

MASTOCYTOSIS

FACTORS THAT CAN EVOKE THE RELEASE OF MAST CELL MEDIATORS

SPECIFIC PROTOCOLS IN RISK SITUATIONS IN PATIENTS WITH MASTOCYTOSIS

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FACTORS THAT CAN EVOKE THE RELEASE OF MAST CELL MEDIATORS

1. PHYSICAL AGENTS

1.1. Frequent

- a. Heat: Use mildly warm water for bath or shower. Do not rub briskly with towel to dry off. When drying hair, use hair dryer only on warm heat.
- b. Cold
- c. Pressure: Traumas to scalp in patients with skin lesions in this area. Avoid Darier's sign (friction of skin lesions), this procedure can evoke a massive mast cell mediators release, especially in large lesions (mastocytomas).

1.2. Rarely

- d. Endoscopies (panendoscopy, rectoscopy, colonoscopy)
- e. Manipulation of GI system/intestines during surgery

2. EMOTIONAL FACTORS (frequent)

- a. Stress (frequent)
- b. Anxiety (frequent)

3. MISCELLANEOUS:

- 3.1. Infections or Fevers of any etiology (frequent)
- 3.2. Teething in children (frequent)
- 3.3. Vaccination in children (infrequent)

4. DRUGS & MEDICATION

- 4.1. Non-steroidal antiinflammatory drugs (NSAIDs)*, are used as analgesic and antipyretic medication. This group includes: Aspirin (acetylsalicylic acid), mefenamic acid, butibufen, diclofenac, fenbufen, fenilbutazone, flurbiprofen, ibuprofen, indometacine, ketoprofen, ketorolac, meclofenamate, metamizole, nabumetone, naproxen, propifenazone... among others.
Acetaminophen is usually well tolerated in mastocytosis, in this sense it is not initially restricted.

- 4.2. Opioids and morphine derivatives. These drugs are used in anaesthesia, analgesic and cough therapy. This group includes: morphine, codeine, buprenorphine, meperidine, dextromethorphan, dimemorphan, fentanyl, tramadol... among others.
- 4.3. Alcohol: Rare <0.5% (REMA, unpublished data, 1984 – 2006).
- 4.4. Muscle relaxants and inductors used in general anaesthesia.‡
- 4.5. Beta-blockers are restricted during general anaesthesia, and in cases who suffered previous anaphylactic episodes.
- 4.6. Local anaesthetics¶: Exceptional using amide-derivatives.
- 4.7. Contrast Media used for diverse radiological studies: Rare.
- 4.8. Interferon Alpha 2b#: Exceptional.
- 4.9. Clorodeoxyadenosine or Cladribine (2-Cda): Rare. Only one case was reported (J. Sheik, Beth Israel Hospital, Harvard Medical School, personal communication, September 2002).
- 4.10. Hydroxyurea: Rare. It was reported in only one case (L Escribano, personal communication, June 2007).
- 4.11. Colloids: Substances with high molecular weight used to treat hypotension or hypovolemia, such as dextran (infrequent).

*The frequency of mast-cell mediators release related to the NSAIDs, is 2% in pediatric mastocytosis and 14% in adults. (Sánchez-Matas I, XXVIII Congress of the EAACI).

‡According to the data recorded by REMA's physicians, among 73 adult patients who underwent general anaesthesia, 3 suffered severe mast-cell mediators release symptoms (2 cardiorrespiratory arrests, and 1 coagulopathy with hypovolemic shock), the specific protocols in risk situations in mastocytosis were not followed in these cases (Matito A, 29th Congress of the EAACI). In pediatric mastocytosis, 17 children underwent general anaesthesia, and no severe mast-cell mediators release episodes were reported (CLMast, unpublished data, September 2010).

¶No adverse reactions were recorded in 850 bone marrow biopsies and 1,235 cutaneous biopsies. In these cases, adequate premedication was used (REMA, unpublished data, 1984 – 2006). In 8 cases with previous history of anaphylaxis induced by stress, the bone marrow biopsies were performed in the ICU with premedication, local anaesthesia and sedation (CLMast, unpublished data, September 2010).

