WHAT'S NEW IN THERAPEUTICS ?

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MEDICAL UPDATE GROUP

NOVEMBER 2013

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ORAL ANTITHROMBOTICS

- DESPITE SIGNIFICANT IMPROVEMENTS OVER THE PAST DECADE IN CARDIOVASCULAR RELATED MORTALITY, THE PREVALENCE OF CARDIOVASCULAR DISEASE HAS INCREASED, PARTLY DUE TO AN AGEING POPULATION AND INCREASING RATES OF OBESITY AND DIABETES

- CARDIOVASCULAR DISEASE CONTINUE TO BE A BIG KILLER ATTRIBUTED TO CIRCULATORY DISEASE, WHICH INCLUDES ATHERO AND VENOUS THROMBOTIC CONDITIONS

- RECENT ADVANCES IN ANTIPLATELET AND ANTICOAGULANT THERAPY HAVE RESULTED IN AN INCREASE IN ANTITHROMBOTIC AGENTS ON THE MARKET FOR THESE CONDITIONS, PROVIDING MORE CHOICE TO PHYSICIANS AND PATIENTS BUT POTENTIALLY MAKING TREATMENT DECISIONS MORE COMPLEX

HAEMOSTASIS

- HAEMOSTASIS IS TRIGERRED BY VASCULAR INJURY AND INVOLVES THE TRANSITION OF BLOOD FROM LIQUID TO SOLID STATE. THE PROCESS COMPRISES THREE KEY STAGES AT THE SITE OF VASCULAR INJURY.
  - VASOCONSTRICTION – A DAMAGED BLOOD VESSEL CONSTRICTS TO REDUCE BLOOD FLOW
  - PLATELET PLUG FORMATION – PATELETS ADHERE TO THE SITE
  - BLOOD CLOTTING – COAGULATION THROUGH ACTIVATION OF CLOTTING FACTORS. COAGULATION CASCADE PRODUCES FIBRIN, WHICH TRAPS RED BLOOD CELLS AT THE SITE OF INJURY AND REINFORCES THE PLATELET PLUG. THE RESULT IS A HARD CLOT (THROMBUS) THAT SEALS OFF THE DAMAGED VESSELS, REDUCING BLOOD LOSS

THROMBOSIS

- PATHOLOGICALLY THE PROCESS OF HAEMOSTASIS CAN BE TRIGERRED BY FISSURES OR RUPTURES TO ATHEROSCLEROTIC PLAQUES WITHIN CORONARY OR PERIPHERAL VESSELS.
- IN ADDITION, HAEMOSTATIS MAY BE INITIATED IN RESPONSE TO EXTENDED PERIODS OF IMMOBILITY, PROTHROMBIC STATES (e.g. PREGNANCY, MALIGNANCY) OR FOLLOWING SURGERY PARTICULARLY WHERE PROSTHESIS IS INVOLVED (e.g. HIP, KNEE AND HEART VALVE REPLACEMENTS).
- WHEN THE HAEMOSTATIC PROCESS IS UNCONTROLLED, THE RESULT IS OFTEN THROMBUS FORMATION.
- THE THROMBUS MAY CAUSE OCCLUSION AT ITS SITE OF ORIGIN, OR PART OR ALL OF THE THROMBUS MAY BE DISLODGED AND OCCLUDE ANOTHER SITE (EMBOLISM) LEADING TO EITHER TRANSIENT OR PERMANENT ISCHAEMIA OR NECROSIS

THROMBOSIS

- DIFFERENCES IN BLOOD FLOW AND PRESSURE BETWEEN THE VENOUS AND ARTERIAL SYSTEMS RESULT IN VARIATION IN THE COMPOSITION OF THE THROMBI.
- ARTERIAL THROMBI TEND TO BE RICH IN PLATELET COUNT
- VENOUS THROMBI TEND TO BE FIBRIN RICH
- HENCE THE PRIMARY ANTITHROMBOTIC STRATEGY FOR ARTERIAL THROMBOSIS IS ANTIPLATELET THERAPY AND FOR VENOUS THROMBOSIS IS ANTICOAGULANT THERAPY
- THESE STRATEGIES MAY BE COMBINED IN COMPLEX CASES

ANTIPLATELET AGENTS

ORAL

-ASPIRIN

-DIPYRIMADOLE

-TICLOPIDINE

-CLOPIDOGREL

-PRASUGREL

-TICAGRELOR

NEW ANTIPLATELET AGENTS

INJECTABLE

-TIROFIBAN (AGGRASTAT)

-EPTIFIBATIDE (INTEGRILLIN)

-ABCIXIMAB (REOPRO)

ANTIPLATELET AGENTS WORK BY DISRUPTING KEY STEPS IN PLATELET ACTIVATION VIA A NUMBER OF MECHANISMS, INCLUDING INHIBITION OF PLATELET AGONISTS AND PLATELET ADHESION OR AGGREGATION.

