Anticoagulants and antiplatelet drugs are used in the prophylaxis and treatment of thrombosis complicating disease entities and surgical procedures. The above-mentioned are administered separately or in combination with one another. Heparin and aspirin are classical drugs. They are burdened with side-effects, which include hemorrhagic complications, often life-threatening. Heparin is considered as a safe drug, although not free of complications. Thrombocytopenia is one such complication often requiring the discontinuation of heparin. The above-mentioned used to be a significant problem. The physician was faced with the need to treat thrombosis without the disposal of appropriate drugs. During the past 10 years many new anticoagulants appeared on the market, fulfilling the following criteria:

– efficacy without increased risk of hemorrhage,
– rapid and expected activity,
– easy to administer,
– laboratory control is not required, considering efficacy,
– relative low cost.

The new anticoagulants presented in the study belong to factor Xa inhibitors and direct thrombin inhibitors.

FACTOR Xa INHIBITORS

Fondaparinux

Fondaparinux is a pentasaccharide with anticoagulative activity. Its mechanism of action consists in the neutralization of the active factor X, combining both alternative coagulation pathways. The above-mentioned is possible by means of antithrombin, activated by the drug. Thrombin is insensitive towards the activity of fondaparinux. The biological activity of the drug is excellent with its peak level obtained after 2 hours since administration, and the half-life ranging between 14-20 hours. The drug is eliminated by the kidneys. The drug, which runs under the name „Arixtra” is used in the prophylaxis of venous thrombosis at a dose of 2.5 mg, as well as treatment of deep vein thrombosis and pulmonary embolism, as effectively as heparin. Fondaparinux is administered subcutaneously, once daily, at a dose of 5 mg in case of patients weighing less than 50 kg, 7.5 mg in case of patients weighing between 50-100 kg, and 10 mg in those weighing >100 kg. The drug should not be used intravenously and intramuscularly, while ambulatory administration is not a contraindication. Ambulatory control of the drug is not required, similarly to low molecular weight heparins (LMWH). The drug accelerates clot fibrinolysis. The following drugs potentiate the action of fondaparinux: non-steroid anti-inflammatory drugs, aspirin, clopidogrel, dipiridamol, ticlopidin, and oral anticoagulants.

Bleeding is one of the possible side-effects observed following the administration of fondaparinux, although does not occur more often, as compared to heparins. In case of arterial thrombosis (myocardial infarction and ischemic cerebral stroke) fondaparinux is ad-
ministered in combination with antiplatelet drugs. Fondaparinux is more effective in the treatment of pulmonary embolism and prevention of recurrent thrombosis, as compared to heparin. The drug was positively opinioned by the Committee for Medicinal Product for Human Use, considering management of patients with acute coronary syndromes, unstable angina, as well as myocardial infarction with and without ST segment elevation. Fondaparinux should not be used in case of patients with chronic kidney diseases, coagulation disturbances, hemorrhage, thrombocytopenia, bacterial endocarditis, and known allergy towards the drug. Patients subjected to epidural anesthesia or qualified towards dural sac puncture are at risk of local hemorrhagic complications leading towards neurological deficits, such as transient or permanent paralysis (1). In order to neutralize the effect of fondaparinux recombinant factor VIIa (90 µg/kg) preparations seem effective. The clotting time normalizes 6 hours after drug administration (3).

Idraparinux

Iдрapanirux is a synthetic anticoagulant, similar in structure to fondaparinux, selectively inhibiting factor X. Its half-time is significantly longer than that of fondaparinux, amounting to 6-7 days. Thus, the drug can be used subcutaneously, once a week, at a dose of 2.5 mg, being superior to fondaparinux and heparins (7). Since the product is synthetic (clean) there is no possibility of viral infections and is characterized by well-predictable pharmacokinetics. However, the drug is not free of complications, such as bleeding, especially intracranial. The above-mentioned is rarely observed and mostly concerns elderly patients and those with kidney insufficiency. Iдрапарин is especially recommended in case of deep vein thrombosis and pulmonary embolism, being as effective as oral anticoagulants in case of atrial fibrillation. Iдрапарин reduces the frequency of cerebral ischemia by 2/3. The major superiority of the drug over oral anticoagulants consists in unnecessary anticoagulation laboratory control, and thus, ambulatory administration.

Additionally, recurrent thrombosis is less frequently observed, in comparison to oral anticoagulants. Similarly to heparin the drug is administered during the initial period of prophylaxis and therapy, followed by simultaneous use of 4-5 days of oral anticoagulants, coumarin derivatives (4). Iдрапарин can be administered continuously, although this is burdened with the risk of bleeding, especially if administered for a period of more than six months (8, 9).

DIRECT THROMBIN INHIBITORS

Hirudin

Hirudin is an anticoagulant inhibiting thrombin. It is found in the saliva of leeches. It is obtained by means of genetic-engineering methods. It is a polypeptide composed of 65 amino acids. Hirudin has the ability of specific and reversible thrombin bonding at a proportion of 1:1. Under the influence of the drug thrombin loses all enzymatic abilities. Cofactors are not required and thus, in case of antithrombin and heparin II cofactor insufficiency the anticoagulative effect remains unchanged.

