Aminophylline intoxication: a fatal case

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Abstract

Aminophylline is a widely used drug for breathing disorders, reason why it is of the utmost importance to keep in mind its potential side effects, often life threatening. Severe aminophylline intoxication is associated to an increased morbidity and mortality. Formulations of delayed release are associated to higher complications incidence.1 Regarding a clinical case due to aminophylline intoxication, the authors make a short review on the drug properties, the intoxication type, acute and/or chronic intoxication main clinical manifestations and the due treatment.

Worth mentioning the theophyllinemia found in our clinical case is significantly higher (148ng/ml), than the mentioned in the reminder of published cases.

CLINICAL CASE

Male patient, 48 years old, single with a pathology history known as Chronic Obstructive Pulmonary Disease and Schizophrenia.

Taking as usual monthly medication Haloperidol Decanoate, Lorazepam 2.5 mg id and Filotempo 225 mg 2id. He had important smoking and coffee intake habits. Referred by the Health Center of his residence area to the Emergency Service of Hospital S. Teotónio (HST) in Viseu due to a change on his awareness state and psychomotor restlessness. According information from the patient's father, this had shown suicide intent and behavioral changes in the preceding days.

On admission at the Emergency Service he was aware, not very cooperative showing psychomotor restlessness. Objectively, he was sweating, hypotensive (BP 70/45 mmHg), tachycardic (HR 134 ppm), and no fever; cardiac arrhythmias: tachyarrhythmias, without murmurs; Pulmonary Auscultation: discrete sparse wheezing; abdomen without changes; without foci neurologic signs; without exanthemas or peripheral edemas. The gasometry showed a metabolic acidosis compensated with hyperlactacidemia (GSA: pH 7.34, pCO2 26 mmHg, pO2 77 mmHg, HCO3 16 mmol/l, lactate 11.3 mmol/l, SatO2 100%). Analytically it was to emphasize: normal hemogram, Glucose 400 mg/dL, Urea 64 mg/dL, Creatinine 2.8 mg/dL, Potassium 2.7 mEq/l, CPK 1143 UI/L, Cholinesterases 8.4 KU/L, Alcohol 0 g/dL, Theophyllinemia 148 ng/ml (NT: 10 – 20 ng/mL) and a positive search for benzodiazepines in the urine. The electrocardiogram showed an auricular fibrillation with a ventricular response of 140/m. Thorax X-Ray and cranioencephalic CAT scan did not show any alterations.

A quick deterioration of the clinical condition was observed, with tachyarrhythmia getting worst (with a ventricular response of 240/m) and circulatory shock. Chemical cardioversion was tried with amiodarone and electric cardioversion, at no avail, being administered 1 mg of propranolol endovenous with frequency control. Afterwards, a clonic-tonic generalized convulsion with cardiorespiratory arrest (CRA) in asystolia. Advanced life support was immediately started, having recovered to idionodal rhythm after 15 minuted of resuscitation procedures. After the CRA the metabolic acidosis was kept, repeated convulsions and severe hypotension, without tolerance to amines by tachydysrhythmia. He was hyperventilated, anticonvulsive therapy was started and aggressive fluid therapy, having achieved haemodynamic/circulatory stability (measurable blood pressure and diuresis) and seizures control. This clinical condition of circulatory shock with electric instability, associated to seizures and refractory metabolic acidosis was construed as Aminophylline intoxication, regarding the serum dosage carried out.

In this context, the patient was admitted in the Multiple Intensive Care Unit (UCIP) for treatment.

At the UCIP, gastric washes with activated charcoal, already started in the Emergency Service, and veno-venous continuous haemodiafiltration was started. However the patient kept a circulatory sho-

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ck refractory to treatment (amines and fluid therapy support), associated to an epileptic paroxysmal status with the need to induce a barbituric coma.

On the following hours, it was seen a progressive reduction of theophyllinemia (148/ 103/39/13 µg/ml), but without evidence of clinical improvement. It has progressively worsening regarding oxygenating endpoints (PaO2/FiO2: 400 / 200 / 150).

To evaluate the neurologic status, the sedation, curarization, and anticonvulsive therapy were withdrawn with the patient showing a Glasgow Score 3, with absence of the cerebral trunk reflexes. Cerebral death was confirmed 48 hours after admission in the Emergency Service.

DISCUSSION

Aminophylline is a theophylline derivative, with bronchodilator effect, stimulating the cardiac and central nervous system (positive ino- and chronotropic), presenting also diuretic properties and stimulating the acid secretion by the stomach.

