Cardiovascular Pharmacology: Open Access
ISSN: 2329-6607
Noble, Cardiovasc Pharm Open Access 2018, 7:1
DOI: 10.4172/2329-6607.1000231
Case Report Open Access

Anti-Thrombotic Drug Problems

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Received date: December 18, 2017; **Accepted date:** January 10, 2018; **Published date:** January 17, 2018

Abstract

Antithrombotic therapy is associated with significant medical complications, particularly bleeding of the anti-coagulants used long term by the oral route, warfarin is the safest because the dosage is regularly adjusted according to the results of INR tests. There have recently come into common use a number of oral anti-coagulants that are given as a fixed dose with no monitoring. These include rivaroxaban, dabigatran, apixaban and edoxaban and a number of blockers of the coagulation cascade, such as Factor Xa and thrombin in inhibitors. Injected heparin and low-molecular heparins are mostly used for emergency or initial circumstances. The side effects of adminstration of such drugs are haematuria, melena, epistaxis, ecchymosis, hematemesis, haemoptysis, haemorrhagic stroke and heavy periods in women.

Introduction

An 82 year old male patient (weight 110 kg, height 173 cm, BSA 2.3m^2) was admitted to hospital with loss of consciousness. Previous medical history included three major joint replacements and widespread diverticular disease. Pulmonary embolus to the right upper lung lobe was diagnosed by CT contrast angiography. The medical registrar explained to the patient that he would be treated with dalteparin injections. This decision was over ruled by the consultant who discharged the patient on fixed dose rivaroxaban daily 40mg for 21 days followed by 20 mg. No Factor Xa effect monitoring was provided. This ignored the fact that rivaroxaban is contra-indicated in patients with diverticular disease from which the patient suffered. An FDA report [1,2], acknowledged 87,540 people reported to have side effects when taking rivaroxaban. Among them, 38 people (0.04%) had diverticulitis intestinal haemorrhage. This prescription also ignored the fact that the patient was being treated with ibuprofen for osteo-arthritis. Ibuprofen increases the risk of bleeding from rivaroxaban [3,4]. Two months after discharge the patient experienced pain in his left side that he assumed was a side strain. The pain increased in intensity and area of pain which was assumed to be muscular strain. The patient's wife then noticed massive ecchymosis stretching from the top of the natal cleft round to the left anterior axillary line of the abdomen. This faded over the period of the subsequent month. The pain extended into the left iliac fossa beyond the limit of the superficial bruising, suggesting bleeding in deeper tissues.

Rivaroxaban was stopped, but the patient still experienced pain in the same areas, even though the haemoglobin concentration had not decreased. Subsequent abdominal ultrasound scanning and CT scanning failed to reveal any abnormalities. Renal function remained normal. However the pain continues in the same distribution within the chest and abdominal walls. The only treatment is analgesic medication.

Discussion

The first error

The same dose in mg is administered to some people who are of normal, increased or decreased mass. This inevitably means that patients with increased mass (large patient in Figure 1) will be undertreated, being too low on the effect/drug blood concentration curve [5]. A patient with lower body mass (small patient in the figure) is over treated because he/she is too high on the effect/drug blood concentration curve and is very likely to bleed. The fundamental error perpetrated by the drug industry is to develop fixed dose tablets without monitoring and titration of dose. ALL drugs should be administered in mg/Kg and be available in a sufficient number of strength of tablets to enable the physician to prescribe by mg/Kg.

