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LITERATURE REVIEW

Dental treatment in patients with anti-platelet (anti-aggregating) therapy

Manejo odontológico en pacientes con terapia antiagregante plaquetaria

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ABSTRACT

Anti-platelet therapy is nowadays considered essential for those patients who are at risk to sustain strokes (cerebro-vascular events), thrombus formation, as well as in cases of coronary valvular prostheses (stents). This therapy allows prophylaxis before any possible thrombo-embolic event. Tendency to bleeding is doubtlessly one of its secondary effects. It therefore becomes relevant to be knowledgeable with consequences that might be encountered in common dental practice so as to avoid accidents and prevent post-operative bleeding (hemorrhage). The aim of the present study was to present drugs most used in this therapy, discuss their mechanism of action and to develop a defined protocol for the proper care of these patients.

RESUMEN

La terapia antiagregante plaquetaria se considera hoy en día esencial en aquellos pacientes que poseen riesgo de presentar accidentes cerebrovasculares, formación de trombos y en la colocación prótesis valvular o stents coronarios, esta permite la profilaxis ante cualquier evento tromboembólico que se pueda presentar; indiscutiblemente uno de sus efectos secundarios es la tendencia al sangrado, por lo tanto esto hace relevante conocer las consecuencias en la práctica odontológica habitual para evitar accidentes y prevenir hemorragias postoperatorias. El objetivo de este trabajo es presentar los fármacos más usados dentro de esta terapia, su mecanismo de acción y la elaboración de un protocolo definido para la atención adecuada de este tipo de pacientes.

Key words: Anti-platelet therapy, dental management.
Palabras clave: Terapia antiagregante plaquetaria, manejo odontológico.

INTRODUCTION

Hemostasis is a physiological process which consists in the combination of biochemical and cellular events which act jointly to preserve blood in a liquid state within veins and arteries. Through the mechanism of clot formation it prevents blood exit when a vessel is damaged. Hemostasis can be achieved with different mechanisms: vascular reaction, platelet response or primary hemostasis, coagulation activation and fibrinolysis. When the process is altered, significant blood loss can occur, even in very small lesions.[1]

Under physiological conditions, platelets do not interact with blood vessel walls. Nevertheless, platelet adhesion and thrombi formation can occur as response to vascular damage when the endothelium of the extracellular matrix results exposed. Platelets come into contact with exposed collagen and other adhesive proteins and this elicits a change in the platelet shape, passing from being disk-shaped to becoming spherically shaped. They thus emit pseudopods which can duplicate cellular diameter. At that point, they secrete the content of their granules, attracting thus other platelets to the damaged site to then form a primary hemostatic plug. These metabolic and morphological changes are called platelet reactions. These reactions entail adhesion, activation, degranulation and aggregation.[1]

Certain drugs interfere with normal platelet function. In recent years, indications and number of patients subjected to platelet therapy (PT) have increased. When these patients must be subjected to a surgical intervention, there is a need to discontinue PT and subject the patients to a possible risk increase to thrombo-embolic-cardiovascular complications. On the other hand, if treatment remains unaltered, the

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patient might be at risk of presenting hemorrhagic complications during or after the operation.[2-4]

PT is routinely used to prevent venous and arterial thrombosis in patients at risk due to ischemic heart disease, prosthetic valves, coronary stents, primary prophylaxis of coronary thrombosis, as secondary prevention in adverse thrombo-embolic events in patients with coronary thrombosis history, cerebrovascular accidents as well as unstable angina.[3-6]

A suitable drug for PT would be one that could inhibit platelet activation ways, stimulate inhibition, or both events at the same time (in a measure as close to ideal as possible). This drug should be effective when taken by mouth, it should exhibit suitable anti-thrombotic potential, lack systemic toxicity and significant hemorrhage risk. Nevertheless, none of the existing available platelet inhibitors satisfy these requirements in a 100%.[5,7]

Acetylsalicylic acid *(Figure 1)*. Is the most studied. Its anti-platelet effect is elicited when it irreversibly blocks the platelet cyclooxygenase enzyme. (COX) responsible for thromboxane A_2 production (platelet aggregation inductor),[8] therefore its action endures all along the platelet life (7 to 10 days). Even in low dosages (75-160 mg/day) it has proven to be effective in cases of stable and unstable angina, acute myocardial infarction, ischemic ictus, severe carotid stenosis, among others.[9-11]

Once ingested, acetylsalicylic acid is rapidly absorbed into the upper small intestine, after 20-30 minutes noticeable plasmatic concentrations can be achieved which peak at 60-120 minutes. Absorption rate depends on several factors such as dissolution and disintegration speed, intestinal and gastric pH, speed of gastric depletion, as well as presence of food in the digestive tract. Once absorbed, it bonds to plasmatic proteins, mainly albumin, metabolized in the liver, and is mainly excreted through the kidneys. Dosage varies widely: from 30 mg/day up to 1,500 mg/day depending on the severity of the cardiovascular disease.[5,6] Among its adverse effects the following can be counted: gastro-intestinal disorders such as epigastric pain, dyspepsia, erosive gastritis or ulceration, nausea, vomit, and constipation, upper gastrointestinal tract complications related to hemorrhagic events, and increase of cerebral hemorrhage.[5]