MODE OF ACTION OF ORAL ANTIPLATELET AGENTS

1. ASPIRIN ⟶ COX 1 INHIBATOR ⟶ BLOCKS FORMATION OF THROMBOXANE (A PLATELET AGONIST) .ALTHOUGH ASPIRIN HAS A SHORT HALF LIFE (20 MINS), BECAUSE INHIBITION IS IRREVERSIBLE, THE EFFECT LASTS FOR THE LIFESPAN OF THE PLATELET (USUALLY 8-10 DAYS)

2. DIPYRIDAMOLE WORKS BY INCREASING THE CONCENTRATION OF THE PLATELET AGGREGATION INHIBITOR CYCLIC AMP BY INHIBITING ITS ENZYMATIC DEGRADATION

MODE OF ACTION OF ORAL ANTIPLATELET AGENTS

3. THE THIENOPYRIDINES TICLOPIDINE, CLOPIDOGREL AND PRASUGREL REDUCE PLATELET ACTIVATION BY NON-COMPETITIVELY AND IRREVERSIBLY BLOCKING THE BINDING OF ADP TO P2Y12 RECEPTORS ON THE PLATELET MEMBRANE. ADP INDUCED PLATELET AGGREGATION IS INHIBITED.
4. TICAGRELOR IS A DIRECT REVERSIBLE P2Y12 RECEPTOR ANTAGONIST BLOCKING THE BINDING OF ADP

MODE OF ACTION OF INJECTABLE ANTIPLATELET AGENTS

TIROFIBAN, EPTIFIBATIDE AND ABCIXIMAB $\longrightarrow$ ARE GLYCOPROTEIN IIb/IIIa INHIBITORS.

GLYCOPROTEIN IIb/IIIa RECEPTORS ARE SITUATED ON THE PLATELET MEMBRANE AND ARE INVOLVED IN PLATELET AGGREGATION .INHIBITION PREVENTS PLATELET AGGREGATION.

USES FOR ORAL ANTIPLATELETS

- **MYOCARDIAL INFARCTION OR UNSTABLE ANGINA** DUAL ANTIPLATELET THERAPY (LONG-TERM ASPIRIN 75mg od AND A P2Y12 BLOCKER). THIS DUAL THERAPY IS ADVOCATED FOR 12 MONTHS, THEN CONTINUE WITH ASPIRN MONOTHERAPY.
- **ELECTIVE PERCUTANEOUS CORONARY INTERVENTION** WITH BARE METAL STENTS, DUAL ANTIPLATELET THERAPY (ASPIRIN 75mg od AND CLOPIDOGREL) FOR AT LEAST 28 DAYS, THEN LONG-TERM ASPIRIN MONOTHERAPY. FOR INTERVENTION WITH DRUG-ELUTING STENTS, DUAL ANTIPLATELET THERAPY (AS ABOVE) FOR AT LEAST 12 MONTHS, THEN LONG-TERM ASPIRIN MONOTHERAPY.
- **STABLE ANGINA OR DOCUMENTED CORONARY ARTERY DISEASE** LONG TERM ASPIRIN (75mg od).
- **ISCHAEMIC STROKE (EXCLUDING ATRIAL FIBRILLATION RELATED)** LONG-TERM CLOPIDOGREL (75mg od). IF CLOPIDOGREL (PLUS PROTON PUMP INHIBATOR) IS NOT TOLERATED, DIPYRIDAMOLE MODIFIED RELEASE(200mg bd) PLUS ASPIRIN (75mg od) IS AN ALTERNATIVE. WHERE BOTH CLOPIDOGREL AND DIPYRIDAMOLE ARE NOT TOLERATED OR CONTRAINDICATED, ASPIRIN (75mg od). AND WHERE CLOPIDOGREL AND ASPIRIN ARE NOT TOLERATED OR CONTRAINDICATED, DIPYRIDAMOLE MODIFIED RELEASE (200mg bd).
- **PERIPHERAL ARTERIAL DISEASE** LONG-TERM CLOPIDOGREL (75mg od).
- **MULTIVASCULAR DISEASE** LONG-TERM CLOPIDOGREL (75mg od).
- **TRANSIENT ISCHAEMIC ATTACK** LONG-TERM DIPYRIDAMOLE MODIFIED RELEASE(200mg bd) PLUS ASPIRIN (75mg od). IF ASPIRIN IS NOT TOLERATED OR CONTRAINDICATED, DIPYRIDAMOLE MODIFIED RELEASE (200mg bd).