The activity of hirudin is immediate. Directly after intravenous administration APTT and TT are prolonged. The kidneys are responsible for hirudin clearing with the half-life ranging between 60-100 min. The above-mentioned can be extended to 5-9 hours following bonding with polyethylene glycol.

As opposed to low molecular weight heparins (LMWHs) hirudin penetrates into the thrombus and neutralizes thrombin, which is connected to fibrin filaments. Simultaneously, hirudin inhibits the deposition of platelets inside the thrombus. Such substances as plasma proteins and the vascular endothelium do not neutralize hirudin, thus the anticoagulative activity is easily predictable. Hirudin prevents platelet aggregation induced by thrombin. As opposed to heparin, thrombocytopenia is not observed. Hirudin inhibits the bonding of thrombin with thrombomodulin, necessary for the activation of C and S proteins (5).

The negative aspect of hirudin is connected with hemorrhagic complications, as a consequence of its bonding with thrombin, and inhibition of platelet activation by means of induced thrombin.

Preclinical experiments undertaken on animal models demonstrated the greater antithrombotic effect of hirudin, as compared to heparin, especially in case of disseminated intravascular clotting.
Clinical investigations in case of hirudin considered the following situations: PTCA, myocardial infarction, and venous thromboembolic disease. Hirudin was administered at a dose of 20 mg (intravenous bolus) before PTCA, followed by continuous infusion at a dose of 0.16 mg/kg during a period of 24 hours. Complications, such as myocardial infarction were observed in 1.4% of patients, in comparison to the group subjected to heparin therapy – 10.3% patients.

Death or recurrent myocardial infarction was observed in 6.8% of cases, as compared to heparin – 16.7%. Bleeding was observed in 4.7% of patients receiving heparin, and 1.2% treated by means of hirudin. Intracranial bleeding was observed in one patient after heparin injection. The above-mentioned was not observed after hirudin. Hirudin proved to be an effective anticoagulant in case of heparin-induced thrombocytopenia (6).

Additionally, hirudin proved effective in the prevention of venous thromboembolic disease, considering patients after endoprosthesis implantation or knee joint plasty. The drug was intravenously administered 12-24 hours after the surgical procedure, at a dose of 1mg/kg body weight, every 8 hours. The above-mentioned dose prevented deep vein thrombosis, its risk estimated at 2%.

Lepirudin

Lepirudin is a recombinant hirudin, its activity similar to that of hirudin. It is a polypeptide consisting of 65 amino acids, different from hirudin by the substitution of several amino acids. The half-life of lepirudin after intravenous administration amounts to 40 min, while that after subcutaneous administration-approximately 120 min. Lepirudin clearance is possible by means of the kidneys. Thus, in case of renal insufficiency the dose of lepirudin should be reduced.

Lepirudin is an alternative in case of patients with heparin-induced thrombocytopenia (10). Patients with proper renal function receive lepirudin at a dose of 0.4 mg/kg (bolus) followed by intravenous infusion 0.1-1.15 mg/kg/h as to maintain the level of APTT 1.5-2.5 its normal value. After the administration of lepirudin the kaolin-kephalin time (APTT) is linearly prolonged, proportionally to the dose of the drug. Lepirudin is responsible for the biosynthesis of its antibodies in 50% of cases treated by means of the anticoagulant for a period of more than 5-7 days (6).

Lepirudin-antibody complexes do not prolong anticoagulation activity. However, they prolong its renal clearance (11).

Hirulog (bivalirudin)

Hirulog is a synthetic peptide composed of 20 amino acids, being a fragment of the hirudin molecule. The N-end of the complex [D–Phe–Pro–Arg–Pro–(Gly)] reacts with the catalytic center of thrombin, reversibly inhibiting its function. The half-time of intravenously administered hirulog amounts to 25 minutes. Its activity is rapid, the peak obtained after 15 minutes. Hirulog is eliminated by the kidneys and metabolized in the liver. Only 20% of the anticoagulant is eliminated with urine. Following subcutaneous injection the maximum concentration of the drug is observed after 1-2 hours. There is no drug available, which neutralizes the effect of hirulog (12). The recommended dose of hirulog consists of an intravenous bolus – 1 mg/kg followed by intravenous infusion (2.5 mg/kg/h) for a period of 4 hours. If required this period can be prolonged to 20 hours (0.2 mg/kg/h). Clinical trials demonstrated that hirulog is as effective as heparin, especially in combination with aspirin considering patients subjected to PTCA (13).

Argatroban

Argatroban is a low molecular, arginine derivative synthetic peptide, which bonds specifically and reversibly with the catalytic center of thrombin. Thus, the drug prevents fibrinogen lysis and platelet activation. In comparison to heparin, argatroban is a more potent thrombotic inhibitor developing after vascular injury.