Clopidogrel and ticlopidine *(Figures 2 and·3)* are chemically related. These drugs are recommended for patients intolerant to acetylsalicylic acid. Clopidogrel is mainly recommended due to its association to lesser amounts of secondary effects than ticlopidine. These drugs act by means of hepatic activation: the active metabolite selectively and irreversibly inhibits platelet aggregation induced by adenosine (adenosindiphosphate) (ADP), preventing thus bonding mechanism to the platelet receptor. Thus, activation of glycoprotein GIIb/IIIa complex results altered. Since this complex is the most important receptor for fibrinogen, its inactivation prevents fibrinogen bonding to platelets, and this finally inhibits platelet aggregation, and platelets remain altered for the rest of their lives. Maximum plasma concentrations are achieved one hour after drug administration. They are irreversibly bonded to plasma proteins; approximately 50% are eliminated through urine, 46% are eliminated in feces along a five day period. Plasma half-life is approximately 8 hours. Platelet inhibition is achieved 2 hours after drug oral administration; Inhibition maximum limit is achieved at 3-7 days. Clopidogrel is administered though a daily 75 mg dosage. Ticlopidine is administered in a twice a day, 250 mg dosage.[4,5,8,10,11]

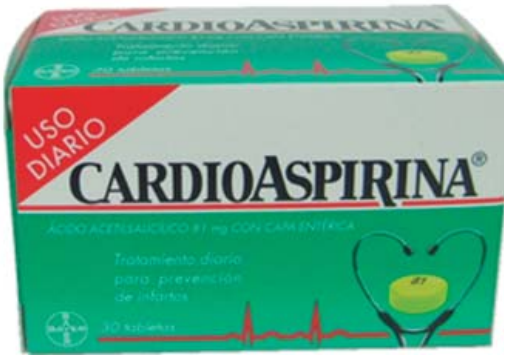

Figure 1. Acetylsalicylic acid commercial presentation in Venezuela.

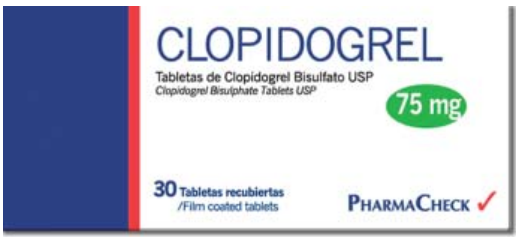

Figure 2. Clopidrogel comercial presentation in Venezuela.

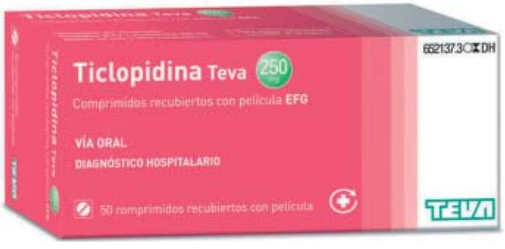

Figure 3. Ticlopidine comercial presentation in Venezuela.

Among negative effects elicited by the aforementioned drugs, the following can be found: gastrointestinal disorders such as diarrhea, nausea, dyspepsia, flatulence; hematological disorders such as agranulocytosis, aplastic anemia, pancytopenia, thrombotic thrombocytopenic purpura, eosinophilia, neutropenia, leukemia, thrombocytopenia and thrombocytosis. At hepatic level the following can be observed: increase of hepatic enzymes and bilirubin, 8 to 10% increase of serum cholesterol. Dermatological manifestation could include pruritus, skin rash; central and peripheral nervous system disorders could include headaches, dizzy spells, vertigo and paresthesia.[5]

Double therapy with acetylsalicylic acid and clopidogrel has become common practice for secondary prevention for patients previously afflicted with atherosclerotic diseases associated to thrombi formation such as cerebrovascular incidents, stent placement operations and for patients resistant to acetylsalicylic acid.[1,6,11]

Interactions are generally observed with other hemostasis-altering drugs such as oral anti-coagulants, other platelet anti-aggregating agents, thrombolytic agents and NSAI.[4]

DENTAL MANAGEMENT OF PATIENTS SUBJECTED TO ANTI-AGGREGATING PLATELET THERAPY

Patients subjected to PT therapy must fulfill the following protocol for the undertaking of simple extractions:[1]

- Previous consultation with treating physician to determine safety of discontinuing anti-platelet treatment for several days.
- Discontinuing PT treatment 3 or 4 days before extraction, since there is sufficient amount of platelets to ensure proper hemostasis.
- During procedure, make use of measures which promote formation of stable clot.
- Restore PT one day after extraction in cases where no post-operative bleeding is observed.

