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Aldicarb Poisoning: Symptoms of Poisoning Inhibitors Carbamate Acetylcholinesterase

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1 Introduction

Acute poisoning with pesticides is a public health problem because it is responsible for 300,000 deaths per year worldwide. [1] Inevitably, they are the products of choice for autolysis attempts because of their wide availability [2]. There are two types of inhibitors of cholinesterases: organophosphates and carbamates. The former are used as pesticides or as a chemical weapon, the latter are rather insecticides used in agriculture or neurotropic drugs (Alzheimer's disease, myasthenia gravis).

The Aldicarb is a phytosanitary product, carbamate, prohibits the use in the European Union and which until 2007 enjoyed a derogation for sugar beet and vines in France. There are certainly unused stocks available for fraudulent use even today. The Aldicarb or 2-methyl-2- (methylthio) propionaldehyde-O- (methylcarbamoyl) oxime is used as a pesticide since 1965 under the trade name Temik © (cropscience Aventis, France) or Cardinal © (Bayer cropscience, France) and illegally as a rodenticide ("Tres Pasitos"). Due to the use of pesticides in agricultural regions like Aquitaine and after a previous case of criminal poisoning Aldicarb at the University Hospital of Bordeaux [3], we describe in this observation, the classic symptoms of poisoning to carbamate insisting toxidrome cholinergic caricature which is the single clinical element in a concealed exhibition context.

2 Observation

Our case is that of a woman of 40 who no particular history and takes no treatment apart from dietary supplements as part of a diet. The history of the disease began around 12:30 pm by malaise with paresis and paresthesia of the left hand. The patient had asthenia, diarrhea and vomiting, then decided to go and rest in his room at 13:00. She was found unconscious in his bed by his family around 13:30.

The initial assessment conducted by the SAMU team found a GCS 9, global hypotonia associated with tight bilateral miosis, wheezing with rhonchus diffuse and saturation 68% on room air and a significant salivation. Blood pressure was 160/40 mmHg, heart rate 55/min. The combination of a miosis, diarrhea with vomiting and bronchial and salivary hypersecretion suspect was a muscarinic syndrome. The injection of 1 mg of atropine allowed to regain a heart rate of 70 / min but without respiratory or neurological improvement. Intubated due to neurological failure and hypoxic pulmonary likely by inhalation, she was transferred to intensive care.

In the ICU, hemodynamics were initially stable without catecholamine with a blood pressure at 110/80 mmHg, a heart rate of 90 / min. SpO2 was 94% under a FiO2 of 70%. The brain scan, lumbar puncture and EEG were unremarkable. Biology found hypokalemia to 2.81 mmol/L, blood gases were within a mixed acidosis and capillary blood glucose was 2.21 g/L.

She quickly introduced a respiratory deterioration of aspiration pneumonia with acute respiratory distress syndrome aggravated septic shock requiring the use of pressor amines. Finally extubated six days later, she was transferred in monitoring for further investigations.

A thorough toxicological investigation did not find a contact with any toxic. The patient informed us she was doing for two months a strict low-calorie diet combined with daily physical hyperactivity with a loss of 10 kg. The main hypothesis seemed then be hypokalemia Contributed by deficiency with muscle and neurological symptoms. She could reach his home after correction fluid and electrolyte disorders and instructed to discontinue her diet.

The same evening, the ambulance was contacted at 21:30 for vigilance disorders with dyspnea at the family country house. Support by the Smur found a coma with GCS 8, bilateral miosis, salivation, sweating and a heart rate of 53 / min. After initial treatment with 80 mg of furosemide and a test negative flumazenil, she was finally intubated due to respiratory distress.

In the ICU, hemodynamics was stable without amines, saturation was 100% under FiO2 50%, it had a 33.6 ° C hypothermia, and hyperglycemia to 3 g / L. No metabolic disorder initially found, including serum potassium 3.85 mmol / L, there was, however leukocytosis 21.7 G / L (18.42 G / L neutrophils). The chest X-ray did not find infectious outbreak, the brain scan was normal. At J1, it presented a significant need for potassium intake without etiology found encouraging us to realize a abdominopelvic CT scan (Fig. 1) including looking for a neuroendocrine adrenal tumor, finding a pancolique inflammation with effusion of Douglas. On termination of sedation she remained somnolent, he continued tight bilateral miosis not resolutive after a test with naloxone as well as bradycardia with hypotension. It also included sweating, salivation and a severe diarrhea with vomiting despite nasogastric tube. This probable cholinergic syndrome was consistent with poisoning inhibitors indeterminate nature of cholinesterase or cholinomimetics. Treatment with pralidoxime was established by injection of 1,400 mg relayed by 500 mg / h for three days after making all plasma and urine samples for toxicology screening and a hair sample to affirm the involvement of a toxic during the first hospitalization. Vomiting and 'hypersal'hypersalivation is amendèrent, wards regained a normal size, and heart rate returned to normal gradually. The next day, the plasma activity of pseudocholinesterase returned collapsed below the detection limit of 1000 U/L.

Extubated on Day 3, the questioning found no toxic voluntary decision or arguments for any autoagressif gesture. Secondarily, liquid chromatography coupled to detection by mass spectrometry in tandem found a serum concentration of Aldicarb 5700 ug / L, of Aldicarb sulfone (metabolite) to 58 mg / L and Aldicarb sulfoxide (metabolite) to 4500 mg / L may explain all the symptoms. Before returning home, we sent our patient to a medical examiner to our emergency reception center for victims of abuse to put in place the necessary legal steps. The first post information reported by the patient orientaient us to a criminal case.

