Procoagulant Drugs

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Rainer B. Zotz, Nikola Zotz, and Christoph Sucker

12.1 Procoagulant Drugs

Procoagulant drugs are non-transfusional agents that are primarily used when bleeding is the consequence of a specific defect of hemostasis. In this chapter, the pharmacological properties and uses of desmopressin, antifibrinolytics, and vitamin K will be reviewed. Desmopressin, with its various procoagulant pharmacological effects, is used in the prevention and treatment of bleeding related to congenital and acquired coagulation factor deficiencies or platelet function disorders. Antifibrinolytics (inhibitors in particular steps of fibrinolysis) are the treatment of choice in bleeding caused by hyperfibrinolysis. Because of their low cost and their mild side effects, desmopressin and antifibrinolytics are also used as blood-saving agents in surgery. Vitamin K is given in states of vitamin K deficiency which lead to vitamin K deficiency bleedings. This is relevant to patients taking vitamin K antagonists in cases of urgent invasive procedures, asymptomatic and excessively elevated INR values, and bleeding.

12.2 Desmopressin

12.2.1 Description

Desmopressin is an analogue of the naturally occurring human antidiuretic hormone, vasopressin. It was first synthesized in 1967 by removing the N-terminal amino

R.B. Zotz (✉) • N. Zotz
Centrum für Blutgerinnungsstörungen und Transfusionsmedizin (CBT),
Immermannstrasse 65 a, Düsseldorf 40210, Germany
e-mail: zotz@hemo-stasis.de

C. Sucker
LaboMed Gerinnungszentrum Berlin, Tauentzienstrasse 7 b/c, Berlin 10789, Germany
e-mail: sucker@labomed.de

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group and substituting L-arginine with D-arginine (DDAVP, desamino-d-arginine vasopressin; full name, 1-desamino-8-D-arginine vasopressin). This modification leads to an extensive loss of the molecule's vasopressive effect, while the duration of its antidiuretic activity is significantly prolonged. These clinically useful attributes made it the drug of choice for the treatment of central diabetes insipidus (Vavra et al. 1968; Kohler and Harris 1988; Mannucci 2008). In the 1970s, it was observed that desmopressin also raises the level of plasma coagulation factor VIII when infused into healthy volunteers (Cash et al. 1974; Mannucci et al. 1975). This effect is due to the selective binding of desmopressin to the vasopressin receptor subtype 2 (V2R). When endothelial V2R are activated, they cause cyclic adenosine monophosphate (cAMP)-mediated signaling, leading to the exocytosis of Weibel-Palade bodies, where von Willebrand factor (vWF) is stored and then released. After the administration of desmopressin, a fast increase of vWF levels in plasma can be observed. The details of the simultaneous increase of factor VIII levels in plasma are still not fully understood, although the mechanism can be explained as an indirect increase due to vWF secretion, making more factor VIII binding sites available.

The Weibel-Palade bodies also store tissue plasminogen activator (t-PA), which is released in the same way as vWF. This leads to profibrinolytic activity, as t-PA converts plasminogen to plasmin and thus initiates fibrin degradation. This activity is enhanced by fibrin binding (Irigoyen et al. 1999; Kaufmann and Vischer 2003). For that reason, the concurrent administration of tranexamic acid is discussed.

In addition to the increased vWF, factor VIII, and t-PA levels in plasma, other procoagulant mechanisms are induced by desmopressin, e.g., its effect on platelet function. It was possible to show that desmopressin enhances platelet adhesion to the subendothelium. This is unaffected by the vWF concentration in plasma. Therefore, other agonists must facilitate the adhesion of platelets; however, the mechanism of their response to desmopressin is not fully understood (Sakariassen et al. 1984; Lethagen 1997; Balduini et al. 1999). Several findings suggest that intercellular messengers, secreted by monocytes, may play a role in the hemostatic effects of desmopressin. As a consequence of the vWF release, P-selectin, a component of the membrane of Weibel-Palade bodies and an important cell adhesion molecule for thrombocytes and monocytes, is integrated in the membrane of the endothelial cells. This enhances platelet adhesion and adhesion of monocytes to the extracellular matrix of endothelial cells. Furthermore, the monocytes upregulate the expression of tissue factor through a simultaneous expression of inflammatory cytokines (Galvez et al. 1997; Pereira et al. 2003).