#Mast-cell mediators related symptoms were not reported in 23 cases who underwent of interferon therapy. In all cases antimediation premedication was used according to the REMA's specific protocols, and the 3 initial doses were given in the ICU (Escribano L, unpublished data, 1995 – 2006).

SPECIFIC PROTOCOLS IN RISK SITUATIONS IN PATIENTS WITH MASTOCYTOSIS

A. Protocol in general anesthesia

Some medications used in pre-anesthesia, induction and maintenance phase or during the post-anesthesia period can evoke anaphylactic/anaphylactoid reactions, and alterations in blood coagulation. These reactions are due to the release of mast-cell mediators, some of them are stored in the mast-cells such as histamine, heparine or tryptase; while others are synthesized during the process of mast-cell activation (PGD₂, LTC₄). The capacity of some of these drugs to induce mast-cell degranulation was reported *in vitro*; furthermore, several case reports about life-threatening crisis related to anesthesia in patients with mastocytosis, can be found in the medical literature. In our series, the frequency of these severe episodes in adult patients who underwent general anesthesia is 4.1% (Matito A, 29th Congress of the EAACI).

Mast-cell activation can be triggered through cross-linking of high-affinity Fc receptors for IgE (FcεRI), Fcγ receptors for IgG, or complement proteins among others. The mediators released target at tissues and organs such as the heart, the blood vessels, the skin, the lungs, among others, resulting in cardiovascular, hemodynamic and metabolic disorders similar to those observed in anaphylactic reactions or serious coagulation disorders.

General anesthesia is an obvious risk for patients who suffer from mastocytosis or systemic mast cell activation disorders (SMCAD).

These protocols are supported on the experience of the Spanish Network on Mastocytosis, and an exhaustive review of the literature.

NOTE. The doses of drugs must be adjusted according to the body weight, comorbidities and drug-interaction.

A.1. GENERAL PREPARATION (ANTIMEDIATOR PREMEDICATION)

A.1.1. Corticosteroids (i.e. prednisone, methylprednisolone) 8 hours, and 1 hour before the anesthesia (**optional**)

A.1.2. Dexchlorpheniramine (Polaramine®): IV one hour before the anesthesia, (other H₁- antihistamines can be used)

A.1.3. Ranitidine: one hour before the anesthesia

A.1.4. Montelukast (Singulair®): 24 and 1 hour before anesthesia (Castells M, Brigham and Women's Hospital, Harvard Medical School, personal communication, September 2003)

A.2. PREMEDICATION

A.2.1. Sedation is important to avoid anxiety. Benzodazepines can be used.

A.3. INDUCTION AND MAINTENANCE

A.3.1. Etomidate (induction)

A.3.2. Propofol

A.3.3. Ketamine

A.3.4. Inhalants of the "flurane" family

During the maintenance phase, these drugs must be used in enough concentration to guarantee a deep anesthesia.

A.4. MUSCLE RELAXANTS

A.4.1. Vecuronium

There are no data about the safety of other muscle relaxants

A.5. OTHER CONSIDERATIONS

A.5.1. Opioids and morphine derivatives must not be used in mastocytosis. In our series, 24 anesthetic procedures (18 under general anesthesia, 4 under epidural anesthesia, and 2 sedations) were performed using pethidine, fentanyl or remifentanyl; one of them, who was not given antimediation therapy before the general anesthesia (with anesthetic drugs different to the recommended in this protocol) suffered a severe mast-cell mediators release episode. (CLMast, unpublished data, June 2009). Nevertheless, in our experience fentanyl and remifentanyl can be safely used if they were tolerated before in the patient suffering from mastocytosis.

A.5.2. The colloids can evoke anaphylactic reactions in mastocytosis and must not be used.

A.5.3. Do not use beta-adrenergic or alpha-adrenergic blockers.

A.5.4. Tryptase serum levels before, during and after surgery should be analyzed.

A.6. ANALGESIA

The medications previously tolerated by the patient are allowed. Each patient should have a medical report from a Specialized Center in this sense.

If the analgesic drugs tolerated by the patients are unknown, provocation tests should be performed with the corresponding medications at a Specialized Unit under strict and monitored supervision.

A.7. TREATMENT OF EPISODES OF ACUTE MEDIATOR RELEASE DURING ANESTHESIA

A.7.1. Anaphylactic shock: Epinephrine, Corticosteroids, H1 and H2 antihistamines; and Glucagon (if the patient is under the effect of beta-blocker).