3 Discussion

Carbamates represent a heterogeneous family of molecules characterized by the presence of carbamyl function type -O-CO-NH-. The Aldicarb has the characteristic of binding to the site esterase through structural analogy with acetylcholine (Fig. 2). Competitive inhibition by carbamylation of the active site is reversible unlike organophosphates which, by phosphorylation, produces strong covalent bonds. [4]

Physiologically, there are three types of enzymes cholinesterase activity: globular acetylcholinesterase neuronal acetylcholinesterase and plasma butyrylcholinesterase (or pseudocholinesterase) [5]. It is not possible to measure the activity of neuronal cholinesterase in plasma but it seems that the globular activity is very similar to that of the nervous system. [6] However, the measurement of blood cell activity is not available in emergency while measuring the pseudocholinestérasique activity is more readily available. A moderate decline in activity seudocholinestérase may be in situations like pregnancy, liver cirrhosis or a taking metoclopramide [4], but a major collapse below the detection threshold directs more readily on organophosphate poisoning or carbamates.

As regards Aldicarb, the oral LD50 is 0.8 mg / kg in rats [7]. Aldicarb is rapidly oxidized by hepatic microsomal enzymes Aldicarb sulfoxide, which is then metabolized more slowly by oxidation and hydrolysis in Aldicarb sulfone. Aldicarb sulfoxide and sulfone, high anticholinesterase activity, are then detoxified by hydrolysis oximes and nitrites. In mammals, 80% of metabolites are excreted in the urine within the first 24 hours [8]. Clinical

signs of poisoning appear within 5 minutes in case of ingestion of large doses highlighting the speed of digestive absorption although it is also described transcutaneous passages. The rapid elimination of this product allows theoretically spontaneous recovery within 6 h.

All clinical signs are grouped in a toxidrome named "cholinergic syndrome" or "cholinergic crisis". This includes toxidrome muscarinic component (bradycardia, hypotension, hypercrinie, diarrhea, vomiting, bronchoconstriction, miosis), a nicotinic component (twitching, muscle paralysis) and a central component (disorder of vigilance, convulsion). Carbamate poisoning occurs most often in pure form muscarinic, nicotinic syndrome is rarer than organophosphates and limited central syndrome has vigilance disorders [9,10]. The deep and multi-factor hypoxia is responsible for early death in the absence of treatment. Hypokalemia is frequently described with acute poisoning by cholinesterase inhibitors in connection with important digestive losses diarrhea but especially by a cell transfer phenomenon due to hyperadrenergy the initial phase of the cholinergic syndrome. [11] This phenomenon also explains leukocytosis and hyperglycemia in the initial phase of the intoxication [12]. Digestive invasion type pancreatitis [13] or peritoneal effusion [10] is sometimes described, however the scannographic highlight of colitis is a novelty of our clinical case.

The antidote is the first line atropine by its antagonistic action on the postsynaptic acetylcholine receptors [5]. In this indication, the dosage is much higher than its usual effect vagolytic and includes a loading dose of 1 to 2 mg followed by reinjection iterative resolution to muscarinic syndrome. Pralidoxime acts specifically on organophosphates by enzymatic regeneration by activating spontaneous dephosphorylation of its active site. Its use is based on a bolus of 30 mg/kg followed by an interview with the syringe autopulsée at a dose of 8 mg.kg-1.h-1. [14] In contrast, in the case of carbamates, enzyme inhibition is reversible spontaneously in a few hours and the use of pralidoxime is unnecessary and not recommended [15-17].

The first intervention of the SAMU team, initial treatment with atropine was wise but the doses were too low and the diagnostic approach was unfortunately interrupted by the need for tracheal intubation. Several series show the advantage of very high doses of atropine early to fight against the effects of acetylcholine. [18] It is sometimes necessary to use tens of milligrams to obtain an efficiency judged by the drying up of bronchial secretions more than the resolution of miosis. [17] There are several different administration protocols: some are based on a loading dose of 2 mg every 5 to 10 minutes followed by continuous administration of 1 to 6 mg / h [19,20] others require bolus croissants iterative 3 mg doubles every 5 min [6,15]. In our clinical case, the family-examination during the first hospitalization in the ICU did not allow us to talk again toxic hypothesis and to continue treatment in this direction. The second intervention Samu seemed to move initially on benzodiazepine intoxication invalidated by a test negative flumazenil. The impregnation toxic seemed this time since, greater lifting sedation, cholinergic signs were always present.

The uncertainty about the possibility of poisoning by pesticides has led us to use the pralidoxime. In fact many studies question the use of oxime as part of carbamate poisoning [6.21]. Indeed, several tests on laboratory animals show an increase of anticholinesterase effect by the use of pralidoxime during carbamate poisoning [22] and in particular used alone in the absence of atropine [23]. The improvement in clinical status of our patient addicted to carbamates, was probably secondary to spontaneous regeneration cholinesterase. However, one might consider the use of pralidoxime and second-line in combination with atropine in case of severe poisoning inhibitor of acetylcholinesterase unidentified [24] but also in case of ineffectiveness or atropine mixed poisoning with organophosphorus [25].

4 Conclusion

The great diagnostic difficulty is noted in the context of a concealed intoxication that prevents a uniform therapeutic management as proposed by the different recommendations. Close collaboration between clinicians, biologists and toxicologists is essential to mention the different diagnoses and propose specific therapeutic approaches. Atropine remains the reference antidote for poisoning cholinesterase inhibitors, pralidoxime not considering together in second-line in limited indications.

Conflict of interest

The authors declare no conflict of interest.

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