12.2.2 Clinical Uses

The different procoagulant pharmacological effects of desmopressin make it an oft used drug for the treatment of several congenital and acquired bleeding disorders (Mannucci 1998). It is also being evaluated as a blood-saving agent in surgery or trauma (Mannucci and Levi 2007), as recent studies have shown that red blood

cell transfusion is significantly associated with infection, ischemic postoperative morbidity, prolonged hospital stays and increased associated costs, and decreased long-term survival (Murphy et al. 2007).

12.2.2.1 Desmopressin in Inherited Bleeding Disorders (von Willebrand Disease, Hemophilia A, Factor XI Deficiency, Platelet Function Disorders)

The chief virtue of desmopressin – the direct release of vWF – has two main functions in hemostasis. VWF is an adhesion protein that redirects circulating platelets to sites of vascular injury, particularly through larger multimers, which is essential for platelet plug formation. Furthermore, in plasma it forms a complex with coagulation factor VIII, thereby protecting it from inactivation and clearance (Weiss et al. 1977; Wise et al. 1991; Sadler 1998). This accounts for its most established applications in several inherited bleeding disorders, first of all von Willebrand disease (vWD) and mild hemophilia A. The mainstay of treatment in these patients is the replacement of the deficient protein at the time of spontaneous bleeding such as hemarthrosis or mucosal bleeding or before invasive procedures are performed (Franchini 2007).

VWD is categorized into three major types with several subtypes (Favaloro 2011). In patients with type 1 vWD and baseline vWF and factor VIII levels higher than 10 IU/dL, desmopressin is most effective (Mannucci 1997). In vWD types 2A, 2M, and 2N, a variable response pattern occurs, and the decision to use desmopressin should be made based on the results of a test infusion. Its use in vWD type 2B is traditionally considered contraindicated because of the transient appearance of thrombocytopenia, but there are a few case reports where it has been used safely. Patients with vWD type 3 are usually unresponsive to desmopressin (Gralnick et al. 1986; Casonato et al. 1994; Mannucci 2001).

The magnitude of the response of factor VIII to desmopressin usually varies in patients with hemophilia A as well and is not always linked to the basal levels of factor VIII coagulant activity (FVIII:C). However, an effective application of desmopressin is only reasonable in patients with mild hemophilia A (FVIII:C >5 %). A test infusion should be carried out to assess the efficacy in each patient to be treated. Therapeutic indications must, furthermore, take into account the type of bleeding episode or surgical procedure and the factor VIII levels that must be attained and maintained. Patients with severe hemophilia A do not respond to desmopressin at all (Castaman 2008).

A number of patients with vWD and hemophilia A are unresponsive or display adverse effects to desmopressin. In these cases recombinant interleukin-11 is being tested as an alternative hemostatic agent (Ragni et al. 2013).

Although limited, data from the available literature suggest a potential role for desmopressin in patients with milder factor XI defects for the treatment of bleeding episodes and the prevention of postoperative bleeding (Franchini et al. 2009).

The increase in adhesiveness of platelets to the subendothelial matrix and the augmentation of platelet aggregation by means of desmopressin has been proved to be efficacious in platelet function disorders (Cattaneo 2002). Independently of their classification (Podda et al. 2012), these are characterized by impaired platelet-dependent

hemostatic functions, associated with bleeding diatheses of varying severity, and manifested in mild to severe mucocutaneous bleeding. Due to the rarity and heterogeneity of these disorders, results of the treatment with desmopressin are only reported in a few case series and have not been corroborated by means of thorough clinical trials (Coppola and Di Minno 2008). The types of inherited platelet function disorder for which some evidence of the efficacy of desmopressin has been shown include delta-storage pool diseases, disorders of granule secretion, signal transduction disorders, thromboxane receptor deficiency, and May-Hegglin anomaly. Weaker evidence has been provided for Bernard-Soulier syndrome, Hermansky-Pudlak syndrome, and arachidonate metabolism defects. In severe platelet dysfunctions, such as Glanzmann's thrombasthenia, which is characterized by a missing or dysfunctional glycoprotein (GP) IIb/IIIa receptor on platelets, desmopressin has no clinically relevant efficacy (Nurden et al. 2012).

