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Lithium – Evaluation of a BAR

Assessment Values in Biological Material - Translation of the German version from 2013

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BAR (2012)	**50 µg lithium/l urine** Sampling time: not fixed
MAK value	–
CAS number	7439-93-2
Formula	Li
Molar mass	6.941 g/mol
Melting point	180.54 °C
Boiling point	1342 °C
Density at 20 °C	0.534 g/cm^3

Lithium belongs to the group of alkali metals and is a soft, silver-white metal. When cut open, it turns first yellowish, then grey. Lithium is the lightest of all metallic elements. It has a widespread occurrence in nature. Lithium and its compounds have several applications in industry, for example in the aerospace industry, in the production of rubber, batteries, photographic materials or X-ray films.

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1 Metabolism and Toxicokinetics

More than 90% of the absorbed lithium is eliminated via the kidneys (Arancibia et al. 1986). The half-life of the lithium plasma concentration is given as less than 24 hours (Allain et al. 1994). Obach et al. (1988) calculated a biological half-life of 17 ± 6 hours for lithium in plasma after oral administration. The half-life in saliva is 22 ± 14 hours.

The biomarker suggested by the toxicokinetic data is lithium in urine.

2 Critical Toxicity

Since around 1950, the therapeutic use of lithium salts in psychiatry has become extensive.

With increasing application, numerous adverse effects including lithium intoxications have been observed. In the scientific literature, many detailed descriptions of the side effects occurring in lithium therapy are available.

The main effects of lithium intoxication are neurological symptoms (apathy, myasthenia, ataxia, agitation, fasciculation, tremor, epileptiform attacks, stretching tonus, drop in blood pressure, shock and coma). In addition, gastrointestinal disorders (nausea, vomiting, diarrhoea) as well as an impairment of the renal function (in some cases acute renal failure) can occur. Hypopotassaemia, hyponatraemia and hypercalcaemia are further complications. Cardiovascular side effects of lithium therapy may also occur: in the electrocardiogram, for example, repolarization disturbances with a reversible flattening of the T wave may also be found. Occasionally, negative T peaks also occur.

A comprehensive description of the toxicity of lithium salts can be found in the report by Aral and Vecchio-Sadus (2008).

A lithium intoxication is generally the sequel of an overdose where control of the lithium level is absent, or of a reduced lithium clearance (in cases of dehydration, electrolytic fluxes etc.).

Therapeutic monitoring

The recommended initial dose in a lithium therapy in psychiatry is as a rule 12–24 mmol (450–900 mg) lithium carbonate/day, according to age and weight (Grandjean and Aubry 2009). As maintenance dose, Grandjean and Aubry (2009) describe 25–35 mmol (925–1300 mg) lithium carbonate for patients < 40 years, 20–25 mmol (740–925 mg) for patients aged 40–60 years and 15–20 mmol (550–740 mg) for patients > 60 years.

The administered daily lithium dose correlates significantly with the lithium level in serum. The narrow therapeutic range of lithium requires optimum monitoring based on analysis of lithium in serum. It is generally accepted that the therapeutic dose as internal exposure should be 0.6–0.8 mmol lithium/l serum (corresponding to 4.2–5.6 mg/l serum), although some authors favour a serum lithium level of 0.8–1.2 mmol/l (corresponding to 5.6–8.3 mg/l serum) (Grandjean and Aubry 2009).

In the USA, a daily diet-related intake of 1 mg lithium is recommended for adults (70 kg) (Aral and Vecchio-Sadus 2008).

3 Exposure and Effects

There are no relevant occupational-medical or environmental studies available for the external or internal exposure and effects.

Bencze et al. (1991) investigated the external and internal lithium burden following occupational exposure to a lithium-aluminium alloy. No usable data could be obtained which would allow to establish a biological limit value.

4 Selection of Indicators

An increased absorption of lithium and its salts can be detected by analysing lithium in the biological body fluids, i.e. whole blood, serum, plasma, urine or saliva. In therapy control in the field of psychiatry, lithium is determined in plasma or serum (El Balkhi et al. 2009; Grandjean and Aubry 2009). The usefulness of saliva as a matrix for the detection of lithium is subject to debate (Obach et al. 1988). Urinalysis is preferred for the quantification of occupational or environmental exposures. In the literature, there are numerous data available for the parameter lithium in urine as reference value of environmental exposure (Abou-Shakra et al. 1989; Dol et al. 1992; Heitland and Köster 2004, 2006; Iguchi et al. 1999). Furthermore, the fact that more than 90% of the lithium absorbed by the organism is excreted via the kidneys is an argument in favour of lithium in urine as parameter (Arancibia et al. 1986).

