About baclofen withdrawal syndrome

À propos d’un syndrome de sevrage au baclofène

Introduction
Baclofen acts as an agonist of gamma-aminobutyric acid (GABA) B receptors. This medication decreases muscle spasticity caused by multiple sclerosis or spinal cord injury. Since 2008, off-label baclofen is prescribed for alcohol use disorders. This off-label baclofen use resulted to the publication of a best-selling book, *The end of my addiction*; written by Olivier Ameisen [1]. This cardiologist first postulated that suppression of symptoms should be the aim of treatment for addiction. Baclofen was the drug of choice for suppressing motivation to consume alcohol. Its effect is dose-dependent.

To date, results from randomized clinical trials are conflicting [2,3]. The French medicines and healthcare products regulatory agency published a “temporary recommendations for use” for baclofen use in patients with alcohol use disorders. Whereas standard maintenance dose is 40–80 mg/d, maximal reported doses for alcohol use disorders range from 71 to 284 mg/d [4]. Clinical manifestations of withdrawal syndrome include restlessness, insomnia, confusion, hallucinations, seizures, psychotic mania or paranoid states, dyskinesia, fever and worsening spasticity. The abrupt withdrawal of oral baclofen resulted to unexplained fever description or extrapyramidal syndrome with dystautonomia after weaning dose of 240 mg/d [5-7]. We report here a case of baclofen withdrawal syndrome secondary to an abrupt cessation of very high-dose treatment for alcohol use disorders, mimicking neuroleptic malignant syndrome in a 33-years-old patient.

Case report
A 33-years-old female was admitted to emergency room for fatigue, vomiting and neurological disorders. In her past medical history, we noted alcohol consumption (150 g/d), active smoking and hypothyroidism (treated with levothyroxine). Clinical examination revealed acute neurological disorders including confusion and extremity and head tremors. Blood sample analysis showed hypokalemia (1.5 mmol/l), hyponatremia (124 mmol/l), hypochloremia (52 mmol/l), and increased bicarbonates (51 mmol/l). Serum ethanol concentration was 1.3 g/l. As a history of convulsions was suspected, a brain computed tomography scan and a lumbar puncture were considered as normal.

She was admitted to the nephrology acute care unit. At day 4, her clinical status worsened. She was febrile (40 °C), tachypneic, tachycardic, icteric, oliguric with mottling at the level of lower limbs. She had an extracellular dehydration. Mean arterial pressure was above 70 mmHg. The Glasgow Coma Scale score was assessed at 13. Confusion was diagnosed with a spatial disorientation. Her pupils were dilated and reactive to light. She did not exhibit sensory or motor deficit. The plantar response was in flexion. The patient had a global increased muscle tone, predominating at the level of head rotated to the left side and upper limbs. Laboratory values showed a plasma lactate concentration at 8 mmol/L, a rhabdomyolysis with creatine phosphokinase (CPK) concentration at 6185 UI/L, an hepatic cytolysis [aspartate transaminase (AST) 215 UI/L, alanine transaminase (ALT) 104 UI/L], cholestasis (GGT 1485 UI/L, alkaline phosphatase 258 UI/L), hyperbilirubinaemia at 61 μmol/L. Prothrombin time, platelets and the other biological variables were in normal ranges. The patient was then transferred to intensive care unit (ICU).

A transthoracic echocardiography showed signs suggesting a preload dependence. Abdominal echocardiography and whole-body computed tomography scan did not show abnormal images. The family reported that the patient received up to 560 mg/d baclofen for alcohol-dependence suppression. The medication was initially prescribed by a psychiatrist. The patient developed self-medication. Because she had an acute gastroenteritis, the patient stopped abruptly her treatment by baclofen. In parallel, she reduced her alcohol consumption (acute gastroenteritis can explain the initial metabolic alkalosis, hypokalemia and hyponatremia). Her management consisted of fluid resuscitation with crystalloids (2 l). Baclofen (60 mg/d) was reintroduced. Clonidine and benzodiazepine (oxazepam) were administered for treating the withdrawal syndrome. After two days in the ICU, blood sample showed an increase of rhabdomyolysis (CPK peaked at 26,144 IU/L). There was no acute renal failure. Increased muscle tone and hyperthermia (body temperature at 40 °C) persisted. In the next days, the patient experienced a full recovery, all biological variables were in normal range, and there were no argument for alcoholic hepatitis diagnosis. The ICU team requested a psychiatric consultation. Then, the patient was transferred to psychiatry unit. A report was sent to our drug-monitoring department for safety issue with baclofen.

Discussion
The mechanism of action of baclofen is not fully understood. It activates the GABA-B receptor. It acts as muscle relaxant in patients with increased motor tone. The structural analogy with the GABA, a neurotransmitter involved in addictions, has led practitioners to make the assumption that baclofen could suppress alcohol-dependence [8]. This led to its use to treat withdrawal syndromes. Higher doses than in patients with spasticity are administered in this indication. However, the French medicines and healthcare products regulatory agency clearly states that the dose of 300 mg/day should never be exceeded. A reduction of dose should be considered regularly. The lowest effective dose should be used in those patients. In addition, it is...
stated that treatment should be gradually decreased in order to avoid a withdrawal syndrome. Indeed, its brutal interruption may be associated with a withdrawal syndrome. Symptoms include hallucinations, delusion, confusion, disorientation, and nausea. Tachycardia, tremors, seizures, autonomic dysfunction, hyperthermia and muscle rigidity are observed. The clinical picture suggests a neuroleptic malignant syndrome. However, malignant syndromes may develop with a wide variety of treatments. They are characterized by the development of consciousness disturbances, hyperthermia, autonomic nervous system dysfunction and muscle rigidity. Actually, the clinical picture of our patient shared the features of the diagnostic criteria outlined in the Diagnostic and statistical manual of mental disorders. Disorders for the neuroleptic malignant syndrome including severe muscle rigidity and high temperature as well as tremor, tachycardia, elevated CPK and impaired consciousness [9].

Risk factors for developing a withdrawal syndrome associated with baclofen interruption are the duration of exposure, brutal interruption, high doses and oral administration. The rapid disappearance of symptoms after the medication reintroduction confirms the diagnosis [6,10-13]. In our patient, the reintroduction of baclofen rapidly led to a clinical improvement. However, the use of adjunctive drugs like clomazone or benzodiazepine probably interferes with the baclofen reintroduction.

In conclusion, the number of patients treated with high-dose baclofen is constantly increasing. The baclofen withdrawal syndrome should be suggested in patients with neurological impairment and muscle rigidity. The management relies mainly on the reintroduction of baclofen.

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References

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Cryptococcose neuro-méningée : y penser en dehors du VIH

Cryptococcal meningitis: It is not only an AIDS-associated disease

Introduction
La cryptococcose est une pathologie opportuniste bien décrite chez les sujets porteurs d’un déficit immunitaire profond, en particulier le virus de l’inmunodéficience humaine (VIIH). C’est une infection fungique grave, notamment en raison de son tropisme neuro-méningée. Son diagnostic est difficile en l’absence de facteur favorisant au premier abord. Nous rappor-tons ici le cas d’une cryptococcose neuro-méningée d’évolution favorable chez un patient de 63 ans non VIH. Il sera découvert au