12.2.2.2 Desmopressin in Acquired Bleeding Disorders (Acquired vWD or Hemophilia A, Liver Cirrhosis, Uremia, Drug-Induced Platelet Disorders)

Desmopressin has been used in several acquired bleeding disorders, most importantly in acquired von Willebrand disease (AvWD) and acquired hemophilia A.

AvWD occurs in association with a variety of underlying disorders, most frequently in lymphoproliferative and myeloproliferative disorders, other malignancies, and cardiovascular disease. The bleeding pattern and the laboratory findings are similar to the congenital form of vWD. Classification, diagnosis, and the mechanism of the vWF deficiency in patients with AvWD are largely influenced by the underlying disorder or causative agent. Treatment should pursue two strategies: treating the underlying disorder if possible and treating AvWD itself (Sucker et al. 2009; Tiede et al. 2011). Desmopressin can be used to prevent and control bleeding in some patients with AvWD. However, success rates depend on the underlying disorder: they were low in cardiovascular (10 %) and myeloproliferative disorders (21 %), but higher in autoimmune (33 %), lymphoproliferative (44 %), and other neoplastic disorders (75 %) (Federici et al. 2013).

Acquired hemophilia A is a rare bleeding disorder in which patients present with bleeding episodes that are often spontaneous and life-threatening. It is caused by autoantibodies to factor VIII. While a minority of cases are associated with a variety of conditions, e.g., pregnancy, autoimmune disorders, cancers, and drugs, it occurs mostly in patients without concomitant diseases. Predictors of a clinical response to desmopressin include a low inhibitor titer (<5 Bethesda units) and a residual FVIII:C level greater than 5 % (Franchini and Lippi 2011). Current registry data reveal a good response in acquired hemophilia treated with desmopressin as a first-line agent (Baudo et al. 2012).

Desmopressin can also be used in patients with acquired platelet function disorders such as uremia, a complex metabolic disorder with a platelet dysfunction being the main factor responsible for hemorrhagic problems (Mannucci et al. 1983; Lee et al. 2010). In patients with liver cirrhosis who need invasive procedures, a benefit from treatment with desmopressin was shown several times (Burroughs et al. 1985;

Mannucci et al. 1986; Agnelli et al. 1995), but could not be confirmed in later trials (Wong et al. 2003; Pivalizza et al. 2003).

Finally, drug-induced bleeding disorders, especially if caused by antiplatelet agents, can be treated successfully with desmopressin (Levi et al. 2011). Theoretically, desmopressin could also be used in an attempt to control acute bleeding caused by novel anticoagulants (Brem et al. 2013).

12.2.2.3 Desmopressin as a Blood-Saving Agent in Surgery

Since it was first suggested in the mid-1980s that desmopressin could reduce blood loss and transfusion requirements in surgery (Salzman et al. 1986), numerous studies and several meta-analyses have proved, and failed to prove, a positive effect from its administration. One of the two latest analyses concluded that there was no convincing evidence that desmopressin minimizes transfusion or blood loss in surgical patients who do not have congenital bleeding disorders (Carless et al. 2004). The other analysis concluded that desmopressin reduces blood loss and transfusion requirements only slightly, but without a reduction in the proportion of patients who received transfusions (Crescenzi et al. 2008). Stratifying these trials into patients with a high risk of bleeding due to aspirin intake and/or a surgical intervention with expected high blood loss on the one hand and patients with a low risk of bleeding on the other, it can be shown that the use of desmopressin significantly reduces blood loss and the number of red blood cell units transfused in the high-risk group. In contrast, in subjects with low risk of bleeding, no significant benefit from using desmopressin was found (Zotz 2009).

12.2.3 Administration and Dosage

Desmopressin is usually administered by intravenous infusion and should be diluted in saline solution and slowly infused over the course of approximately 30 min. To obtain a maximum response from factor VIII and vWF, the optimal dose is 0.3 μg/kg. After 1 h the peak plasma levels are 3–5 times higher than baseline for factor VIII and almost 3–5 times higher than baseline for vWF. Half-life varies as well: in the ranges of 2–5 h for circulating factor VIII and of 6–9 h for vWF. A subcutaneous injection of 0.3 μg/kg produces a similar response, but peak plasma levels are reached more slowly. The recommended dose for children is similar to that for adults. When body weight is greater than 10 kg, the drug should be diluted in 50 mL of fluid, whereas in young patients weighing less than 10 kg, the volume of fluid should be 10 mL (Villar et al. 2002). In children under the age of 1 year, desmopressin should be used with caution because of adverse effects (see below).