NEW ORAL ANTIPLATELET AGENTS

PRASUGREL

- POTENT INHIBITOR OF ADP AT P_2Y_{12} RECEPTOR
- MORE POTENT THAN CLOPIDOGREL
- CLOPIDOGREL AND PRASUGREL ARE PRO DRUGS AND ARE METABOLICALLY TRANSFORMED IN THE LIVER BY CYTOCHROME P_{450} ENZYMES INTO THEIR PLATELET INHIBITING METABOLITES.
- VARIABLE METABOLIC ACTIVITY OF CYTOCHROME P_{450} ENZYMES CONTRIBUTES TO THE OBSERVED INTER INDIVIDUAL VARIABILITY IN CLOPIDOGREL'S INHIBITORY EFFECT.
- PRASUGREL IS LESS AFFECTED THAN CLOPIDOGREL BY VARIATIONS IN THE P_{450} ENZYMES.

NEW ORAL ANTIPLATELET AGENTS

TICAGRELOR

- ORAL ADENOSINE DI PHOSPHATE (ADP) ANTAGONIST
- BLOCKS ADP INDUCED PLATELET AGGREGATION
- IS A REVERSIBLE P2Y12 RECEPTOR ANTAGONIST UNLIKE CLOPIDOGREL/PRASUGREL WHICH BIND IRREVERSIBILY
- REPRESENTS AN ADVANTAGE IF PATIENT HAS TO UNDERGO CABG OR OTHER SURGERY AS THERE IS A FASTER RECOVERY OF PLATELET FUNCTION HENCE A DECREASED IN RISK OF BLEEDING
- DOES NOT REQUIRE METABOLIC ACTIVATION HENCE HAS A MORE RAPID ONSET OF ACTION COMPARED TO CLOPIDOGREL/PRASUGREL
- METABOLISED BY CYP3A4 ENZYME AND HENCE WILL BE AFFECTED BY DRUGS THAT INDUCE OR INHIBIT THIS ENZYME.
- PLASMA HALF LIFE IS 6-13 HRS SO TWICE DAILY DOSING IS NEEDED

NEW ORAL ANTIPLATELET AGENTS

1) COMPARED TO CLOPIDOGREL, TICAGRELOR DECREASES THE RATE OF ALL CAUSE MORTALITY, VASCULAR MORTALITY OR MI WITHOUT AN INCREASE IN RATE OF MAJOR BLEEDING
2) COMPARED TO CLOPIDOGREL, PRASUGREL DECREASES THE RATE OF ISCHEMIC EVENTS INCLUDING STENT THROMBOSIS BUT INCREASES THE RISK OF MAJOR AND FATAL BLEEDING IN PATIENTS UNDERGOING PCI WITHOUT CHANGES IN OVERALL MORTALITY
3) PRASUGREL AND TICAGRELOR HAVE COMPARABLE EFFICACY AND SAFETY EXCEPT PRASUGREL IS MORE PROTECTIVE FOR STENT THROMBOSIS BUT WITH AN INCREASED RISK OF MAJOR BLEEDING

NEW ORAL ANTIPLATELET AGENTS

PLACE IN THERAPY OF ACS

- CLOPIDOGREL REMAINS THE MAINSTAY OF TREATMENT FOR THE MOMENT AND IS RECOMMENDED FIRST LINE IN PATIENTS WITH HYPERSENSITIVITY TO ASPIRIN OR IN DUAL ANTIPLATELET THERAPY WITH ASPIRIN.
- THE REVERSIBILITY OF TICAGRELOR MAY BE ATTRACTIVE, IN THAT IT ALLOWS FASTER RECOVERY OF PLATELET FUNCTION AND THEREFORE GREATER THERAPEUTIC FLEXIBILITY, PARTICULARLY IN SURGICAL PATIENTS.
- REDUCTION IN NON FATAL MI/STENT THROMBOSIS FOR PRASUGREL AND BENEFIT IN MI/VASCULAR AND TOTAL MORTALITY FOR TICAGRELOR SEEM PROMISING.
- MORE DATA NEEDED TO SITUATE THEIR EXACT PLACE IN THERAPY OF ACS AS THE INCREASE OF EFFICACY COMPARED TO CLOPIDOGREL HAS GENERALLY BEEN AT THE EXPENSE OF INCREASED BLEEDING.
- DESPITE ASPIRIN AND CLOPIDOGREL DUAL THERAPY, A GOOD PROPORTION OF PATIENTS CONTINUE TO EXPERIENCE RECURRENT ATHEROTHROMBOTIC EVENTS, SO THE ADVENT OF THESE NEW DRUGS COULD REPRESENT A HOPE FOR SUCH PATIENTS.

