Actas Dermosifiliogr. 2009;100:7-16

REVIEW ARTICLE

Anticoagulation and Antiplatelet Therapy in Dermatology

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Abstract. An increasing number of patients who are receiving anticoagulation or antiplatelet therapy require cutaneous surgery. Such pharmacotherapies are usually suspended based on experience in gynecologic, thoracic, and abdominal surgery. However, this practice may increase the risk of suffering a thromboembolic event. We review perioperative management of anticoagulant and antiplatelet therapy, complications associated with suspending therapy, and side effects.

Key words: anticoagulants, warfarin, heparin, surgery, acetylsalicylic acid, bleeding.

ANTICOAGULACIÓN Y ANTIAGREGACIÓN EN DERMATOLOGÍA

Resumen. Cada vez es mayor el número de pacientes que recibe tratamiento anticoagulante o antiagregante y que debe someterse a cirugía cutánea. Interrumpir estos tratamientos para prevenir el sangrado es una práctica habitual, extrapolada de las experiencias en cirugía ginecológica, torácica y abdominal. En este contexto, la suspensión de dichos tratamientos puede incrementar el riesgo de sufrir un evento tromboembólico. Realizamos una revisión sobre el manejo peroperatorio de los tratamientos anticoagulantes y antiagregantes, de las complicaciones acontecidas tras su suspensión, así como de sus efectos secundarios.

Palabras clave: anticoagulantes, warfarina, heparina, cirugía, ácido acetilsalicílico, sangrado.

Introduction

The number of patients scheduled for surgery who are taking anticoagulant or antiplatelet medication is growing: between 1.5% and 3.7% of patients undergoing cutaneous surgery are on anticoagulant therapy with warfarin, and it is estimated that some 25% are taking acetylsalicylic acid (ASA).[1] When patients are referred for cutaneous surgery, the dilemma facing the surgeon is whether or not to interrupt such therapy bearing in mind the risk this entails of increasing the incidence of thromboembolic events. The importance of this decision was highlighted recently by Schanbacher and Bennett[2] when they reported the cases of 2 patients who had thromboembolic strokes 1 week after undergoing cutaneous surgery for which treatment with warfarin had been suspended for 3 and 7 days prior to surgery, respectively.

This decision to suspend antiplatelet or anticoagulant therapy rarely depends on the prescribing physician, but rather is taken by the surgeon on the basis, usually, of personal experience rather than scientific evidence. Moreover, the surgeon is often unaware of the patient's actual level of thromboembolic risk.[2]

In spite of the high numbers of patients on antiplatelet and anticoagulant therapy and the fact that surgeons may have no information about why such therapy has been prescribed or the patient's current level of anticoagulation, no randomized double-blind studies have assessed the risk of perioperative bleeding.

When they surveyed the members of the American College of Mohs Surgery, Kovich and Otley[3] found that 80% of the surgeons discontinued treatment with warfarin before surgery, while only 26% did so in the case of ASA.

We will first differentiate between anticoagulation and antiplatelet therapy, analyzing the respective complications and interactions. We will then review the most commonly reported adverse effects associated with these drugs.

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Manuscript accepted for publication April 3, 2008.

Anticoagulants

The indications for anticoagulant therapy include the prevention of venous thromboembolism, the treatment of deep vein thrombosis, primary prevention of myocardial ischemia, acute myocardial ischemia, prosthetic heart valve,

Table 1. Anticoagulation Levels by International Normalized Ratio (INR) Values

INR	*Anticoagulation Level*
< 2	Low
2-3	Moderate
≥ 3	High

Abbreviation: INR, international normalized ratio.

atrial fibrillation, and valvular heart disease. In most of these diseases, the patient's international normalized ratio (INR) should be maintained between 2 and 3. An INR above 5 is associated with a high risk of major bleeding.[4] If the patient's INR is 4 or more, the anticoagulant regimen should be adjusted before surgery.

Coumarins (Warfarin and Acenocoumarol)

The coumarins (dicumarol and warfarin sodium) are synthetic derivatives of 4-hydroxycoumarin. They inhibit vitamin K-dependent coagulation factors and also interfere with the synthesis of proteins C and S. The effect of these agents peaks between 72 and 96 hours after oral administration, although response varies considerably from patient to patient. Consequently, both the dose and the INR must be monitored. Bleeding complications may develop hours or days after surgery. The risk arising from the discontinuation or reduction of anticoagulation therapy varies depending on the underlying disease.