The preferred route for home treatment is intranasal administration with an optimal dose of 300 μg in two puffs; in children this should be reduced to one puff. As intranasal administration elicits a slower and less marked response (maximum factor VIII level of approximately 2.5 times higher than baseline value), subcutaneous or intravenous routes of administration should be chosen if the maximum response is desired (Villar et al. 2002).

Repeated doses of desmopressin over short intervals of time are associated with a phenomenon known as tachyphylaxis – the progressively lower rises in the factor VIII and vWF levels. This must be taken into account when planning treatment for a prolonged period of time, e.g., in surgery with treatment lasting 7 days or longer. The factor VIII level should be checked daily, and blood samples should be taken 1 h after the completion of the infusion. In such cases it is particularly important to monitor the plasma sodium level (Vicente et al. 1993).

12.2.4 Side Effects and Contraindications

Desmopressin can cause side effects in about 30 % of patients, but in the vast majority of cases, these are transient and mild. Administration is frequently accompanied by headache, facial flushing, and a mild decrease in blood pressure and heart rate (Mannucci 1998). More severe, but rarer, are episodes of fluid overload, severe hyponatremia, and seizures due to the modest antidiuretic effect of the hemostatic agent. This affects mostly very young patients after the administration of several doses or patients receiving hypotonic fluids. Thus, desmopressin should be used with caution in small children and patients with congestive heart failure or renal insufficiency. Fluid intake should also be regulated.

There are reports of the occurrence of arterial thrombotic episodes associated with the use of desmopressin, but no significant difference in the frequency of venous and arterial thrombosis could be shown in cardiac, orthopedic, or other major surgeries. Nevertheless, in patients with a history of cardiovascular events or diffuse atherosclerosis, caution should be exercised when considering desmopressin treatment (Castaman 2008).

Finally, desmopressin is not contraindicated in an uncomplicated pregnancy. A recent review determined it had a good safety record and was effective in selected cases in reducing bleeding complications associated with pregnancy and childbirth (Trigg et al. 2012). However, as with all drugs, in this indication desmopressin should be used with caution.

12.3 Antifibrinolytics

12.3.1 Description

Antifibrinolytics work by inhibiting particular steps of fibrinolysis. There are three agents that have antifibrinolytic activity in humans: the kallikrein inhibitor, aprotinin, and two synthetic derivates of the amino acid lysine, tranexamic acid and aminocaproic acid. As aprotinin has been withdrawn from the world market because of safety issues (Fergusson et al. 2008), this chapter focuses on the lysine analogues that are effective alternatives and may be safer for patients (Hutton et al. 2012). Most of the clinical and efficacy data concern tranexamic acid, as it is the only available antifibrinolytic agent in some places. It also has a favorable risk-benefit ratio,

and it has been used for years in cases of most types of bleeding or surgery in patients with congenital or acquired bleeding disorders (Schulman 2012).

The antifibrinolytic amino acids tranexamic acid (*trans*-4-(aminomethyl)cyclohexane carboxylic acid) and aminocaproic acid (6-aminohexanoic acid) both operate by blocking the lysine binding sites on plasminogen molecules, inhibiting the formation of plasmin and therefore inhibiting fibrinolysis. Tranexamic acid is about ten times more potent than aminocaproic acid and binds to both the strong and weak sites of the plasminogen molecule to a higher extent (Mannucci 1998). The mechanism also has a protective effect on thrombocytes, because the inhibited conversion of plasminogen to plasmin prevents the plasmin-induced cleavage of several receptors on thrombocytes (Quinton et al. 2004).

12.3.2 Clinical Uses

Because of their mode of action, antifibrinolytic amino acids are used in disease patterns with an expected local or generalized hyperfibrinolysis. This is relevant for nonsurgical and surgical bleeding. Recent studies and reviews have shown evidence that tranexamic acid reduces blood transfusion particularly in patients undergoing nonelective surgery.

