# ABSTRACT

Lithium Poisoning: determinants of inter-individual variability and requirement for extracorporeal removal in lithium poisoning

**Methods:** We developed rat models to mimic the different lithium poisoning patterns in humans. This lecture will present various experimental data obtained aiming to better understand the determinants of inter-individual variability in lithium poisoning. We also collected clinical data obtained in lithium-poisoned patients. This lecture will present guidelines to improve indications of hemodialysis.

**Results:** First, we showed that prolonged rat exposure results in brain lithium accumulation, which is more marked in the presence of renal failure. Differences in plasma and brain kinetics at least partially explains the observed variability between intoxication patterns. Severity of lithium-induced encephalopathy measured based on EEG is dependent on the poisoning pattern. Similarly, differences in lithium-related effects in overdose on locomotor activity between poisoning patterns are explained by the duration of lithium exposure better than by its brain accumulation. Regarding hemodialysis in lithium-poisoned patients, EXTRIP workgroup recommends hemodialysis if kidney function is impaired and serum lithium >4.0mmol/L; in the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias, irrespective of serum lithium. EXTRIP workgroup suggests hemodialysis if serum lithium is >5.0mmol/L; if confusion is present; and if expected time to obtain a lithium <1.0mmol/L with optimal management is >36 h. We showed that performance of simple Paris criteria (serum lithium ≥5.2mmol/L or serum creatinine ≥200µmol/L) are better.

**Conclusions:** Our experimental models suggest that the three different presentations of lithium poisonings in humans differ due to lithium blood pharmacokinetics and brain distribution. Poisoning severity if related to the duration of exposure and to the brain accumulation of lithium. Hemodialysis is recommended in patients with severe Li poisoning. However, its indications and benefits are still debated.

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**研究方法：**

以大鼠作為模型，模擬人體內鋰鹽中毒的不同模式，本講座將分享實驗數據，同時也蒐集了鋰鹽中毒患者的臨床數據，以進一步了解鋰鹽中毒個體間差異的決定因素，並將提出改善血液透析適應症的指導方針。

**研究結果：**

我們發現長時間的暴露會導致大鼠腦中鋰的蓄積，這在腎衰竭的情況下更為明顯。血漿和腦部分布動力學的差異至少部分解釋了先前所觀察到的中毒模式之間的差異。根據腦波檢查所量測由鋰誘發的腦病變的嚴重程度取決於中毒模式。同樣地，於不同中毒模式中，過量攝入鋰對大鼠的自發活動的影響具有差異性，相較於腦部累積，更可以採用鋰暴露的持續時間作為解釋。

對於鋰鹽中毒患者的血液透析適應症，一般建議血清鋰 >5.0 mmol/L進行血液透析；若患者有腎功能受損則建議血清鋰 >4.0 mmol/L進行血液透析；若患者出現意識狀況惡化、癲癇發作或危及生命的心律失常，無論血清鋰濃度如何皆應進行血液透析；若患者意識混亂(GCS: 12-13分)，中毒後36小時預期血清鋰濃度仍 >1.0 mmol/L建議血液透析*。而我們的研究發現，使用巴黎標準(Paris criteria)：血清鋰 ≥ 5.2 mmol/L或血清肌酸酐 ≥ 200 µmol/L (≥ 2.26 mg/dL)作為血液透析適應症標準較為簡單且適用。

*譯註：預期血清鋰濃度計算公式為$Ct = C0 \times e^{-kt}$，Ct: future concentrations, C0: initial concentration, k = (0.161 × eGFR + 6.47)/55，本講座講者引述文獻為Buckley等人於2020發表於British Journal of Clinical Phamacology之研究。

**結論：**

我們的實驗模型顯示，人體中毒個案存在三種不同的中毒表現，因鋰鹽於血中之藥物動力學和大腦分佈具有差異性。中毒的嚴重程度與持續暴露時間和大腦中鋰的累積有關。嚴重鋰鹽中毒患者建議進行血液透析，然而其適應症和益處仍有爭議。