Case Report

Angioedema Related to the Use of Streptokinase

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Angioedema is a rare reaction to streptokinase, acute and potentially fatal, which should be quickly diagnosed and treated to guarantee the best prognosis for the patient. We describe here the case of a 65-year-old man, who displayed an anaphylactic reaction after the beginning of thrombolysis with streptokinase, which was quickly treated, and remained hospitalized for one week in the Intensive Care Unit.

Despite the sparse discussion in the literature (the most recent references are more than five years old), we still consider as relevant the possible allergic reaction to streptokinase for our social reality, in which the use of streptokinase continues to be frequent, considering its cost and benefits.

An allergic reaction or hypersensitivity to a drug is defined as an immunological response to this drug or to its metabolites which results in an adverse B-type reaction. Sometimes the patient may be allergic to an entire drug class because the base of the immunological reaction is in certain common antigens to them, since the reaction to streptokinase which introduces antibodies of the types IgG and IgE against the antigens of the *Streptococcus* of the Beta hemolytic group[1].

Allergic reactions to Streptokinase are frequent one and their gravity is such that it does not draw our attention. In general, allergies are prevalent in 1.7 to 18% of the patients submitted to thrombolysis using streptokinase, these reactions not being systemic. The anaphylaxis itself occurs in 15 out of 10000 patients [Dickewicz et al[1] and GISSI study[2]] and is characterized by an acute reaction, with diffuse erythema, pruritus, urticaria, angioedema, bronchospasms, larynx edema, hyperperistalsis, hypertension, cardiac arrhytmia, isolated or together, hemolytic anemia. The majority of the symptoms develop rapidly (five to 30 minutes) after exposure.

Case Report

Male, 65-year-old patient, white, born and raised in Campinas, plumber/electrician, retired, married. Of his own accord, he sought out the Emergency Ward of the Hospital das Clínicas of UNICAMP on the 6th of April, 2002. He complained of pain in the left elbow after exercising one month ago, being that on this day he developed, immediately after having sexual relations with his wife, oppressive precordial pain irradiating out towards the left elbow beginning at 1:00 h, without any other accompanying symptoms. Upon being treated in this service, the pain continued for more than three hours with the same characteristics as before, with greater intensity and irradiating just towards the back. He was medicated with Oxygen through a nasal catheter, 200 mg of acetylsalicilic acid orally, 5 mg Isordil under the tongue, 5 mg metoprolol intravenously, three hours 20 minutes after having requested a cardiac examination. The patient had a history of smoking one pack a day (since six years old), a known but untreated condition of congenital dyslipidosis. He denied having diabetes mellitus, systemic arterial hypertension, similar prior history of chest pains, stroke, heavy bleeding, ulcer of the gastrointestinal tract, trauma, use of sildenafil, drug addiction, asthma, allergies.

The physical examination showed, good general condition, good color, hydrated, acyanotic, anicteric, afebrile, well nourished, eupneic, conscious, well-oriented, a steady pulse of 76 bpm, blood pressure of 150/100 mmHg.

The cardiac auscultation reveals a rhythmic cardiac beat, two hyperphonetic murmurs with the first sound muffled with an aortic focus and a diastolic murmur +/6+ in this focus. The pulmonary auscultation showed no change, (vesicular symmetric murmur present, without any adventitial sound), the abdominal examination noted the liver in right costal margin, hemiclavicular line, hydroaerial sounds present, with no murmurs or masses. Full pulse present, bilaterally symmetrical, with no edemas.

X-ray of the thorax was taken (with the purpose of evaluating other possible causes of the thoracic pain irradiated to the back), that revealed a slightly enlarged cardiac area without widening of the mediastinum, with slight pulmonary congestion. The electrocardiogram with sinusoidal rhythm, 1st degree atrioventricular block, upper level misalignment of the ST segment of 2 mm V1, 4 mm V2, 3 mm V4, with upper level misalignment of the ST segment of 1 mm in DII, DIII and aVF (fig. 1).