12.3.2.1 Antifibrinolytic Amino Acids in Nonsurgical Bleeding (Upper Gastrointestinal Bleeding, Bleeding in the Urinary Tract, Menorrhagia, Congenital and Acquired Bleeding Disorders)

For patients with upper gastrointestinal bleeding, clinical trials testing tranexamic acid have presented differing results. A meta-analysis from 1989 including patients with peptic ulcers, mucosal erosions, and other causes of bleeding found considerable reductions in recurrent bleeding, the need for surgery, and mortality (Henry and Oconnell 1989). When compared with a placebo, a recently prepared review demonstrated a beneficial effect of tranexamic acid on mortality, but not on bleeding or transfusion requirements (Gluud et al. 2012). As no randomized clinical trials on the benefits and harms of antifibrinolytic amino acids for upper gastrointestinal bleeding in patients with liver diseases have been conducted so far, their use in these patients can neither be recommended nor advised against (Marti-Carvajal et al. 2012).

Bleeding in the urinary tract may occur after prostatectomy resulting in hematuria. In clinical trials tranexamic acid or aminocaproic acid reduced blood loss in patients who had undergone prostatectomy by up to 50 %, as compared with a placebo. There was no reduction in mortality or the need for transfusion. In patients with bleeding from the upper urinary tract, this kind of treatment is contraindicated because of the risk of residual clots in the ureter and bladder (Mannucci 1998).

In women with heavy menstrual bleeding not induced by organic causes, tranexamic acid reduces blood loss by about 40–50 % (Bonnar and Sheppard 1996; Lukes et al. 2010).

Patients with congenital or acquired bleeding disorders may also benefit from the use of antifibrinolytic amino acids in cases of epistaxis, gingival bleeding, or menorrhagia. Furthermore, these agents are useful for the prevention of bleeding following minor surgical procedures or dental extractions (Seligsohn 2012).

12.3.2.2 Antifibrinolytic Amino Acids in Surgical Bleeding (Cardiac Surgery, Total Knee and Hip Arthroplasty, Orthotopic Liver Transplantation, Trauma)

Antifibrinolytic drugs are widely used in surgery. A 2011 review confirmed relevant reductions in blood loss and the use of allogeneic red cell transfusion when compared with placebo in adult patients scheduled for nonurgent surgery. There were no serious adverse events (particularly vascular occlusion, renal dysfunction, or death) when antifibrinolytic acids were applied (Henry et al. 2011).

The use of antifibrinolytic amino acids in surgery has been studied most thoroughly for cardiac surgery. In a meta-analysis from 2009, including 49 trials where all 3 antifibrinolytic agents were evaluated, the need for transfusion was reduced with tranexamic acid, aminocaproic acid, and aprotinin. Although aprotinin did not increase the risk of death, compared with a placebo, the point estimate was higher in the indirect comparison with tranexamic acid, there was a strong statistical trend in the direct comparison with tranexamic acid, and there were similar numbers in the direct comparison with aminocaproic acid. There was no increase in the risk of myocardial infarction with these agents (Henry et al. 2009).

In total hip and knee arthroplasty, there are currently 50 published peer-reviewed studies that evaluate the effectiveness of tranexamic acid. Meta-analyses of this literature have demonstrated that the use of tranexamic acid leads to significant reductions in both perioperative blood loss and the proportion of patients requiring postoperative transfusion (Watts and Pagnano 2012).

There is some evidence that antifibrinolytic drugs show efficacy in reducing red blood cell requirements in patients undergoing orthotopic liver transplantation. The effect depends not only on the patient's preoperative condition but also on the donor's liver quality as well as surgical conditions during the hepatectomy and anhepatic stages. Therefore, it will be important to identify patients who could benefit from prophylactic treatment in further evaluations (Sabate et al. 2012).