Treatment should be discontinued or the dose reduced a number of days before surgery, and therapy should be reinstated on the day the surgical intervention takes place.[5] In most patients, it takes 4 days for the INR to reach 1.5 after withdrawal of warfarin and it is generally accepted that surgery can be safely performed once this level has been attained. When oral anticoagulation therapy is reinstated, it takes 2 days for the INR to reach 2. This means that a patient who stops taking warfarin 4 days before surgery and starts again immediately after the intervention will have a subtherapeutic INR for approximately 2 days before and 2 days after surgery, and will be only partially protected against thromboembolic events during this period.[6]

Oral anticoagulant therapy with coumarins is usually monitored by measuring prothrombin time (PT). This test determines the time it takes for fibrin clots to form when factor VII is activated using extracts of factor III of diverse origins, phospholipids, and ionic calcium (thromboplastin). Due to differences in extraction methods and the composition of the tissues used to obtain the laboratory reagents, different thromboplastins give rise to very different procoagulant properties. This problem was addressed by establishing the international normalized ratio (INR), defined as the ratio between the value in seconds obtained in the plasma of the patient and the value obtained with a plasma sample or batch of plasma samples designated as "normal" (Table 1). Prothrombin time increases with reductions in 3 of the 4 vitamin K-dependent procoagulant clotting factors (factors II, VII, and X).[5]

It should be remembered that certain drugs modify the pharmacodynamic properties of warfarin by inhibiting synthesis or increasing catabolism of vitamin K-dependent clotting factors, or by interfering with other pathways of hemostasis (Table 2). Foremost among the drugs that potentiate the anticoagulant effect of warfarin are the second- and third-generation cephalosporins (which inhibit vitamin K synthesis), thyroxine (which increases metabolism of the coagulation factors), clofibrate, salicylates at doses higher than 1.5 g/day, paracetamol, and, to a lesser extent, heparin.[5]

Furthermore, certain medications, such as ASA, nonsteroidal anti-inflammatory drugs (NSAIDs), penicillin (in high doses), and moxalactam, may increase the risk of bleeding when they are administered concomitantly with warfarin because they inhibit platelet function. ASA is of particular importance because its use is extremely widespread and it has a prolonged effect on hemostasis. The clinically significant risk of bleeding increases in patients taking high doses of ASA and warfarin (INR 3-4). Other drugs, such as erythromycin and certain anabolic steroids, potentiate the anticoagulant effect of warfarin through poorly understood mechanisms. The sulfamides and other broad-spectrum antibiotics also enhance the anticoagulant effect of warfarin because they reduce bacterial flora and this may lead to vitamin K deficiency. However, the effect only occurs in patients whose diet is deficient in vitamin K.[5]

Alcalay[7] evaluated bleeding complications during and after surgery in 16 patients on warfarin therapy who underwent cutaneous surgical procedures. His results indicate that the risk of perioperative bleeding does not increase in patients on warfarin undergoing surgery for skin tumors when the INR is between 2 and 3.5.

In a retrospective study of 653 patients, 26 of whom were taking warfarin, Otley et al[8] analyzed the occurrence of severe bleeding complications (intraoperative or postoperative bleeding lasting more than 1 hour and not controlled with compression, acute hematoma, graft or flap necrosis, and suture dehiscence greater than 2 mm). INR values were not determined prior to surgery. Only 1 of the 26 patients receiving warfarin therapy developed bleeding complications. The difference between the 2 groups (continuation of warfarin therapy compared to interruption of treatment 3 days prior to surgery) was not statistically significant. The authors concluded that the

Table 2. Drug and Food Interactions with Warfarin. Levels of Evidence.