Once the diagnosis of coronary syndrome was made with the upper misalignment of the ST segment, acute heart infarction of the antero-septal wall, we began treatment 30 minutes after the request for the coronary evaluation (time for the evaluation of the case and confirmatory examinations). At 4:00 h, the patient had blood pressure of 130x90 mmHg, having begun thrombolysis with Streptokinase 1500000 U intravenously. After the infusion of 1/6th of the dose of the thrombolite, the patient developed progressive hoarseness and nasal obstruction which brought up the hypothesis

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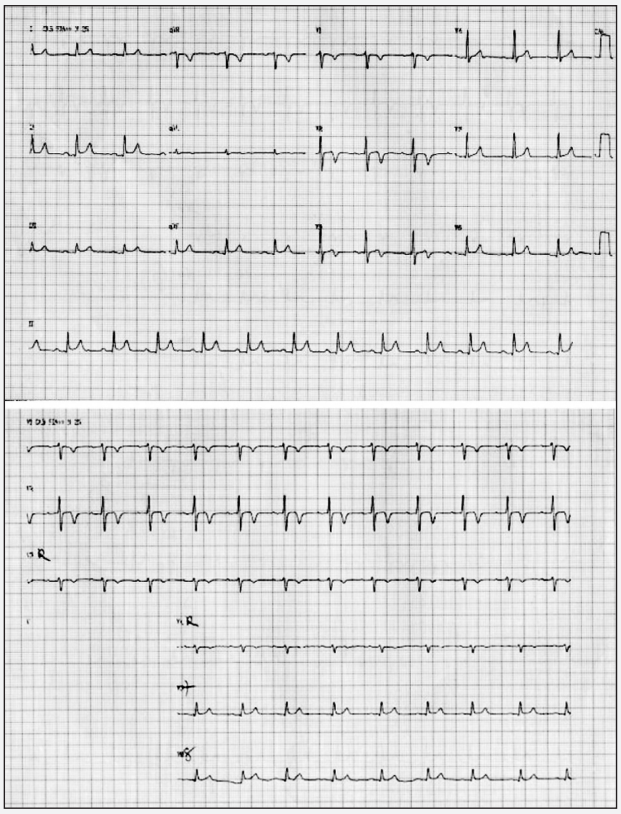

Fig. 1 - 16 Lead ECG before thrombolysis.

of secondary angioedema due to the use of Streptokinase. The infusion of the thrombolite was suspended immediately, and 01 ml of adrenaline was injected (with a dilution of 1:1000) intravenously and two applications with an interval of 5 minutes between them, another 5 ml of the 1:10000 solution; and hydrocortisone 01g intravenously. The patient developed rapidly respiratory difficulty and wheezing, being submitted to orthotracheal intubation with some difficulty because of the edema in the glottis and the vocal cords with easy local bleeding (reached a transitory saturation of 48% for less than a minute). He displayed serious hypertension needing a vaso-active drug for the reversal of the situation after the ortho-tracheal intubation. He also developed edema of the eyebrows, lips and tongue.

The patient did not display the classic success signs of the thrombolysis, maintaining the upper misalignments after 2 hours from the streptokinase and the enzymatic curve peaked with creatine phosphokinase - 250 and the MB fraction = 85 mg/dL 15 hours after the beginning of the pain (fig. 2).

Maintained with treatment governed by the immunology with continuous cortisone therapy (hydrocortisone 500 mg intravenously 8/8 hours) for three days and later scheme for the progressive reduction. He displayed hemolytic anemia due to activation of the complement in the anaphylactic shock, according to the analysis of the hematology service. On 04/13/2002, the patient had the intubation removed with no interference, and no longer displayed any mucous edemas.