A.7.2. Hypotension: Fluid therapy (avoid colloids), Dopamine, Dobutamine.

A.7.3. Hemorrhagic syndrome. Treatment according to the coagulation alterations.

See specific protocols available in different countries.

B. Protocol in local anesthesia

The techniques of local anesthesia (including epidural) must be considered as the first choice in patients with mastocytosis, therefore, they must be used instead of general anesthesia when feasible.

The use of antimediator premedication (see above) can be useful to avoid mast cell-mediator release induced by stress.

B.1. Oral premedication should be used for skin or other tissue biopsies (bone marrow), dental interventions or minor surgery.

B.2. Amide derivatives such as bupivacaine, lidocaine or mepivacaine should be used in these procedures.

C. Radiological exams with a contrast media

Clinical experience as well as *in vitro* research studies, have shown that most of intravenous contrast agents used for radiologic procedures can evoke mast-cell mediators release.

In this sense, these agents should be avoided; however if they are strictly necessary, the nonionic (low molecular weight) contrast agents must be chosen, since they decrease the risk of mast-cell degranulation. This group of agents includes: iohexol, iopamidol, iopromida, ioxilan, ioversol, iodolatan and iodixanol.

The procedure must be carried out under strict supervision with adequate monitorization.

In addition, every patient must be given antimediator premedication previous to the intravenous contrast agent*:

- C.1. H1-antihistamines (Dexchlorphenamine: Polaramine[®]): one hour before the radiologic contrast.
- C.2. Ranitidine: one hour before the radiologic contrast.
- C.3. Corticosteroids: 13, 7 and 1 hour before the radiologic contrast. **Optional**, these doses can be modified according to any practitioner criteria.
- C.4. Montelukast (Singulair[®]): 24 and 1 hour before the radiologic contrast. Recommended only in cases with previous mast-cell mediators release episodes related to contrast agents.

* An allergic work-up must be performed in patients who suffered an allergic reaction or a mast-cell mediators release episode related to contrast agents, in order to detect specific sensitizations (IgE mediated mechanism) to the contrast agents, and to avoid their use.

*These medications should be adapted according to the availability in each country.

D. Labor and delivery

This procedure can be carried out with epidural or general anesthesia, following the protocols recommended in this text.

Antimediator premedication is mandatory, since both the labor and the stress can evoke a mast-cell mediators release episode.

Delivery inductors as oxytocine can be used.

Fentanyl or remifentanyl in epidural anesthesia, can be used only in patients who tolerated them after the onset of mastocytosis.

In our series (REMA), a total of 45 deliveries were recorded in women with mastocytosis; 32 epidural, 2 general and 1 local anesthesia were used, and no life-threatening release crisis were reported. (Matito A, Int Arch Allergy Immunol 2011).

Antimediator premedication (at the beginning of labor and/or 1 hour before the anesthesia)

- D.1. *H1 antihistamines
- D.2. Ranitidine
- D.3. Corticosteroids before the anesthesia (optional)

*These medications should be adapted according to the availability in each country.

E. Protocol in mast-cell mediators related symptoms triggered by hymenoptera sting (bee, wasp or red-ant). Sporadic cases after sting or bite of other insects were reported.

E.1. Mild symptoms without hypotension or cardiovascular compromise: H1 antihistamines, ranitidine and corticosteroids.

E.2. **Anaphylactic shock**

Immediately LIE ON ONE'S BACK

E.2.1. Injection of intramuscular epinephrine 1 in 1000 solution; or auto-injectable epinephrine devices (Altellus, EpiPen, Anapen, Twinject...) 0,3 in adults and 0,15 in children. The patients and their relatives must be trained to use the device.

E.2.2. Go to the emergency room, to complete evaluation and treatment. Tryptase must be measured in the following 1-3 hours after the anaphylaxis.

***Epinephrine must be used only in systemic reactions with severe hypotension, laryngeal/uvular angioedema, or syncope/presyncope.**

***Epinephrine must be used whenever there is a strong suspicion of an anaphylactic shock is going on.**

*These medications should be adapted according to the availability in each country.

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Guidelines

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