Along with its inhibiting function on fibrinolysis and its protective effect on thrombocytes, tranexamic acid has also been shown to modulate the inflammatory response to injury. However, the exact mechanism in surgery and trauma is as yet poorly understood (Rappold and Pusateri 2013). Studies on the use of tranexamic acid in trauma populations have only been conducted for the last few years. A recently published retrospective review (MATTERs study), including critically injured combat victims treated with tranexamic acid, demonstrated that unadjusted mortality was reduced in the group receiving tranexamic acid and the survival advantage was greatest in patients who received massive transfusions. The use of tranexamic acid was also, in an adjusted analysis, independently associated with survival (Morrison et al. 2012). A 2010 randomized prospective trial in patients

after traumatic injury (CRASH-2 trial) reported a reduction of in-hospital mortality in the group that received tranexamic acid. Furthermore, when tranexamic acid was given within 3 h of injury, mortality attributable to bleeding was reduced (Shakur et al. 2010; Roberts et al. 2011). In patients with traumatic brain injury, neither moderate benefits nor moderate harmful effects can be excluded (CRASH-2 Collaborators (Intracranial Bleeding Study) 2011). There is evidence that tranexamic acid reduces blood transfusions in patients undergoing emergency or urgent surgery (Perel et al. 2013).

12.3.3 Administration and Dosage

The half-lives of tranexamic acid and aminocaproic acid are 2.3 and 2 h, respectively. They can be administered orally (in the form of tablets or as an oral solution) or intravenously.

For the treatment of acute bleeding syndromes, due to elevated fibrinolytic activity, it is suggested that 5 g of aminocaproic acid be administered during the first hour of treatment, followed by a continuous rate of 1 g/h. This method of treatment should be continued for about 8 h or until the bleeding situation is under control. In trials regarding the reduction of perioperative blood loss, dose regimens for aminocaproic acid varied significantly. Loading or bolus doses ranged from 75 to 150 mg/kg; maintenance doses ranged from 1 to 2 g/h or 12.5 to 30 mg/kg/h infused over varying time periods (Henry et al. 2011).

The dosage recommendations for tranexamic acid are as follows: as intravenous injection in local fibrinolysis, 0.5–1 g two to three times daily, and in generalized hyperfibrinolysis, 1 g (15 mg/kg) every 6–8 h. The general recommendations for oral application are 3–4 g daily. In trials regarding the reduction of perioperative blood loss, dose regimens for tranexamic acid differed significantly with varying doses and time frames for drug administration. In trials involving cardiac surgery, the loading or bolus doses ranged from 2.5 to 100 mg/kg. The maintenance doses for these cardiac trials ranged from 0.25 to 4.0 mg/kg/h delivered over 1–12 h. A similar variation was observed in trials not involving cardiac surgery (Henry et al. 2011). Dosing of tranexamic acid must be reduced in patients with renal dysfunction.

12.3.4 Side Effects and Contraindications

The side effects of tranexamic acid and aminocaproic acid are dose dependent. They usually involve the gastrointestinal tract (nausea, vomiting, abdominal pain, and diarrhea). Headache and dizziness can also be observed. Sometimes allergic reactions may occur. No striking increase in the risk of thrombosis was observed when the drugs were used during operations (Mannucci 1998; Henry et al. 2011). The use of tranexamic acid in moderate (24 mg/kg) to high doses ($\geq$100 mg/kg) is associated with convulsive seizures after cardiopulmonary bypass (Kalavrouziotis et al. 2012; Koster et al. 2013).

12.4 Vitamin K

12.4.1 Description

Vitamin K was discovered by chance in 1929 and was immediately associated with blood coagulation. Vitamin K is a group of structurally similar, fat-soluble vitamins that cannot be synthesized by the human body, but are provided via nutrition and gastrointestinal bacterial flora. This group of vitamins includes two natural vitamers: vitamin K_1 and vitamin K_2. Vitamin K_1 – also known as phylloquinone, phytomenadione, or phytonadione – is synthesized by plants, and the highest concentration is found in leafy green vegetables. Vitamin K_2 – also known as menaquinone – constitutes the main storage form in animals and has several subtypes which differ in isoprenoid chain length. Vitamin K enables the posttranslational γ-carboxylation of coagulation factors II (prothrombin), VII, IX, and X and proteins C, S, and Z. Prothrombin and factors VII, IX, and X represent the classic vitamin K-dependent plasma clotting factors and participate in the formation of a fibrin clot. In contrast, proteins C, S, and Z are inhibitors of the procoagulant system. Protein C exerts its inhibitory activity by inactivating factors Va and VIIIa and enhances fibrinolysis with protein S as a cofactor. Protein Z serves as a cofactor for the inhibition of factor Xa by protein Z-dependent protease inhibitor (Ferland 2012).