The echocardiogram performed on 04/18/2002, showed contractive dysfunction of the left ventricle with basal- mid- and apical and antero-apical septal hypokinesis, compatible with antero-septal infarction, cardiac chambers with normal dimensions (aorta = 35 mm, left atria = 36 mm, final diastolic diameter of the left

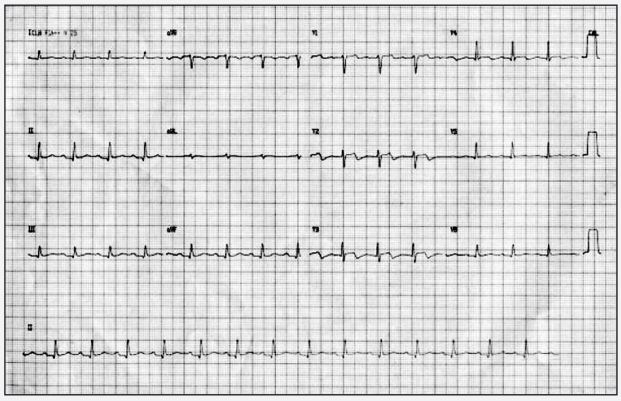

Fig. 2 - 12 Lead ECG after thrombolysis.

ventricle = 48 mm, systolic end diameter of the left ventricle = 27 mm, septum and back wall = 10 mm, Ejection Fraction – 70%).

On 04/19/2002, he was submitted to a cardiac catheterization that revealed prior descending arteries with obstruction of 70% in the closer third, first diagonal branch with ostial 70% circumflex artery with 40% and right coronary with no lesions, Ejection Fraction of 81%. On 05/13/2002, he was submitted to a myocardial revascularization (internal left mammary artery for the prior descendent, by means of a bypass vein for the first diagonal) without complications (fig. 3).

Discussion

A review published in the JAMA[3] in December, 1997, emphasized the importance of recognizing and orienting the handling of patients with reactions to drugs. Despite the low frequency of allergic reactions to streptokinase, its recognition is also something less than desirable. We imagine that the slight gravity of the more frequent reactions contributes greatly to this fact. Slight allergies (with cutaneous reactions or minor edemas of mucous tissues) are prevalent in 1.7 to 18% of the patients submitted to thrombolysis and anaphylaxis occurs in only 15:10.000 patients[1,2]. Despite being rare, this type of reaction cannot be prevented or

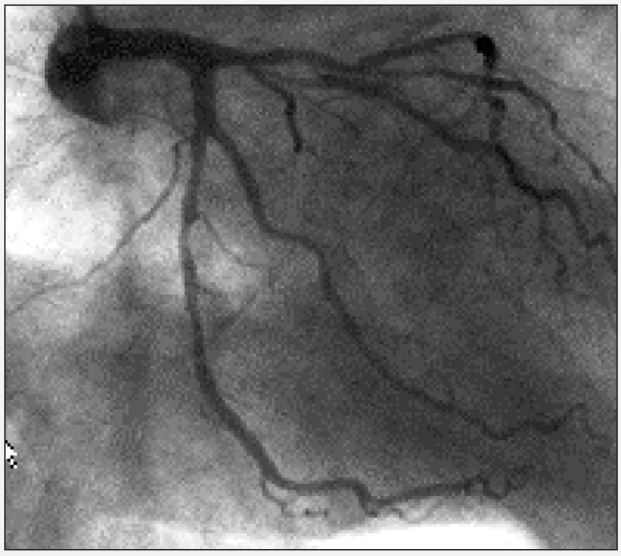

Fig. 3 - Coronary angiography showing left anterior descending stenoses of 70%.

predicted, since cutaneous testing has little efficacy in emergency cases (such as a myocardial infarction), being more utilized in few cases, for example: specific protocols for situations of reactions to specific drugs, reactions during treatment with multiple drugs and cases of patients with the necessity to be submitted to new exposures of agents known to be allergenic.