Brennan & al recently introduced new recommendations for handling these patients. It consists on not discontinuing PT before extraction-type procedures, since bleeding during the surgical procedure is controllable with habitual local hemostatic precautions such as suture, mechanical compression with gauze, gelatin sponge, oxidized cellulose, among others. Usually, no hemorrhage problems arise, unless bleeding time becomes very long. With respect to patients subjected to aspirin and clopidogrel double therapy and who are going to undergo dental surgical treatment (multiple extractions, osteotomies, implant placement, among others) there is no scientific evidence supporting postoperative bleeding complications. Nevertheless, anti-thrombotic function loss is possible in cases where PT is discontinued, with its ensuing cardiovascular consequences. In view of all the aforementioned facts, clinical history is an essential factor in predicting possible hemostatic alterations. Laboratory tests before surgical intervention are therefore crucial.[2,3,9,12,13,14,15-19]

Giner[20] conducted a study at the Oral Surgery Graduate Program of the Central University of Venezuela. In that study he compared platelet function in patients subjected to acetylsalicylic acid treatment for over 6 months with a healthy control group. He concluded that 80% of patients under PT exhibited reduced platelet function and presented greater amounts of hemorrhage in operations when compared with the control group. This hemorrhage, due to the fact that it was not excessive, could be controlled with local hemostatic measures.[20] Another research project conducted by Cespedes[1] at the Oral Surgery Graduate Program of the Central University of Venezuela compared platelet function and bleeding time in patients subjected to dual therapy of acetylsalicylic acid and clopidogrel with a control group. He found both values to be altered and therefore timely hemostatic measures had to be undertaken so as to control bleeding during surgical events.[1]

BEHAVIOR TO OBSERVE BEFORE ORAL SURGERY EVENT[1,4,6,7,10,17,19-22]

PRIOR TO SURGICAL EVENT

1. Comprehensive and exhaustive history must be recorded. In it, the following facts are to be determined:

- Basic pathological examination to determine use of anesthetic without vessel constrictor.
- Bleeding problems encountered in previous oral procedures.
- Spontaneous bleeding.
- Bleeding during prolonged periods, hematoma or ecchymosis in the presence of minor cuts or trauma.
- Other systemic diseases which could increase bleeding time such as: liver conditions,

alcoholism, congenital coagulation disorders thrombocytopenia, among others.
- Ingestion of other prescribed drugs.

2. In cases of dual therapy, consultation with treating physician to determine whether or not to discontinue one of the drugs, as well as cardiovascular surgery performed less than 6 months before.
3. Prescription of serological tests such as full hematology, PT, PTT. Bleeding time and clot retraction.
4. Planning of surgery in the early morning hours, if possible at the beginning of the week, so as to be able to solve post-operative hemorrhagic events.
5. Taking blood pressure.
6. Assessment of periodontal tissue health since presence of inflammation would increase bleeding risks.
7. Patient must be informed of the possibility of bleeding risks during operation as well as after the event.
8. For patients with valvular prostheses and coronary stents, antibiotic prophylactic therapy with 2 g amoxicilin must be considered. Allergic patients might require Clindamycin 600 mg 1 hour before surgery in order to avoid risks of infectious endocarditis.

DURING THE OPERATION

1. Procedures must be achieved in a restricted oral cavity area (by quadrants). Whenever isolated extractions are indicated, these must be performed in several appointments.
2. Anesthetic punctures must be carefully performed using aspiration technique. Truncal anesthetic technique must be avoided whenever possible.
3. Perform procedures in the most atraumatic possible manner.
4. Use of 3-0 absorbable sutures.
5. Hemostatic plugs: regenerated oxidized cellulose, absorbable gel sponges, collagen or fibrin and bone wax, followed by tension-free sutures and digital pressure with gauze.
6. Resort to electrical cauterization in cases where hemostatic measures are not sufficient.

AFTER THE OPERATION

1. Taking blood pressure.
2. Assessment of patient at least one hour after the surgical event, in the dental office, before discharging him.
3. Provide the patient with written instructions indicating usual post-operative measures to take after a customary oral surgery event.
4. Acetaminophen or paracetamol is the only analgesic agent to be administered since non NSAI increase risk of bleeding episodes.
5. In cases when uncontrolled bleeding is present for more than one hour with presence of ecchymosis or large size hematoma, inform the patient he must attend the dental office.

CONCLUSIONS

Patients treated with anti-platelet therapy attending dental practices where extractions or procedures involving bleeding are performed can be managed without modification to their treatment as long as consultation with their physician in undertaken. Laboratory tests must be performed and knowledge must be acquired on patients´ diseases. With all this knowledge, surgical interventions can be undertaken without incurring in complications, as long as all hemostasis measures are taken, always bearing in mind the fact that discontinuance of PT could bring about fatal cardio-vascular consequences for the patient.

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