NEW ORAL ANTICOAGULANTS

HISTORY OF ORAL ANTICOAGULATION

- WARFARIN WAS OF ONE OVER 100 COUMARIN DERIVATIVES INVESTIGATED FOLLOWING THE SYNTHESIS IN 1940 OF DICOUMAROL – THE ANTICOAGULANT IN MOULDY CLOVER HAY THAT HAD BEEN CAUSING FATAL HAEMORRHAGE IN NORTH AMERICAN CATTLE SINCE 1920.
- INITIALLY DEVELOPED FOR RODENT CONTROL
- IN 1951 – A SUICIDE ATTEMPT BY A US ARMY RECRUIT DREW ATTENTION TO ITS EFFECTS IN HUMANS WHICH LED A COUPLE OF YEARS LATER TO ITS CLINICAL USE
- IN 1955 – GIVEN TO PRESIDENT EISENHOWER AFTER A HEART ATTACK
- BEFORE WARFARIN, FOR THROMBOEMBOLIC COMPLICATIONS THERE WERE ONLY ASPIRIN AND HEPARIN AVAILABLE AND IT WAS NOT PRACTICAL TO GIVE DAILY INJECTIONS OF HEPARIN
- WARFARIN WAS THUS HAILED AS A “MAJOR BREAKTHROUGH”

HISTORY OF ORAL ANTICOAGULATION

- WARFARIN IS A VITAMIN K ANTAGONIST THUS BLOCKING VITAMIN K WHICH IS IMPORTANT IN THE SYNTHESIS OF CLOTTING FACTORS II, VII, IX, X AND ANTICOAGULATION PROTEIN C AND S. ALL ARE REQUIRED IN THE COAGULATION CASCADE FOR THE FORMATION OF THROMBIN AND ULTIMATELY FIBRIN, THE FIBROUS PROTEIN THAT COMBINES WITH PLATELETS TO FORM BLOOD CLOTS.
- RIVAROXABAN (XARELTO – ONCE DAILY DOSING)
- APIXABAN (ELIQUIS – TWICE DAILY DOSING)

&

DABIGATRAN (PRADAXA – TWICE DAILY DOSING)

ARE TWO NEW ORAL ANTICOAGULANTS RECENTLY INTRODUCED.

WARFARIN – A HIGHLY EFFECTIVE DRUG BUT WITH HUGE DRAWBACKS

INDICATIONS OF WARFARIN

- PREVENTION AND TREATMENT OF VTE AND PULMONARY EMBOLISM
- POST OPERATIVE PROPHYLAXIS IN PATIENTS UNDERGOING JOINT SURGERY OR INSERTION OF ARTIFICIAL HEART VALVES.
- FOLLOWING LARGER MI ESPECIALLY OF THE ANTERIOR WALL OR WITH LEFT VENTRICULAR ANEURYSM.
- POTENTIALLY THE GREATEST USE IS STROKE PREVENTION IN PATIENTS WITH AF → PATIENT SELECTION AND ADHERENCE PROBLEMS + CAREFUL DOSE TITRATION / REGULAR MONITORING MEAN THAT ONLY A SMALL PROPORTION BENEFIT FROM THIS THERAPY

PROS AND CONS OF WARFARIN THERAPY

PROS

- EVIDENCE BASE SHOWS CLEAR BENEFITS
- ONCE DAILY ADMINISTRATION (LONG HALF-LIFE)
- AVAILABILITY OF A SPECIFIC ANTIDOTE TO REVERSE ANTICOAGULATION
- LOW COST
- REGULAR MONITORING SUPPORTS PATIENT ADHERENCE