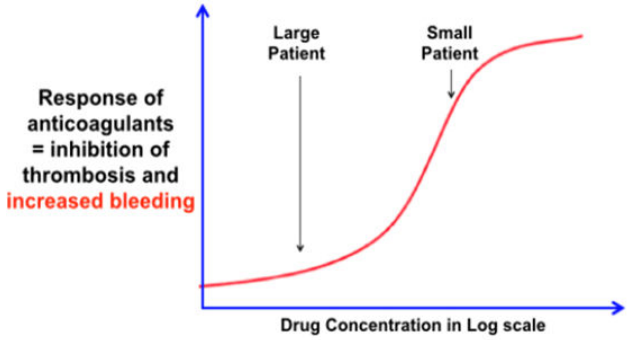

Figure 1: Schema to highlight why drugs should only be prescribed in mg/Kg body mass. If the drug concentration is unknown, a large patient is likely to be too low on the the concentration/effect curve and be undertreated. A small patient may be too high on the concentration/effect curve and bleed.

The second error

Every human individual is unique; they are not all identical to the average. The same drug dose should not be applied to everybody because the receptor mechanisms of actions vary from individual to individual. In order for correct dosage to be achieved, each patient should have the effect and the blood concentration measured, using the appropriate blood tests, assays or bleeding time. Thus, in the case of the patient described, Factor Xa effect monitoring [6], should have been mandatory in the presence of two contraindications (diverticular disease and ibuprofen treatment), in addition to blood concentration measurements (Figure 2).

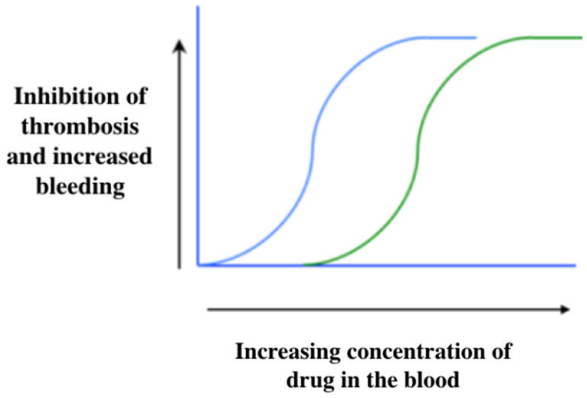

Figure 2: Schema to highlight the fact that individual patients have different sensitivities to drugs. For a fixed dose regime, the patient with the green effect/drug blood concentration curve will be under treated whereas the patient with the blue effect/drug blood concentration curve will be over treated and likely to bleed.

The third error

Checks should always be made for contra-indications. The patient's history and records will provide a list of the diseases present in the patient, and especially in elderly patients, these can be multiple. Most doctors work with a computer from which they can access the internet and search for each of these diseases for which the proposed drug treatment is contra-indicated. If this had been carried out in the case described above, the FDA report [2], that rivaroxaban is contra-indicated in patients with diverticular disease would have appeared in an instant, and an alternative treatment prescribed.

The fourth error

Checks should always be made for possible drug interactions. The patient's history and records will provide a list of the drugs being administered on repeat prescriptions for chronic conditions, especially in elderly patients in whom these are often multiple. Most doctors work with a computer from which they can access the internet and search for each of these drugs with which the proposed drug treatment may interact. It is a similar problem to that illustrated in Figure 2, a shift in sensitivity to the drug, e.g., moving the effect/drug blood concentration curve to the left. If this had been carried out in the case described above, the WebMD and RxList reports [3,4], that ibuprofen increased the risk of bleeding from rivaroxaban would have appeared in an instant, and an alternative treatment prescribed.

Anti-platelet agents

The problems described for anti-coagulants (that are indicated for treatment of venous thrombosis, pulmonary embolism and atrial fibrillation) above apply equally to anti-platelet agents that are indicated for treatment of arterial thrombosis. Figure 4 quotes the examples (with mode of action indicated) of aspirin, clopidogrel, ticagrelor, prasugrel, and elinogrel and there are some that block the glycoprotein (GP) IIb/IIIa receptor itself (Figure 4) but they cause excessive bleeding and are usually only used for emergency situations. The most commonly used therapy is so-called dual antiplatelet therapy, which is a combination of aspirin and clopidogrel. According to the FDA reporting system [7], "Both aspirin and clopidogrel were associated with haemorrhage, but the association was more noteworthy for clopidogrel. The total number of co-occurrences was not large enough to compare the association with bleeding complications for the another 5 antiplatelets" (Figure 3).