Level of Evidence	*Potentiation*	*Inhibition*	*Without effect*
I	Alcohol (in large quantities in presence of concomitant liver disease), amiodarone, anabolic steroids, clofibrate, cotrimoxazol, erythromycin, fluconazole, isoniazid, metronidazole, miconazole, omeprazole, phenylbutazone, piroxicam, propafenone, propranolol, sulfinpyrazone, sulfamides	Barbiturates, carbamazepine, cholestyramine, griseofulvin, nafcillin, rifampicin, sucralfate, high vitamin K-content foods, large amounts of avocado	Alcohol, antacids, atenolol, bumetadine, enoxacin, famotidine, fluoxetine, ketorolac, metoprolol, naproxen, nizatidine, psyllium, ranitidine
II	Paracetamol, chloral hydrate, ciprofloxacin, dextropropoxyphene, disulfiram, itraconazole, quinidine, phenytoin, tamoxifen, tetracycline, flu vaccine	Dicloxacillin	Ibuprofen, ketoconazole
III	Acetylsalicylic acid and salicylates, disopyramide, fluorouracil (5FU), ifosfamide, ketoprofen, lovastatin, metolazone, moricizine, nalidixic acid, norfloxacin, sulindac, tolmetin, topical salicylates	Azathioprine, cyclosporine, etretinate, trazodone	
IV	Cefamandole, cefazolin, gemfibrozil, heparin, indomethacin, sulfisoxazole		Diltiazem, tobacco, vancomycin

Levels of Evidence I: strong evidence based on at least one systematic review of a series of well-designed randomized clinical trials. II: strong evidence based on at least 1 well-designed randomized clinical trial with an adequate sample size carried out in the appropriate clinical setting. III: evidence from well-designed nonrandomized clinical trials, pre- and post-treatment cohorts, case series, and case-control studies IV: evidence from well-designed non-experimental studies carried out by more than one center or research group. Adapted from Kovich O and Otley CC[3]

risk of hematoma or severe bleeding in patients who continue warfarin treatment is low. This minimal risk of bleeding is more acceptable than the risk associated with the thromboembolic events that may occur if anticoagulant therapy is discontinued.

Kargi et al[9] undertook a prospective study of 102 patients, of whom 21 were on warfarin and 37 were taking ASA. Five patients receiving oral anticoagulant treatment developed complications (hematoma, persistent bleeding, graft necrosis, or wound infection). These results were statistically significant when compared to the group not receiving such treatment. The authors concluded that, while it was not necessary to interrupt treatment with warfarin, hemostasis should be a particular concern in these patients.

Billingsley and Maloney[10] carried out a prospective study of 332 patients undergoing Mohs surgery, 12 of whom were taking warfarin. Five of these 12 patients had excessive bleeding during surgery (defined as bleeding taking longer than 3 minutes to control). When good hemostasis was achieved, no postoperative bleeding was observed. The authors concluded that it may not be necessary to discontinue warfarin therapy in patients undergoing dermatologic surgical procedures because they found no significant differences in postoperative bleeding complications between the group of patients taking warfarin and the controls.

In a retrospective study, Ah-Weng et al[11] reviewed 68 patients who underwent minor cutaneous surgery without interrupting warfarin treatment. INR values, which were measured before surgery, ranged from 1.1 to 3.4 (mean 2.5). There were no cases of excessive bleeding, hematoma, dehiscence, or necrosis. The authors concluded that surgery can safely be performed in these patients, and recommended determining INR values before surgery to identify individuals at higher risk of developing bleeding complications due to an abnormally high INR.

In a prospective study, Dixon et al[12] assessed the risk factors associated with postoperative bleeding in patients undergoing surgical excision of skin tumors. They studied 5950 patients and the INR was determined before surgery in all cases. Treatment with warfarin or ASA was only interrupted when the INR was higher than 3. They identified the following independent factors associated with postoperative bleeding: older age (67 years or older), concomitant warfarin therapy, surgery on or around the ear, and closure with a skin graft or flap. They also made the point that while most of the cases of postoperative bleeding were not life threatening, withdrawal of anticoagulant or antiplatelet therapy in patients at risk for thromboembolism could have a fatal outcome.

The most recent study is by Blasdale and Lawrence,[13] who evaluated the frequency of bleeding complications in warfarinized patients undergoing cutaneous surgery. This

Table 3. Types of Heparin Commercially Available in Spain.

Unfractionated heparin	*Low-molecular-weight heparin*
Calcium heparin	Enoxaparin sodium (Clexane)
Sodium heparin	Dalteparin sodium (Fragmin)
	Bemiparin (Afatinal)
	Tinzaparin sodium (Innohep)

prospective study enrolled 65 patients taking warfarin and 92 controls. The incidence of intraoperative and postoperative bleeding was recorded in both groups. The authors concluded that the risk of postoperative bleeding was greater in the patients on warfarin. However, since no correlation was found between the severity of postoperative bleeding and the INR determined before surgery, they concluded that measurement of INR was not a useful tool for identifying patients at higher risk for bleeding. No statistically significant differences were found between the 2 groups with respect to the risk of intraoperative bleeding. The authors concluded, therefore, that warfarin therapy should not be discontinued before cutaneous surgery. However, they did recommend the following measures in anticoagulated patients: careful planning of the surgical technique to be used, meticulous hemostasis, and postsurgical follow-up.