An allergic reaction or hypersensitivity to any drug could be defined as an immunological response to a drug or its metabolites that result in an adverse reaction. Many times the allergic reactions depend on previous exposure (sensibility) of prolonged exposure, but in other cases the patient may be allergic to an entire class of drug because the base of the immunologic response is in certain common antigens to them. What is most important is that all drugs may cause adverse effects.

Keeping in mind the large number of patients accompanied by cardiologists using several medicines over a long period of time, we emphasize the importance for doctors to maintain themselves up-to-date with respect to adverse reactions to drugs citing their incidence in the United States of America: they occur in 6 to 10% of the common population (studies suggest that reactions to the majority of the drugs utilized may occur in 1 to 3% of the patients who use them)[4] among these 0.2 to 29.3% required hospitalization for this reason. Among the hospitalized patients, this incidence is greater: 15 to 30%, of which the registration of fatal events is about 1:10000[3,5]. Deaths associated with drugs occur in 0.01% of surgical patients and in 0.1% of clinical patients (greater incidence among multi-drug users)[3-6].

These statistics include all types of adverse reactions, even those of the A type - common and predictable, which may occur in any person. They occur in 80% of the adverse reactions, being a result of known pharmacological reactions to drugs. But in the case of reaction to streptokinase we see a reaction that is included in adverse reactions of the B type - not common and unpredictable. Known as intolerance, idiosyncrasies, hypersensibility and allergies or pseudo allergies. The allergic reactions are immunologically measured and have the following characteristics: 1) they occur in a small number of patients; 2) they require prior exposure to the drug or to one from a chemically-related group; 3) they develop rapidly after re-exposure; 4) they produce common syndromes and immunological reactions.

Factors related to the drug being used may increase the risk of immunological (allergic) reactions: drugs with greater molecular weight have a greater propensity to set off immunological reactions, but drugs with low molecular weight, after bonding with the carrier proteins, may also set off such reactions. The prior presence of specific antibodies is not a pre-condition for these reactions[3]. Also factors related to the patient may increase this risk (female sex, presence of a history of allergies to other medication of the same class, among other factors).

The immunological reactions to many drugs may be presented clinically in many ways, rapidly mentioned below[3].

Involving multiple organs: 1) Anaphlyaxis: acute reaction with life at risk, consistent with diffuse erythema, pruritus, urticaria, angioedema, bronchospasms, larynx edema, hyperperistalsis, hypertension, cardiac arrhytmia, isolated or together. The analphylaxis develops rapidly (5 to 30 minutes after exposure). Some authors reserve the term just for reactions measured by IgE, and classify as anaphylactoid reactions the identical clinical symptoms measured by IgG. Examples: Anaphylaxis with the use of Penicillin occurs in 0.01 to 0.05% of the patients with a mortality rate of 400 to 800 patients per year, the use of contrasts occurs in 4 to 13% of the patients, with greater prevalence in women, with AAS precipitating asthmatic reactions and less serious cutaneous reactions; other examples are: streptokinase, protamine, conversion enzyme inhibitors, vancomicin, ciprofloxacine[3].

2) Related to Histamines: indistinguishable from reactions measured by IgE, with immediate hypersensibility for mastocytes. An example with vancomicin - Syndrome of the red man - dependent on the dose and on the velocity of infusion direct stimulus on the skin mastocytes.

3) Stevens Johnson and Multiform Erythema[3]: polymorphic and erythmic eruptions caused by drugs in 10 to 20% of the cases (symmetrical lesions with preferences for the extremities, with target lesions, cutaneous rash uticaria and vesicles. In the cases of Stevens Johnson mucous lesions occurred - conjunctive lesions and cutaneous loss may arrive at 10%. Half of the cases are related to drugs and the re-exposure causes reoccurrence. Examples: sulphonamides, anti-convulsants, non-steroid anti-inflammatories and allopurinol[3]. The mortality rate is close to 5% and the involvement of the organs worsens the prognosis. The early use of corticosteroids reduces lesions to the organs and improves survival[3].

