response: towards a membrane theory of depression. *J Psychiatr Res* **10**(1):9–18

OHGAMI, H. *et al.* (2009) Lithium levels in drinking water and risk of suicide. *Brit J Psychiatr* **194**(5):464–465

PICKETT, E. & O'DELL B. (1992) Evidence for dietary essentiality of lithium in the rat. *Biol Trace Elem Res* **34**(3): 299–319

SCHRAUZER, G. (2002) Lithium: occurrence, dietary intakes, nutritional essentiality. *J Am Coll Nutr* **21**(1): 14–21

SCHRAUZER G. & SHRESTHA K. (1990) Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. *Biol Trace Elem Res* **25**(2):105–113

Yacobi S. & Ornoy A. (2008) Is lithium a real teratogen? What can we conclude from the prospective versus retrospective studies? A review. *Isr J Psychiatry Relat Sci*. **45**(2):95-106.

ZARSE K. *et al*. (2011) Low-dose lithium uptake promotes longevity in humans and metazoans. *Eur J Nutr* **50**(5):387–389