Patients taking warfarin who urgently require major rather than merely routine cutaneous surgery will benefit from vitamin K treatment to reduce the INR to acceptable levels within 24-36 hours without the administration of blood products. However, if the surgery is very urgent, fresh frozen plasma (FFP) should also be administered.[14] While FFP does not contain platelets, it does contain all of the other coagulation factors, including factors V and VIII. The levels of coagulation factors in FFP are similar to those found in an equivalent volume of circulating plasma in the blood stream of a normal individual. Large volumes of FFP are generally necessary to achieve hemostatic levels of coagulation factors that have been reduced by anticoagulation therapy, since these factors are not concentrated. The risk of circulatory overload is, therefore, the most important limiting factor for the use of FFP to support hemostasis. Patients at high risk for circulatory overload may benefit from treatment with a prothrombin complex concentrate. However, it should be noted that all such blood products entail the risk of parenteral transmission of infections, and should only be used in patients with severe bleeding or candidates for major emergency surgery.[14]

Heparins

There are no studies in the literature that evaluate the efficacy of low-molecular-weight heparin (LMWH) in cutaneous surgery. The data relating to heart surgery are inconsistent, with some studies showing an increase in surgical bleeding in patients on LMWH and others reporting no increase.[15,16] The interval during which patients interrupt anticoagulant therapy can be minimized by switching them from oral anticoagulation therapy to LMWH; this use of bridging therapy reduces the risk of thromboembolism. The dose-effect relationship is more predictable with LMWH than with unfractionated heparin. In addition, activated partial thromboplastin time does not have to be monitored and drug is administered subcutaneously (unfractionated heparin must be administered intravenously and the patient must be hospitalized) (Table 3).[1]

Antiplatelet Therapy

Acetylsalicylic Acid and Nonsteroidal Anti-Inflammatory Drugs

ASA prevents the rapid formation of platelet aggregates in injured vessels by irreversibly inhibiting cyclooxygenase activity and the production of thromboxane A-2 in the platelets. Patients taking ASA are at higher risk for immediate bleeding but not for delayed bleeding. The inhibitory effect lasts for 7 to 10 days (the lifetime of the platelet).

ASA is prescribed to reduce the risk of myocardial infarction and other cardiovascular events. Since the effect of such therapy is irreversible and lasts for the lifetime of the platelet, treatment should be discontinued 10 days before surgery to ensure that there will be a sufficient number of platelets with normal cyclooxygenase activity when the procedure is performed. Therapy can be reinstated the day after surgery.[17]

NSAIDs are prescribed for their anti-inflammatory and analgesic effect. They produce a reversible inhibition of cyclooxygenase activity, and the duration of the effect is limited. Theoretically, cyclooxygenase-2 selective NSAIDs should not affect platelet function.

As in the case of oral anticoagulant therapy, the need to discontinue ASA and other NSAID therapy before cutaneous surgery has been questioned. Although the safety of their use during cutaneous surgery has not been evaluated, it has been shown that they do not increase bleeding in orthopedic surgery.[19]

Bartlett[19] studied 119 patients and compared the outcomes from 2 cohorts: those receiving treatment with ASA, and a control group of patients not taking this

drug. Only 2 of the patients on antiplatelet therapy developed major complications (graft loss due to hematoma and bleeding requiring manual compression). No statistically significant differences were found between the 2 groups in the incidence of either major or minor complications.

In the retrospective study of 653 patients carried out by Otley et al,[8] 286 patients were on either NSAID or ASA therapy when they underwent cutaneous surgery. There were no statistically significant differences in the incidence of bleeding complications between the group receiving antiplatelet therapy and the control group. On the basis of these results, the authors recommended continuing treatment with ASA or NSAIDs during surgery.

Lawrence et al[20] also studied the frequency of bleeding complications in dermatologic surgical patients taking ASA or other NSAIDs. Since the outcomes in this group were similar to those of the controls, those authors recommended assessing bleeding time 7 days before surgery and only withdrawing antiplatelet therapy when the bleeding time observed was abnormally long.