CONS

- SLOW ONSET OF ACTION (5 DAYS TO ACHIEVE A STABLE ANTITHROMBOTIC EFFECT)
- RISK OF HAEMORRHAGE
- CAREFUL DOSE TITRATION – IT TAKES A LOT OF TIME AND DISCIPLINED PATIENT TO GET DOSING RIGHT.
- REGULAR MONITORING → ANTICOAGULANT CLINICS
- NARROW THERAPEUTIC INDEX
- VARIOUS DRUG / FOOD INTERACTIONS OF CLINICAL IMPORTANCE
  - POTENTIATION OR REDUCTION OF ANTICOAGULANT EFFECT WITH ALL RISKS INVOLVED
- INTERPATIENT / INTRAPATIENT VARIABILITY IN PHARMACOKINETICS AND RESPONSE (GENETIC POLYMORPHISMS, AGE, HEALTH STATUS, DIET, ALCOHOL CONSUMPTION)

MANAGEMENT OF VTE (DVT / PE)

- ANTICOAGULATION REMAINS THE CORNERSTONE OF VTE

- IT IS DIVIDED INTO 2 STAGES
  - RAPID ANTICOAGULATION GIVEN TO MINIMIZE THE RISK OF THROMBUS EXTENSION AND FATAL PE
  - EXTENDED ANTICOAGULATION TO PREVENT RECURRENT VTE

RAPID ANTICOAGULATION : HEPARINS, LMWH AND FONDAPARINUX.

LMWH AND FONDAPARINUX – ONCE DAILY SC DOSING

EXTENDED ANTICOAGULATION : WARFARIN

(WARFARIN HAS A SLOW ONSET OF ACTION AND CANNOT BE USED FOR RAPID ANTICOAGULATION)

MANAGEMENT OF VTE (DVT / PE)

- THE MAJORITY OF PATIENTS ON LMWH / FONDAPARINUX ARE NOW TREATED AS OUTPATIENTS. INJECTABLE ROUTE IS A MAJOR DRAWBACK WHICH PROMPTED RESEARCH INTO LONGER ACTING INJECTABLE AND NEW ORAL ANTICOAGULANTS
- NEW ORAL ANTICOAGULANTS ARE RIVAROXABAN, APIXABAN AND DABIGATRAN WHICH ARE ALREADY MARKETED IN THE EUROPEAN UNION/US
- RIVAROXABAN/DABIGATRAN

  NOW AVAILABLE IN MAURITIUS

NOVEL DRUGS

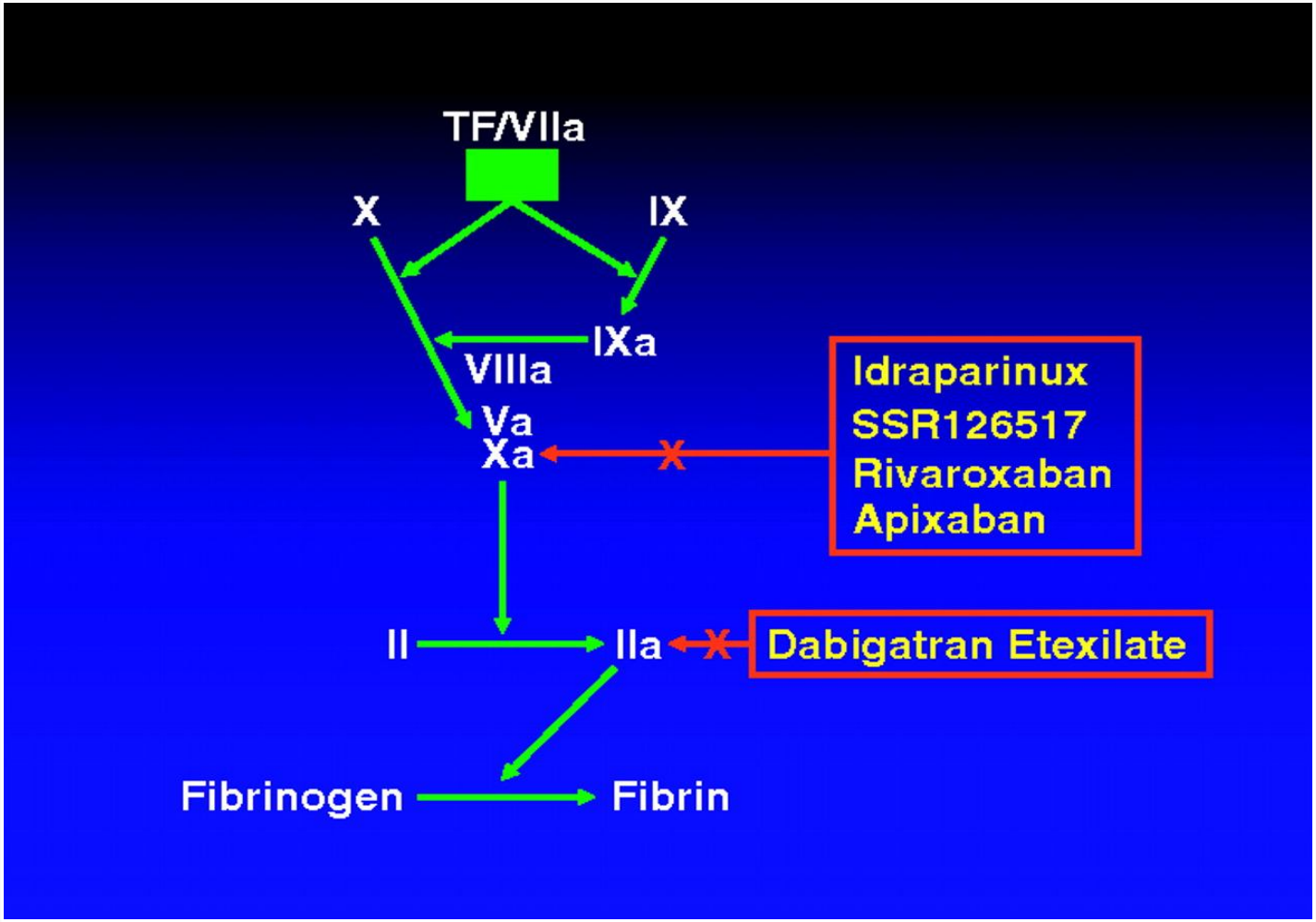
RIVAROXABAN - THE FIRST ORALLY ACTING FACTOR XA INHIBITOR

