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HLS

PHARMACOLOGY فارما

LECTURE المحاضرة

5

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EDITED تعديل

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#معكم_خطوة_بخطوة

Lec.5

*most of natural derived compounds have high antigenicity and cause allergic reactions.

All of antiplatelets and anticoagulant cause bleeding adverse effect (prevent pathological plug and clot formation which is useful, but they also interfere with physiological normal clots that are formed in response to vascular damage).

*some adverse effects of heparin:

1.hypersinsitivity

2.bleeding

3. heparin induced thrombocytopenia (HIT)>> paradoxical phenomena immune mediated

يعني المريض بعد م ياخد ال heparin بعض ال immune reactions attacks platelets response to heparin infusion ,which will cause sever reduction of platelets number.

Rememeber: heparin dose not affect on platelets number, only induces the antithrombin 3,

لانه عدد الصفائح الدموية ممكن يقل كثير بهذه الحالة بنتوقع انه القدرة على تكوين الجلطات رح يقل ويصير نزيف لكن الغريب انه بصير العكس يعني بالرغم من نقص عدد الصفائح الا انه ممكن يصير arterial and venous embolism.

الحل في هذه المشكلة النادرة:

1.discontinue heparin

2.replace with another parenteral anticoagulant as Argatroban.

3.not recommended to switch to LMWH

عند المرضى الي بصير معهم heparin induced thrombocytopenia ما استبدل ال unfractionated heparin to LMWH لانهم بعملو نفس المشكلة يعني في بينهم cross reactivity.

4.osteoporosis ,in chronic anticoagulant users as in patient with prosthetic joint ,(any case that can increase the risk of thrombosis).

*when is heparin contraindicated?

1. hypersensitivity to heparin
2. bleeding disorders as hemophilia (coagulation factor deficiency)
3.alcoholism
4.recent surgery of brain,eye,spinal cord and some of others, due to damage in blood vessels and other tissues (wound is not completely healed after 1 or 2 weeks after surgery), surgery wounds take months to years to be healed.

ARGATROBAN

*synthetic (less hypersensitivity rxn than heparin), parenteral, l-arginine derivative.

*MOA: direct thrombin inhibition, remember the most essential coagulant factor that convert fibrinogen into fibrin clot.

*therapeutic use:

In cases of HIT, or in patients that are risk of developing HIT.

*Ph.kinetics: half life is 40-50 mins, metabolized in the liver.
Monitor: aPTT, HB, hematocrit.
Adverse effects: bleeding.

Bivalirudin, Desirudin

*parenteral, natural derived, analogues of hirudin (derived from medicinal leech.
*MOA: selective, direct reversible thrombin inhibitors.
*therapeutic uses:
Bivalirudin :Wide range of uses as heparin….
1.alternative to heparin in patients undergoing PCI at risk of HIT.
2.pateints with unstable angina undergoing angioplasty
Desirudin:
Used to prevention of DVT in patients undergoing major surgeries as hip or knee joint replacement surgery in this case we said there is high chance to develop thrombosis, another problem in these patients after surgery there is long period of time patients will be immobilized so may develop of DVT.
اي حالة بتعمل stagnation للدورة الدموية تزيد فرصة حدوث ال thromboembolism.

Fondaparinux

*synthetic, pentasaccharide sequence(active part) of heparin.
*MOA:

Similar to LMWH binds to antithrombin III and potentiates neutralization of factor Xa.
*therapeutic use: as heparin
Ttt of DVT,PE, and prophylaxis in abdominal /hip surgeries.
*ph.kinetics: as LMWH predictable which means you don't require frequent monitoring of bleeding time, PTT….
*Adverse effect: bleeding.

Oral anticoagulants

they are interfere with formation of fibrin clot.
The most important group are vitamin K antagonist only drug of them called Warfarin, is derived from coumarin plant source, found in cinnamon.

*warfarin is require frequent monitoring of INR (parameter that measures the time needed for blood to clot), because warfarin has very narrow therapeutic index.

Warfarin is given chronically,

فلازم نضل نراقب نسبته بالدم لانه لو زاد شوي رح يعمل نزيف ولو قل شوي تأثيره رح يضعف ويرجع المريض يصير معه تجلطات.

INR "international normalized ratio" normally is about 1.