In the study cited earlier by Kargi et al,[9] no complications were reported for any of the 37 patients on ASA therapy who underwent cutaneous surgery. The authors of that study concluded that the risk of major complications in dermatologic surgical patients on antiplatelet therapy with ASA was low.

In the study by Dixon et al,[12] treatment with ASA was not associated with an increased risk of bleeding.

Clopidogrel and Ticlopidine

Both clopidogrel and ticlopidine inhibit adenosine-triphosphate-induced platelet aggregation. Their effect becomes apparent between 24 and 48 hours after administration and reaches a peak after 3 to 5 days.

Ticlopidine is used to prevent thrombosis during the insertion of coronary stents and has also been shown to have an effect equivalent to that of ASA in the prevention of thromboembolic events in patients with cerebrovascular disease. Its use is associated with serious and occasionally fatal blood dyscrasias (neutropenia and bone marrow aplasia). Clopidogrel has a similar pharmacological profile and is as effective as ASA in the prevention of thromboembolic cardiovascular events in patients with a history of vascular disease, but it causes fewer side effects.[21]

No studies have assessed bleeding the complications associated with these drugs in the context of cutaneous surgery. However, it seems reasonable to extrapolate to ticlopidine and clopidogrel the complications associated with ASA and the precautions that should be applied when prescribing ASA.[1]

Cutaneous Side Effects of Anticoagulant and Antiplatelet Therapy

The skin is the organ most often affected by adverse drug reactions. Some 3% of hospitalized patients present a cutaneous adverse drug reaction during their stay in hospital.[22] Cutaneous side effects fall into 2 general categories depending on whether the onset is acute or chronic. Acute-onset lesions are usually more or less specific "syndromes" that often constitute emergencies and must be promptly diagnosed and treated. The pathogenesis may be related to the anticoagulant action of the drug or, alternatively, to a hypersensitivity mechanism. Any drug, including those described in this section, can produce a rash, but there are also clinical pictures that are typically associated with the use of these drugs in particular.

Coumarin Anticoagulant Therapy

Treatment with oral anticoagulants can give rise to many different cutaneous adverse reactions including ecchymosis and purpura, bleeding necrosis, bullous maculopapular eruptions, urticaria, and blue toe syndrome (Table 4).[23]

Coumarin-induced skin necrosis is a rare side effect with a prevalence of only 0.01% to 0.1%.[24] This adverse effect almost always occurs within 10 days of starting treatment, and incidence peaks between the third and sixth day. However, cases with later onset have been described, and even with onset as late as 2 years after starting treatment. The etiology may be related to imbalances in the anticoagulant-procoagulant system caused by a rapid decrease in protein C during treatment with courmarins.[24,25] As indicated above, coumarins block the synthesis of protein C, causing its action to decrease rapidly. In fact, the risk of developing this side effect is greater in patients with deficiencies in protein C, protein S, factor V Leiden, antithrombin III, or lupic anticoagulant. Skin necrosis takes the form of very painful erythematous or bleeding plaques, with blisters developing later and evolution towards necrosis of the subcutaneous cell tissue (particularly in areas with abundant adipose tissue, such as the breasts, hips, and thighs). This complication has been reported most often in obese women over 50 years of age who have received treatment for thrombophlebitis or pulmonary thromboembolism. Histologic examination reveals fibrin-platelet clots in the venules and arterioles of the deep dermis and hypodermis, and a varying degree of bleeding. Treatment requires the discontinuation of the anticoagulant therapy and sometimes involves the administration of FFP, intravenous vitamin K, or purified protein C concentrate (only when the patient has a deficiency of this protein). Occasionally, surgical debridement, grafts, or amputation may be necessary[26].

Table 4. Cutaneous Side Effects of Warfarin Therapy

Skin
Abscesses
Acral purpura
Bullous eruptions
Ecchymosis and hematomas
Rash
Exfoliative dermatitis
Bleeding
Livedo reticularis
Necrosis
Pruritus
Blue toe syndrome
Purpura
Ulcerations
Urticaria
Vasculitis
Hair
Alopecia
Others
Gangrene
Hypersensitivity
Lingual hemorrhage
Oral ulceration

Another rare side effect is blue toe syndrome. This syndrome develops 3 to 8 weeks after start of treatment and is more common in men. It is characterized by the sudden onset of bilateral purple discoloration of the toes and the sides of the feet, which blanches with pressure. Symptoms may persist for several months after anticoagulation therapy has been discontinued.[27,28] Coumarin-induced papular rashes are also very rare and few cases have been reported.[29,30] Urticarial rashes and bullous lesions are also exceptional.[24]