DABIGATRAN - ORALLY ACTING DIRECT THROMBIN INHIBITOR

(THE FIRST IN THIS CLASS WAS XIMELAGATRAN WHICH WAS REMOVED FROM THE MARKET DUE TO LIVER TOXICITY)

APIXABAN – A NEW ORALLY ACTING FACTOR XA INHIBITOR RECENTLY INTRODUCED

TARGETS OF NEW ANTICOAGULANTS FOR TREATMENT OF VENOUS THROMBOEMBOLISM



OPPORTUNITIES FOR NEW ANTICOAGULANTS IN VTE TREATMENTS

- INTRODUCTION OF LMWH WAS A MAJOR ADVANCE IN THE MANAGEMENT OF VTE AS THERE WAS NO NEED FOR COAGULATION MANAGEMENT AND PATIENTS SHIFTED TO OUTPATIENT SETTING
- THE NEW ANTICOAGULANTS HAVE THE POTENTIAL TO FURTHER STREAMLINE CARE AND MAY OFFER SAFETY ADVANTAGES OVER EXISTING TREATMENT
- THE NEW ORAL ANTICOAGULANTS:

  - RAPID ONSET OF ACTION → PEAK PLASMA CONCENTRATION WITHIN 2-4 HOURS → CANDIDATES FOR RAPID ANTICOAGULATION

OPPORTUNITIES FOR NEW ANTICOAGULANTS IN VTE TREATMENTS

THE NEW ORAL ANTICOAGULANTS

- ELIMINATE THE NEED FOR INJECTABLE DRUG FOR RAPID ANTICOAGULATION
- CAN BE USED FOR EXTENDED ANTICOAGULATION
- FIXED DOSING
- NO NEED FOR ANTICOAGULATION MONITORING
- WILL PROVE MORE CONVENIENT THAN WARFARIN
- IF RISK OF BLEEDING IS LESS THAN WARFARIN, IT WILL FURTHER EXPAND THE FRONTIERS OF VTE MANAGEMENT

MAJOR DRAWBACKS OF NEW ORAL ANTICOAGULANTS

- NO SPECIFIC ANTIDOTE YET TO REVERSE ANTICOAGULANT EFFECTS
- SIDE EFFECTS? XIMELAGATRAN?
- MORE STUDIES NEEDED ON RISK OF BLEEDING? MONITORING?
- IN THE ABSENCE OF ROUTINE MONITORING , COMPLIANCE IS DIFFICULT TO ASSESS.
- HIGH COST
- THESE ISSUES WILL NEED TO BE ADDRESSED FOR THE EXACT PLACE IN THERAPY OF THESE NEW ORAL ANTICOAGULANTS BE DEFINED