In an Argentinian environmental study, it could also be demonstrated that lithium excretion with the urine is a good way of documenting the intake of lithium from the drinking water. To evaluate exposure to various toxic metals, the concentrations of 31 elements were analysed in the drinking water and in the urine of village inhabitants in a region with potential geogenic exposure. In 161 women from San Antonio de los Cobres in the province of Salta, a village with a very high lithium exposure (1000 µg/l) in the drinking water, the median lithium excretion was 4550 µg/l (range 852–14 300 µg/l) (Concha et al. 2010).

5 Analytical Methods

In the past, atomic absorption spectrometry (AAS) was used to determine lithium in biological materials (Trapp 1985). Today analytical methods using inductively coupled plasma (ICP), which are very sensitive and reliable, are almost exclusively used (Vanhoe et al. 1995). ICP is coupled with mass spectrometry (ICP-MS) (Bocca et al. 2005; Heitland and Köster 2004, 2006) or with optical emission spectrometry (ICP-OES) (Bianchi et al. 2007; Bocca et al. 2005). A tested and reliable ICP-OES method has been evaluated by the MAK Commission's working group "Analyses in Biological Materials" (Schramel et al. 1997). The detection limit is 2 µg/l urine. With ICP-MS methods, the detection limits are < 0.02 µg/l.

6 Background exposure

Table 1 shows the results of studies on the internal lithium exposure of adults not occupationally exposed to lithium, i.e. the lithium levels in whole blood, serum and in urine samples. With the exception of the use of one atomic absorption spectrometric method, all lithium analyses were carried out with ICP techniques. Most results are available for renal lithium elimination. Among these, there are two studies from Germany conducted in the years 2004 and 2006 with reliable ICP-MS analysis (Heitland and Köster 2004, 2006).

Tab. 1 Lithium concentrations [µg/l] in blood, serum and urine from studies on environmental exposure to lithium

Country	Assay material	n	MV	Median	GM	Range	P95	Method	References
Italy	blood	110	0.86 ± 0.54	0.71	n. d.	0.2–1.87[a)]	1.9	ICP-MS	Alimonti et al. (2005)
Switzerland	serum	110	1.82 ± 5.14	1.00	n. d.	< 0.1–7.25[a)]	7.3	ICP-MS	Forrer et al. (2001)
Italy	serum	110	1.09 ± 0.63	0.97	n. d.	0.36–2.2[a)]	2.2	ICP-MS	Alimonti et al. (2005)
UK	urine	50	n. d.	9.6	n. d.	0.8–40.5	n. d.	ICP-MS	Abou-Shakra et al. 1989)
Uruguay	urine	10	n. d.	n. d.	29.3	n. d.	n. d.	F-AES	Dol et al. (1992)
Japan	urine	86	n. d.	n. d.	23.5	8–54	42	ICP-OES	Iguchi et al. (1999)
Germany	urine	63	18	n. d.	14	3–86	47	ICP-MS	Heitland and Köster (2004)
Germany	urine	87	35	n. d.	23	4–237	115	ICP-MS	Heitland and Köster (2006)

[a)] 5^{th}–95^{th} percentile

F-AES = flame atomic emission spectrometry; GM = geometric mean; ICP-MS = mass spectrometry with inductively coupled plasma; ICP-OES = optic emission spectrometry with inductively coupled plasma; MV = mean value ± standard deviation; n. d. = no data; P95 = 95^{th} percentile

7 Evaluation

As described in Section 4, the determination of the urinary lithium excretion is best suited for recording environmentally caused lithium exposure. Table 1 shows the median and mean values and ranges obtained for renal lithium excretion in these studies. The median or mean values vary between 9.6 and 35 µg/l. In three studies, the 95^{th} percentile was calculated. These values vary between 42 and 115 µg/l urine.

For the evaluation of a biological reference value (BAR), the German studies are primarily used, as it is a known fact that the usual lithium excretion is related primarily to the diet. In the studies carried out by Heitland and Köster (2004, 2006) in Germany, the calculated 95^{th} percentiles were 47 and 115 µg/l. From these studies, no reason can be given why there is such a discrepancy in these values despite similar analytical methods used. Essentially, the 95^{th} percentile of 47 µg/l is in conformity with the results from the non-German studies listed (see Table 1; Abou-Shakra et al. 1989; Iguchi et al. 1999). Therefore,

a BAR of 50 µg lithium/l urine

is established.

There is no fixed sampling time required.

However, this value can be regarded as provisional only and must be verified by further studies.

8 Interpretation of results

The BAR for lithium relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l. In addition to this, the Commission considers it useful, for further improving the validity of the analyses, to select a narrower target range of 0.5–2.5 g/l for urine samples. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended (Bader et al. 2016).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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