Heparin

The chief complications associated with heparin therapy are bleeding, thrombosis, and thrombopenia. The risk of these complications is lower with LMWH than with unfractionated heparin. However, all of these drugs can give rise to cutaneous side effects of differing frequency and severity (Tables 5 and 6).[23] Allergic reactions to heparin are a rare side effect. Reactions caused by a cell-mediated type IV hypersensitivity mechanism take the form of pruriginous erythematous plaques, and vesicles and blisters develop in some cases. Onset generally occurs months after starting treatment, although cases have been reported in which the latency period was only 7 to 10 days. The latency period may be shorter in previously sensitized patients. It is important to differentiate between this type of reaction and heparin-induced skin necrosis, a condition characterized by bleeding and necrotic lesions at injection sites. The latter can also affect internal organs and may even be fatal.[24] Cases have been reported in the literature of heparin necrosis associated with a functional and quantitative deficiency in protein S, protein C, and antiphospholipid antibodies.[28] Lesions may develop in distant locations, particularly on the thighs, abdomen, and buttocks, and especially in obese diabetic women. Most of these patients do not present with associated thrombocytopenia or thromboembolisms.[26,28] The lesions may become generalized if treatment is not discontinued.[31]

Heparin-induced thrombocytopenia is a syndrome defined by a platelet count below 100 000/mm^3, a fall in platelet count of more than 50% compared to baseline, resistance to heparin therapy, or the occurrence of thrombosis during such therapy. The syndrome develops in between 1% and 4% of patients 6 to 8 days after treatment. It occurs less often in patients receiving LMWH and in pediatric patients. There are 2 types of heparin-induced thrombocytopenia. The first is characterized by a fall in the platelet count unrelated to any immune mechanism during the first few days of treatment. By contrast, the second type is characterized by the presence of antibodies against platelet factor 4. The result is low platelet levels associated with a hypercoagulable state and the development of thrombosis in the vessels of the skin and other organs. Clinical manifestations include bleeding and occasionally blistered plaques that rapidly become necrotic. Treatment includes withdrawal of heparin and, in some cases, initiation of antiplatelet therapy.[24,32-34] Other symptoms that have been reported include generalized maculopapular rash occasionally with blistering, febrile rash (drug reaction with eosinophilia and systemic symptoms [DRESS]), Lyell syndrome, and flexural rash.[35]

The palmoplantar pruritus that has been observed after subcutaneous or intravenous administration of heparin is mediated by an immediate hypersensitivity mechanism and is probably a reaction to preservatives and contaminants (proteins of animal origin). Immediate reactions mediated by immunoglobulin E are very rare.[24]

Recently, Komericki et al[31] reported a case of acute generalized exanthematous pustulosis caused by dalteparin. This reaction is usually a side effect of treatment with anti-infective drugs.[29]

Table 5. Cutaneous Side Effects of Heparin Treatment

Skin
Allergic reactions
Angioedema
Baboon syndrome
Ecchymosis
Erythema
Rash
Fixed pigmentary eruption
Bleeding
Livedo reticularis
Necrosis
Acral edema
Purpura
Pruritus
Petechiae
Scleredema
Toxic epidermal necrolysis
Ulceration
Urticaria
Vasculitis
Eczemas
Induration
Necrotic lesions at injection sites
Hair
Alopecia
Nails
Pigmentary abnormalities
Others
Anaphylactic reactions
Gingivitis
Hypersensitivity

Table 6. Side Effects of Low-Molecular-Weight Heparins

Enoxaparin
Angioedema
Ecchymosis
Edema
Erythema
Rash
Necrosis
Acral edema
Pruritus
Purpura
Urticaria
Vesicular eruptions
Erythematous maculopapular rash
Anaphylactic reactions
Fat necrosis
Hypersensitivity
Erythema, hematoma, infiltrated plaques, and injection-site necrosis
Dalteparin
Allergic reactions
Bullous eruptions
Rash
Necrosis
Pruritus
Alopecia
Anaphylactic reactions
Hematoma, pruritus, and injection-site edema
Tinzaparin
Abscesses
Allergic reactions
Angioedema
Bullous eruptions
Cellulitis
Ecchymosis
Rash
Necrosis
Pruritus
Purpura
Urticaria
Alopecia
Anaphylactic reactions
Hypersensitivity
Hematoma and bleeding at injection sites