4) Toxic Epidermal Necrolysis: fever, loss of more than 30% of the epidermal surface and visceral involvement with a mortality rate of 30%[3]. The treatment is just support and the use of corticosteroids does not seem to be beneficial.

5) Hypersensibility syndromes: caused by the use of anti-convulsants (phenytoin, carbamazepine, phenolbarbital) begins soon after the first week up to three months from the introduction of the drug and occurs in 1/100 to 1/10000 of the patients. Fever, hepatitis, nephritis, cutaneous lesions. The symptoms are interrupted with the suspension of the drug[3]. Allopurinol and sulfassalazine also may set off such reactions[3].

6) Fever: still unknown mechanism, displays eosinophilia and leukocitosus. It ceases within 48 to 72 hours after the suspension of treatment[3].

Involving just the skin[3]: Reactions to drugs are more frequent (among those hospitalized, the incidence is 1/1000). 1) Urticaria/angioedema: activation of the complement and of the mastocytes directly. (opioids, dextran, polymyxin, insulin, penicillin and heterologous serums); 2) Maculopapule exanthema: symmetric maculopapular erythema in palms and plants or in the region of repose of the patient. Differential diagnosis always with viral infections; 3) Contact dermatitis: sensibilization takes 5 to 7 days but re-exposure causes a reaction within 24 hours.

In the case described, we were led to the diagnosis of secondary anaphylactic reaction to the use of streptokinase because the patient displayed a reaction within the shortest time, with angioedema, bronchospasms, hypertension and hemolysis[1].

With respect to the therapy for the anaphylaxis related to the streptokinase or to any other drug, we should supply oxygen, rapid preparation of the airways (even procedures such a cricothyroidotomy should be indicated for the maintenance of the upper air ways of the patient, independent of having received anti-coagulants, or having been submitted to a pharmacological thrombosis[7-9]). The use of epinephrine is always recommended - even in cases of

infarctions, being that for the less serious cases, a dose of 300 to 500 mg (0.3 to 0.5 ml of a solution of 1:1000) is recommended for a subcutaneous application and repeated every 15 to 20 minutes if necessary. In children 0.01 ml/kg of 1:1000 subcutaneous every 15 to 30 minutes. For more serious cases with hypertension, the intravenous dose is recommended and should be 0.1 mg (in dilution for 10 ml) every 5 to 10 minutes, up to a continuous infusion of 1 mcg/minute. The intravenous diphenidramine also should be utilized in the dose of 1 to 2 mg per Kg up to 50 mg in bolus. Methylpredynisolone 1 to 2 g intravenous in bolus could prevent a later phase of anaphylaxis that occurs within 6 to 12 hours[8]. In the case described, endovenous adrenaline was used, having in mind the seriousness of the anaphylactic situation and the corticosteroid available in the institution at the moment of the emergency. Antihistamines were not used for the first application but the literature instructs that it should also be used. Diphenydramine as well as the dexchlophyramine also should be used in situation of reactions to drugs with good responses. There is still no effective way to prevent or to predict such reactions.

In those cases of patients with prior reactions to the drug, we should keep in mind that the reactions with little clinical relevance could be those of the A type, tending not to reoccur, being dose-dependent that may be well administered [10]. More intense reactions could be of the B type and in these cases the reutilization of the drug and/or the class is counter-indicated. In the event there is necessity, desensitization may be attempted, but it is not effective in the majority of cases. In this manner, it is determined that for patients with a history of allergic reaction to streptokinase, this will always be counter-indicated, with the use of some other thrombolytic therapy in the case of a new thrombosis.

Despite being rare, (15/10000)[2] and largely ignored in the literature (sparse and old references), it is necessary that emergency services be aware of the occurrence of these episodes of allergic reactions to the use of streptokinase. The use of this thrombolytic therapy still is quite frequent in our midst, principally far from the principal urban centers, and in this case, only a timely diagnosis will permit that a rapid intervention makes the recovery of the patient possible.

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