USES OF NEW ANTICOAGULANTS

	DABIGATRAN	RIVAROXABAN	APIXABAN
VTE PREVENTION POST HIP OR KNEE REPLACEMENT	LICENSED*	LICENSED*	LICENSED*
ACUTE DVT TREATMENT, SECONDARY VTE PREVENTION	LICENSE SUBMISSION UNDER EVALUTATION	LICENSED‡	LICENSE EXPECTED
ACUTE PULMONARY, EMBOLISM TREATMENT, SECONDARY VTE/PE PREVENTION	LICENSE SUBMISSION UNDER EVALUTATION	LICENSED	LICENSE EXPECTED
STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION	LICENSED*	LICENSED‡	LICENSED
ACUTE CORONARY SYNDROME		LICENSED	

NEW ORAL ANTICOAGULANTS

- IN THROMBOPROPHYLAXIS AFTER MAJOR ORTHOPEDIC SURGERY
- DABIGATRAN HAS SHOWN IN SEVERAL TRIALS A NON INFERIOR EFFICACY TO ENOXAPARIN WITH A SIMILAR SAFETY PROFILE AND RIVAROXABAN HAS SHOWN A SUPERIOR EFFICACY
- BOTH ARE APPROVED IN THIS INDICATION BY NICE

  EX. RIVAROXABAN IN ONCE DAILY DOSE WITH THE INITIAL DOSE TAKEN 6-10 HOURS AFTER SURGERY. DURATION DEPENDS ON INDIVIDUAL RISK OF VTE

NEW ORAL ANTICOAGULANTS

PLACE IN THERAPY

- REPRESENTS CERTAIN ADVANTAGES OVER WARFAIN IN TERMS OF MONITORING, DOSING AND RAPID AND EXTENDED COAGULATION.

- EXTENDED INDICATIONS: MANAGEMENT OF VTE, PRIMARY VTE PREVENTION, SECONDARY VTE PREVENTION, STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION SEEM ATTRACTIVE.

- LIMITATIONS: RISK OF BLEEDING? NEW DATA EMERGING

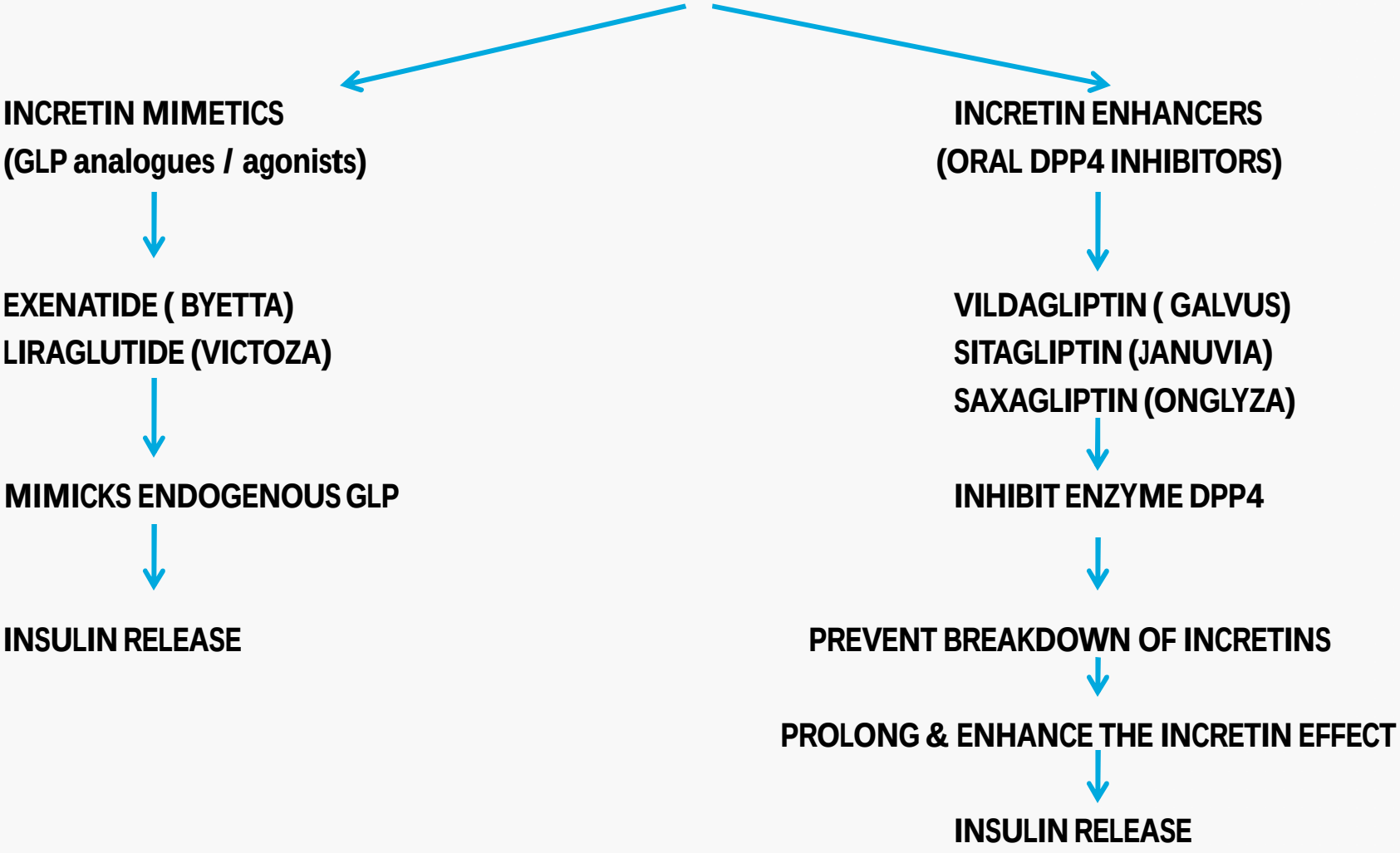
- DOES THIS MEAN THE END OF THE ANTICOAGULANT CLINIC?