المرضى الي بنعالجهم بال warfarin رح نلاقي ال INRزادت عن 1 لانه الوارفارين مضاد للتجلط ف اكيد الوقت المطلوب عشان الدم يتجلط رح يزيد مع استخدامه (الوقت بنحسبه بالدقائق). الوقت المطلوب لتجلط الدم مع استخدام

الوارفارين 2-3 , فلو مريض صار عنده ال INR=6 معناته الوارفارين دخل بال toxic dose, فبكون المريض معه نزيف شديد.

MOA: warfarin inhibits vit.k epoxide reductase, cause depletion of reduced form of vit.k

رح يستمر انتاج عوامل التخثر ولكن مش فعالة

In normal conditions, vit.k is required for the synthesis of coagulation factors II,VII,IX,X in the liver, all of them need activation by carboxylation of glutamic acid residues (vit.k-dependent posttranslational modification " editing on polypeptide chain")

يعني لازم يتم اضافة gamma carboxyl glutamyl residue ,

This active group helps the clotting factors to adhere to activated platelets in the site of injury.

هذا التفاعل الكيميائي مهم عشان يزيد تنشيط عوامل التخثر وتصير تعمل الخثرات بكفاءة افضل في مكان الجرح و هاد التفاعل بحتاج فيتامين k كعامل مساعد وهو في حالة ال reduced وخلال التفاعل رح يصيرله اكسدة ويتحول الى vit.k epoxide (oxidized)

وعشان اضل استفيد من vit.k لازم ارجعه الى reduced form by vit.k epoxide reductase.

*therapeutic uses of warfarin:

Prevention and ttt of thromboembolic diseases:

1.DVT,PE

2.stroke prevention

3.stroke prevention in setting of atrial fibrillation (because in this case pumping function of atria it isn't effective so blood will stasis inside the atria)/prosthetic heart valves.

4.protein C and S deficiency

5.antiphosphalipid syndrome

6.following orthopedic surgeries

*ph.kinetics:

Oral (100% bioavailability),,,highly bound to albumin (this lead to drug-drug interaction)

Sulfonamides(to ttt urinary tract infection) compete the warfarin at the same binding site on albumin, so free form of warfarin will increase so bleeding will happen.

Also due to highly protein binding ,warfarin is affected by plasma PH.

*Warfarin cross placenta, highly teratogenic " is currently listed as category D drug for pregnant women with a mechanical heart valve, and category X for all other indications in pregnant women.

*drug of choice as anticoagulant is heparin in pregnant women.

*ph.kinetics:

Half life is 40 h relatively long. But its effect or time of action may be delayed for 72 to 96 h

يعني تأثيرخ يستمر مدة اطول حتوى صارله ازالة من الجسم

السبب: هو انه ال factor X يحتاج من 48 الى 72 ساعة حتى يتم تصنيعه من جديدو عشان هيك تأثير ال warfarin يستمر من 72 الى 96 ساعه,وعشان هيك تاثير الدواء هاد يظهر بعد يومين الى 3 ايام من اعطائه بالتالي في عرضه انه يصير تجلط بهالفتره

لذلك في بروتوكول انه لما نوصف warfarin خلال اول يومين لازم نعطي معه اشي بشتغل بسرعة مثل ال heparin

*antidote: vitamin K ,require 24 h to overcome the anticoagulant effects of warfarin

ممتاز بس بياخد وقت عشان بدو يصنع newly active coagulant factors

*ph.kinetics:

Warfarin is metabolized in the liver by CYP450 (CYP2C9)

Some drugs as sulfa agents or grapefruit juice can inhibit this system so no metabolism of warfarin>>> potentiation effect that means increase action of warfarin, this is ph.kinetic interaction.

Such of ph.dynamic interaction with warfarin is Aspirin (antiplatelets)

ممكن الاسبرين والوارفارين ينعطوا مع بعض ولكن رح يزيدوا فرصة حدوث النزيف.

Some drugs induce the metabolism of warfarin so decrease its effect.

*adverse effects:

1.bleeding ,,treated by stopping warfarin completely and giving vit k orally or IV,

In severe cases ,,whole blood transfusion ,fresh frozen plasma contains all of active coagulant factors, replace blood factor as VIII..

2.skin necrosis

هون الwarfarin ممكن يعمل اشي عكس المنطق انه ممكن يحفز تكزن الخثرات الصغيرة (microthromboemboli in peripheral small blood vessels ,so occlusion of these vessels which cause ischemia and tissue necrosis)

3.purple toe syndrome (gangrene ischemia) rare

4.dont forget that warfarin is highly teratogenic.