12.4.2 Clinical Uses

The only verified area of application of vitamin K is the therapy and prevention of states of vitamin K deficiency which lead to vitamin K deficiency bleedings that cannot be cured by nutrition. This includes vitamin K prophylaxis in neonates immediately after delivery. The prophylactic administration of vitamin K to pregnant women treated with anticonvulsives, antituberculosis drugs, or coumarin derivates does not seem to prevent deficiency in the newborn infants (Puckett and Offringa 2009). Vitamin K deficiency bleeding has a low incidence in neonates and infants as well as in adults. Reasons for vitamin K deficiency in adults include chronic liver disease, short bowel syndrome, chronic inflammatory bowel disease, and biliary tract obstruction leading to poor nutrition and malabsorption of fat-soluble vitamins (De Simone and Sarode 2013). Until now, no randomized clinical trials have been conducted to assess the benefits and harms of vitamin K use for upper gastrointestinal bleeding in patients with acute or chronic liver disease. Its use in this treatment can neither be recommended nor advised against (Marti-Carvajal and Sola 2012). Impaired vitamin K synthesis can also be caused by a disturbance of gut flora by a broad-spectrum antibiotic therapy.

The most frequent reason for severe vitamin K deficiency bleeding in adults is the intake of vitamin K antagonists (coumarin derivates). Intracranial hemorrhage, for instance, is seen in up to 2 % of patients receiving these drugs and has a mortality rate as high as 79 %. Patients with superwarfarin poisoning represent special

cases. Superwarfarin, available as rodenticide, is 100 times more potent than medicinal vitamin K antagonists and has a half-life of 20–62 days (De Simone and Sarode 2013).

12.4.3 Administration and Dosage

Vitamin K can be taken orally and parenterally by means of intramuscular, intravenous, or subcutaneous injection.

A 2009 review demonstrated that a single dose (1.0 mg) of intramuscular vitamin K after birth is effective in the prevention of classic vitamin K deficiency bleeding in neonates. Oral vitamin K has not been tested in randomized trials for its effect in this indication, neither as a single nor as a multiple dose (Puckett and Offringa 2009).

In patients treated with vitamin K antagonists, there is a need for strategies to reverse the effect of the oral anticoagulation. This is the case when an urgent invasive procedure is required, when an asymptomatic patient presents with excessively elevated international normalized ratio (INR) values, or in bleeding patients. Therapeutic options include interruption of treatment with vitamin K antagonists, administration of vitamin K, and the administration of blood derivatives such as fresh frozen plasma, prothrombin complex concentrates, or even recombinant activated factor VII. The dosage of vitamin K in these indications consists of oral intake or a slow infusion of 5–10 mg of vitamin K, repeated after 12 h if necessary. This leads to an increase in coagulation factor activities within 8–16 h. The half-lives of the various vitamin K antagonists are different: 9 h for acenocoumarol, 6–42 h for warfarin, and 90 h for phenprocoumon. In phenprocoumon, additional doses of vitamin K after 3–4 days may be necessary to avoid new increases in INR and bleeding (Ageno et al. 2012). In patients with superwarfarin poisoning, major acute bleeding should be treated with prothrombin complex concentrates and intravenous vitamin K (10 mg daily for several days) followed by the administration of high doses of long-term oral vitamin K (25–50 mg daily over several months until the superwarfarin efficacy has faded away) (De Simone and Sarode 2013).

12.4.4 Side Effects and Contraindications

The side effects and contraindications of vitamin K depend on the route of administration. The main disadvantages of oral administration are that complete absorption is not certain and can be adversely affected by vomiting or regurgitation. With regard to intramuscular vitamin K administration, hematomas are possible. Intravenous vitamin K administration carries the risk of allergic and anaphylactic reactions, which might be lower when slow administration in saline solution is used, e.g., over 30 min. Subcutaneous administration exhibits a lower risk of hematoma or anaphylaxis; however, drug absorption has been shown to be inconsistent (Burke 2013).

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