Acetylsalicylic Acid

Many cutaneous side effects of ASA have been reported. Some are caused by the antiplatelet action of the drug (such as bleeding, hematomas, ecchymosis) while others are idiosyncratic (dose independent and unrelated to the

inhibition of cyclooxygenase). The most commonly reported adverse effects are rash, urticaria, angioedema, and purpura. However, the following have also been reported albeit with less frequency: fixed drug eruption, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, vasculitis, pruritus, lichenoid eruptions, pustular psoriasis, parapsoriasis, petechiae, acute generalized exanthematous pustulosis, blistering diseases (dermatitis herpetiformis and pemphigus), and hypersensitivity syndrome.[23] Hypersensitivity syndrome is characterized by the presence of a skin eruption, fever, enlarged lymph nodes, visceral involvement (generally hepatitis), and abnormal laboratory test results (eosinophilia and atypical lymphocytosis) that appear between 2 to 6 weeks after start of treatment with a new drug.

Clopidogrel

Clopidogrel, like any drug, can cause allergic reactions. The incidence of such reactions is estimated to be between 1% and 2.5%.[23] Very few studies have evaluated the dermatologic side effects of clopidogrel. The Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared the efficacy of clopidogrel with that of ASA in patients at risk for acute myocardial infarction, ischemic stroke, or ischemic vascular disease. The frequency of severe rash was higher among patients treated with clopidogrel. However, the clinical characteristics of these eruptions have not been well defined.[36] Cases have been reported of thrombocytopenia associated with purpural lesions. These side effects usually develop within 2 weeks of start of treatment. The survival rate is high when the condition is diagnosed promptly, the drug withdrawn, and the patient treated with plasmapheresis.[37] Meissner et al[38] recently reported the case of a patient who developed a clopidogrel-induced pustular psoriasis. They recommend the addition of this drug to the list of medications that may induce or exacerbate psoriasis. Dogra and Kanwar[39] recently reported the first case in the literature of photosensitive lichenoid eruption in a patient treated with this drug. They make the point that the cutaneous side effects of clopidogrel are probably underdiagnosed because they are generally mild and in most cases do not require withdrawal of treatment. Very few cases of hypersensitivity or toxicoderma associated with the use of this drug have been reported in the literature.[40,41]

Ticlopidine

The reported incidence of cutaneous side effects in patients receiving ticlopidine ranges from 1% to 14% depending on the study. In 3% to 4% of these cases, therapy has to be withdrawn due to the severity of symptoms.[42] The most commonly reported cutaneous side effect is an urticarial or maculopapular rash (often with pruritus) that usually affects the trunk but occasionally spreads to the limbs. This rash usually appears during the first 2 weeks of treatment.[43,44] The other skin lesions associated with this drug that have been reported include fixed pigmentary eruption,[45] toxicoderma,[46] urticarial eruptions,[47] erythema multiforme,[47] maculopapular eruption,[47] erythromelalgia,[47] facial erythema, vasculitis,[42] and cutaneous lichen planus.[48]

Ticlopidine also causes thrombotic thrombocytopenic purpura, which generally appears within a few weeks of start of treatment and is caused by microvascular platelet thrombosis, although the mechanism is poorly understood. This reaction is characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, neurological symptoms, and kidney failure. Purpuric plaques may appear.[49] The mortality rate has been reported to be as high as 33%.[50]

Conclusions

In our review of the literature we found no evidence to support the discontinuation of anticoagulant or antiplatelet therapy before cutaneous surgery.

In patients taking anticoagulants it is, however, advisable to determine the INR before surgery when the procedure involves a high risk of bleeding whether because of the surgical technique to be used (extensive excision, grafts, flaps, or the need for general anesthesia), or because the intervention affects an area where the risk of bleeding is higher (face or scalp).

In addition, depending on the underlying disease, the relationship between the thromboembolic risk associated with withdrawal of treatment, the benefits of surgery, and a postoperative period with less risk of bleeding should be assessed.

Addenda

J. Thachil et al[51] have recently published a review of the management of surgical patients receiving anticoagulation or antiplatelet agents. They concluded that the risk of bleeding is low in dermatologic surgery, making it unnecessary to discontinue anticoagulant treatment. If the patient's INR is abnormally high, it should be reduced to within the normal range before surgery.

Conflicts of Interest
The authors declare no conflicts of interest.

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