Thrombin combined with fibrin fibers demonstrates resistance to heparin, and not to argatroban. The drug inhibits platelet aggregation by means of thrombin-thrombus bondage, thus, argatroban is more effective in the treatment of arterial thrombosis, as compared to heparin. Animal investigations (dogs) demonstrated that argatroban accelerates thrombolysis induced by alteplase. It is even more efficient when combined with aspirin. The above-mentioned reduces the
risk of reocclusion (12). The half-life of argatroban ranges between 39 and 51 min. The drug is metabolized in the liver, and is not eliminated by the kidneys. Thus, renal function has no influence on the pharmacokinetics of argatroban (14). The drug has no influence on antibody biosynthesis. The average intravenous dose amounts to 2 µg/kg/min. It can be used as an anticoagulant in case of heparin-induced thrombocytopenia (HIT). Argatroban is recommended as an anticoagulant in case of PTCA (bolus 350 µg/kg followed by intravenous infusion 15-40 µg/kg/min) or in combination with aspirin (325 mg). Bleeding is not observed more often than after heparin (15). Neutralizing drugs remain to be found. The following side-effects were observed: diarrhea, headache and rash. It is worth mentioning that argatroban, contrary to other direct thrombin inhibitors is responsible for INR value elevation. This might pose difficulties when beginning oral anticoagulation.

Xymelagatran / Melagatan

Melagatan is a synthetic dipeptide bonding reversibly with thrombin, inactivating its enzymatic functions. Xymelagatran can be administered intravenously or orally. Inside the human body it converts to melagatran, which also exerts antithrombotic activities. The peak of the drug is observed one hour after oral ingestion (16). Xymelagatran is administered at a dose of 48mg, twice daily for a period of 6-9 days. Significant bleeding complications were not observed when the above-mentioned dose was applied. Based on clinical trials the drug is considered, both as effective, and safer than heparin (17).

Napsagatran

Napsagatran is a potent thrombin inhibitor. Animal experimental investigations demonstrated that it prolongs the clotting time with significant predictability. Bleeding complications are possible, central nervous system hemorrhages were observed. Clinical investigations are under way, aimed at optimizing the dosage of napsagatran in combination with GP IIb, IIIa platelet receptor antagonists in the prevention and treatment of vascular thrombotic lesions (13).

Inogatran

Inogatran is a new, synthetic thrombin inhibitor. It bonds selectively and rapidly with thrombin. The in vitro level of 23 µmol/l prolongs the thrombin time by twofold, while its concentration of 1.1 µmol/l - the kaolin-kephalin time (APTT). Activated platelet aggregation is inhibited by inogatran, at a dose of 17 µmol/l. After the intravenous administration of 1.1 µmol/kg of inogatran its maximum plasma concentration was observed (7 µmol/l), corresponding to a threefold prolongation of the kaolin-kephalin time (APTT). The drug is well-tolerated, side-effects are practically absent, only prolonged bleeding time is sometimes noted. The half-life of inogatran amounts to one hour. The drug is not metabolized and is eliminated from the organism in its unchanged form by means of urine and stool. Thrombin activity markers (thrombin- antithrombin complexes and prothrombin 1+2 fragments) demonstrate a decreasing tendency during intravenous drug infusion. Inogatran has no influence on fibrinolysis or protein C activation. It is a safer drug, in comparison to argatroban and napsagatron (12).

Efegatran

Efegatran consists of three peptide chains, being a potent and direct thrombin inhibitor. The drug is safe. Medical literature demonstrated one case of hemorrhagic complication - presence of hematoma after coronarography. The drug does not prolong the bleeding time. The antithrombotic activity depends on the dose of the drug. The average dose of the drug considering intravenous infusion amounts to 0.63 mg/kg/hour (12).

Control of the activity of direct thrombin inhibitors

Direct thrombin inhibitors prolong the kaolin – kephalin time (APTT). However, the prolongation is not linear, which poses interpretative difficulties considering the required anticoagulant dose. The search for the control of the activity of direct thrombin inhibitors was rewarded with success following the introduction of the blood ecarin clotting time. Ecarin is derived from snake venom (Echis carinatus), clotting blood following the activation
of prothrombin to meizothrombin, which is inactivated by direct thrombin inhibitors, especially hirudin leading towards prolonged blood ecarin clotting time. This prolongation is proportional to the dose of the inhibitor, being superior to the APTT level (18).

It seems that the blood ecarin clotting time will gain full acceptance and will be introduced into the hemostatic laboratory parameters. Until then we will be using APTT values, knowing that the above-mentioned might be unreliable, considering therapy control by means of direct thrombin inhibitors.

The presented drugs found application in the antithrombotic prophylaxis, especially in orthopedic surgery. They are an alternative to heparin, especially in case of heparin-induced thrombocytopenia. Their easy application and lack of need for the control of their activity are responsible for their more and more frequent use.

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