Its action mechanism results mainly of adenosine receptors antagonism and phosphodiesterases inhibition. It is also responsible for an increase on intracellular concentrations (cc) of cAMP, with catecholamine release, promoting lipolysis, glyconeogenesis and glycogenolysis. It also promotes the release of epinephrine to the adrenal medullar cells.

It shows an oral serial peak (1-2 hours) and endovenous (30 minutes), an average lifetime of 8 hours (up to 30 hours if hepatic failure). It undergoes hepatic metabolization (cytochrome P450) and a slight urinary excretion.

Its elimination varies depending on the age, liver function, cardiac and renal and a smoking history.2 The theophylline endogenous clearance is very low comparing to other drugs (≤1 ml/m/kg), with acute overdoses or chronic administrations saturating quickly the drug clearance pathways (a small dose increment leads to a significant serum increase and life threatening).

Severe intoxication, is associated to a significant morbidity and mortality, due primarily to recurrent and maintained convulsive episodes (often associated to hyperthermia), hypotensive and cardiac arrhythmias.3 Regarding the intoxication type it can be considered an Acute form (usually a voluntary/ accidental overdose) and a chronic form.

Chronic intoxication (regardless of the serum level) leads to a higher severity of clinical manifestations (mainly associated with convulsions) occurring when the oral/endovenous theophylline dose exceeds the capacity of the drug clearance (cardiac failure, liver hepatic, smokers, > 60 years/childhood, concomitant drug intake - propranolol, tetracycline, ciprofloxacin, erythromycin, allopurinol, contraceptives). Toxicity increases proportionally with an increase on the serum level (therapeutic serum concentration: 10 to 20 ug/ml). Around 20% present minor signs of toxicity cc > 15 ug/ml, 80% with cc > 25 ug/ml and 25% of patients can show signs of intoxication Major with cc > 30-40 ug/mL.4 There is only one study which refers to a mortality rate in major intoxication of 5%.5 Regarding the clinical manifestations, they can be divided in minor (nausea and vomiting, peptic ulcer reactivation, headaches, shaking, insomnia, hives reactions, palpitations, mild tachydysrhythmias, tachypnoea and hyperthermia) and Major (sudden, serious and in general they are initial signs of – cardiovascular collapse, severe hypotension, serious hydroelectrolytic alterations and ventricular dysrhythmic alterations life threatening.6 The therapeutic approach, goes initially through the necessary support steps (keeping the airways / circulation/ hydroelectrolytic unbalances corrections) and symptomatic (from arrhythmias and seizures). The specific therapeutic steps foreseen go through the need of reduction of the intestinal absorption (gastric wash, multiple doses of activated charcoal (AC) – 50 to 100 g initial, followed by 20 g every 2 hours associated to a cathartic (Sulphate Mg - 250 mg/Kg to 30 g), seizures control (Benzodiazepines and barbiturics); antiarrhythmia therapy (arrhythmias due excessive B adrenergic stimulation); haemodialysis and hemoperfusion assume a huge importance as a therapeutic form in serious intoxications by aminophylline.

The drug pharmacokinetics features, (small distribution volume and a drug low clearance rate - 0.7 to 1 ml/min/Kg in non smokers adults), allow a significant drug removal using haemodialysis and hemoperfusion techniques. Activated Charcoal hemoperfusion shows an extraction ration higher than haemodialysis, however this last technique has the advantage of correcting simultaneously electrolytic abnormalities, common in such condition. When such techniques are not available, Aminophylline clearance can be achieved with longer sessions of arterio-venous or veno-venous continuous haemodiafiltration.

In the mentioned conditions such techniques will be kept until theophyllinemia is obtained <25 mg/L (indications: clinically unstable patient, seizures, arrhythmias, theophyllinemia > 100 mg/L, chronic intoxication with an age above 60 years old and theophyllinemia > 40mg/L, youngster with a chronic intoxication and theophyllinemia > 60mg/L, theophyllinemia > 60mg/L in patients at high risk of seizures – liver disease, cardiac failure, severe hypoxemia (PaO2<40mmHg), intolerance to activated charcoal.7,8,9

Regarding our clinical case we emphasize some particulars: a) the pathologic background and the patient's drug habits; b) the kind of intoxication that, considering the suicidal intent and the increased level of shown theophyllinemia, points to an acute intoxication ; c) the presence of all expected clinical manifestations for a severe intoxication; d) an increased theophyllinemia (without evidence in the published literature of such a high theophyllinemia; e) to perform the recommended therapy for this kind of intoxications, but without any therapeutical success.

The authors, with the report of this Clinical Case, aim to alert the physicians that use in its daily prescription this drug, for the importance of a rigorous use and adjusted to the patient, always anticipating the potential secondary effects of this drug. ■

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