//////////////////////////

Oral anticoagulants: direct agents……. Direct inhibitors for some coagulant factors:

Dabigatran:

MOA: direct thrombin inhibitor (both clot bound and free)

ما ننسى انه اهم واحد هو الثرومبين لتكوين الخثرة.

*therapeutic uses: 1. Prevention of thromboembolism/ stroke in patients with nonvalvular atrial fibrillation.

2.ttt of DVT,PE if already received heparin (so cant used to ttt acute DVT otherwise may occur paradoxical reaction and clot formation)

3.prophylaxis against DVT,PE

*ph.kinetics:

Oral, eliminated renally.

*Adverse effects:

1.bleeding 2. Contraindication in patients with mechanical heart valves 3. Caution in patients with renal impairment

* antidote: monochlonal antibody Idarucizumab

**** direct oral factor Xa inhibitors: that interfere with conversion of prothrombin into thrombin

من اسم المجموعة بستنتج الميكانيزم تبعتهم

1.**apixaban** 2. **Betrixaban** 3. **Edoxaban** 4. **Rivaroxaban**

1,3,4 all of them are used to prevention + ttt of DVT,PE

Betrixaban is used only in prevention of DVT,PE in at risk hospitalized patients.

*adverse effects:

Bleeding ,,,, no antidote , to treat this problem :

1.whole blood transfusion 2. Giving factor X

3.Fresh frozen plasma

THROMBOLYTICS:

*antiplatelets and anticoagulants cannot destroy the already formed clot.

*fibrinolysis is physiological process that dissolve already formed fibrin clot.وهذه العملية بتصير عشان الخثرة ما تكبر اكثر من المطلوب وتكون ع قد الجرح فقط. وذلك بتحفيز ال plasminogen فبيتحول الى plasmin ,

البلازمين هو المسؤول عن تكسير الفايبرين.

*MOA of thrombolytics:

Accelerates clot dissolution, so maintain blood flow within blood vessel.

*clot becomes more resistant to lysis whith time (age)

يعني كل م اعطيت هاي الادوية بوقت ابكر بكون افضل وفرصة تكسير الجلطة اعلى وال survive لمريض ال MI اعلى.

*remember: clot dissolution can be accompanied by INCREASE risk of local thrombosis

كانه بكسر الجلطة الى جلطات صغار فهدول الجلطات في امكانية انهم يرجعوا يلتحموا مع بعض لذلك لازم نعطي مضادات التجلط بالاضافة ل fibrinolytics

*therapeutic uses:

1.ttt of myocardial infarction (MI) ,

Best way to give: intracoronary by catheterization.

But mostly given IV.

2.stroke (debatable)

3. Rarely used to ttt of DVT,PE due to risk of bleeding, these are treated by antiplatelets anticoagulants

*adverse effects: bleeding

لانهم بكسروا الجلطات الطبيعية الي بتصير في حالات الجروح بالاضافة لتكسر الpathological thrombus

*contraindicated in:

1. pregnancy (causing intrauterine bleeding)

2.active/healing wound

3.history of cerebrovascular accident (CVA)

4.brain tumor (this drug cause intracranial bleeding)

5.head trauma (this drug cause intracranial bleeding)
6.Intracranial bleeding 7. Metastatic cancer

Alteplase and Tenecteplase

Alteplase: tPA originally derived from melanoma cells but now obtained by recombinant DNA technology,

Used for: MI, acute ischemic stroke, massive PE

Tenecteplase: recombinant tPA (longer half-life)
❑Binding affinity to free plasminogen :Tenecteplase >alteplase BUT Alteplase has higher affinity for fibrin-bound plasminogen “fibrin selective”

Used for MI only.

ملاحظه: في ادوية قديمة مش مطلوب نعرفها الي هم ,,, streptokinase, urokinase ,,في فيديو تفصيلي بشرح موضوع ال thrombolytics مطلوب

*هاد الجدول مهم جدا.

Heparin Vs Warfarin

MOA	Inactivates thrombin and factor Xa	Inhibits synthesis of clotting factors
Route	IV or subQ	PO
Teratogenic	Does not cross placenta or into breast milk	Crosses placenta (**teratogenic**)
Onset	Rapid (minutes)	Slow (hours)
Duration	Brief (hours)	Prolonged (days)
Drug interactions	Few drug interactions	Many drug interactions
Elimination	Eliminated renally	Eliminated hepatically
Monitoring	aPTT	INR
Antidote	Protamine	Phytomenadione (Vitamin K)

Good luck.....