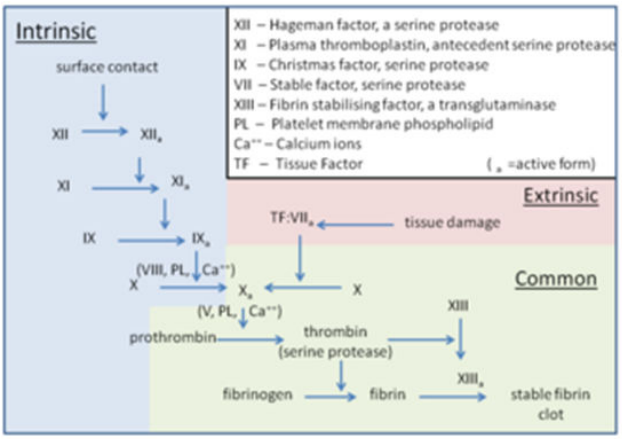

Figure 3: The coagulation cascade. Antagonism of any step may result in anti-coagulation. Rivaroxaban inhibits both free Factor Xa and Factor Xa bound in the prothrombinase complex. It is a highly selective direct Factor Xa inhibitor with oral bioavailability and rapid onset of action.

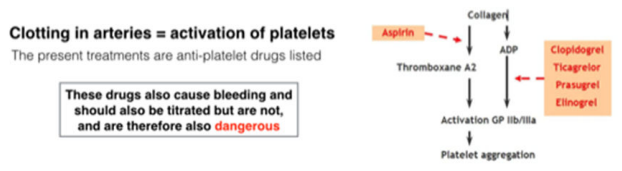

Figure 4: The same problems as those caused by anti-coagulation occur with anti-platelet treatment of the types illustrated.

I have experienced a small female, discharged after an acute coronary syndrome, on clopidogrel standard dose of 75 mg, who died of a cerebral haorrhage in a different hospital; this was not reported as an adverse event of anti-platelet therapy. This makes me suspect that

bleeding as a result of this treatment occurs more often than the FDA statistics express.

A prospect in arterial disease

The problem in the case of arterial disease was solved by consideration of the pathophysiology of the disease [8]. Thrombotic occlusion occurs within arterial stenoses within which there is increased blood velocity and shear stress caused by convective acceleration. The activation of platelets at these sites is due to the increased shear stress, followed by thrombus growth due to activation of more platelets via the serotonin 5HT2A platelet receptor, a positive feedback phenomenon. This process is completely abolished by 5HT2A antagonists [9]. Moreover, as there is no serotonin in tissues other then brain and platelets, the 5HT2A receptor antagonist used by McAullife et al. [9], has no effect on bleeding time as confirmed in human patients [10], without significant adverse effects. The consistent refusal of the pharmaceutical industry to develop a 5HT2A antagonist for treatment of arterial disease is another fact that is not understandable.

Conclusion

Fixed dose antithrombotic drugs carry a high risk of bleeding as an adverse event, because the concentration of the drug in the blood is unknown. Small patients and patients with increased sensitivity to these drugs are particurly at risk, as are patients with other diseases and patients taking other drugs with which the anti-thrombotic drug interacts. It is recommended that, in cases of venous thrombosis, pulmonary embolus and atrial fibrillation, for which the anticoagulant class of drug is indicated as treatment, the doses should be delivered in mg/Kg body mass, not as mg, and there should be titration of dose, and close continuous monitoring. In the case of arterial disease, for which anti-platelet drugs are used, this practice should be halted and replaced by treatment with a serotonin 5HT2A antagonist, e.g., Th001 (ArteclereTM TM), which inhibits arterial thrombus but causes no bleeding [10]. The pharmaceutical industry should make such drugs available as soon as possible.

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