INCRETIN BASED THERAPIES FOR TYPE 2 DIABETES – CURRENT ASPECTS & FUTURE PROSPECTS

THE INCRETIN SYSTEM

- INCRETINS ARE A TYPE OF GASTRO INTESTINAL HORMONE THAT CAUSE AN INCREASE IN THE AMOUNT OF INSULIN RELEASED FROM THE BETA CELLS OF ISLETS OF LANGERHANS
- THEY ALSO INHIBIT RELEASE OF GLUCAGON FROM THE PANCREAS → LIVER REDUCES ITS PRODUCTION OF GLUCOSE
- EXAMPLES: GLP (GLUCAGON LIKE PEPTIDE)/ GIP (GLUCOSE DEPENDENT INSULINOTROPIC PEPTIDE)
- INACTIVATED BY ENZYME DPP4 (DIPEPTIDYL PEPTIDASE)
- PATIENTS WITH TYPE 2 DIABETES HAVE A SIGNIFICANT REDUCTION OF THE INCRETIN EFFECT IMPLYING THAT PATIENTS HAVE DECREASED CONCENTRATION OF INCRETIN OR RESISTANCE TO ITS EFFECT.

INCRETIN BASED THERAPIES



ORAL DPP4 INHIBITORS
(VILDAGLIPTIN, SITAGLIPTIN & SAXAGLIPTIN,LINAGLIPTIN)

- INHIBITS THE ENZYME (DPP4) – SELECTIVE DPP4 INHIBITOR
- DPP4 INHIBITORS ENHANCE THE INCRETIN EFFECT.
- WHEN BLOOD SUGAR IS HIGH, INCRETIN WORKS IN TWO WAYS TO HELP THE BODY REGULATE BLOOD SUGAR LEVEL : IT TRIGGERS THE PANCREAS TO RELEASE INSULIN/SIGNALS THE LIVER TO REDUCE PRODUCTION OF GLUCOSE.
- INCRETINS ALSO SLOW THE RATE OF ABSORPTION OF NUTRIENTS IN THE BLOOD STREAM BY REDUCING GASTRIC EMPTYING AND MAY INDIRECTLY REDUCE FOOD INTAKE.
- DPP4 INHIBITORS THEREFORE ENHANCE THE BODY'S OWN ABILITY TO CONTROL BLOOD SUGAR BY INCREASING ACTIVE LEVELS OF INCRETIN.

ORAL DPP4 INHIBITORS

- RISK OF HYPOGLYCAEMIA IS LOW AS THEY WORK ONLY IN THE PRESENCE OF GLUCOSE. POSTPRANDIAL, WHEN GLUCOSE LEVELS ARE HIGH, INCRETINS ARE RELEASED AND DPP4 INHIBITORS PREVENT ITS BREAKDOWN TO LOWER BLOOD SUGAR LEVELS.
- WEIGHT NEUTRAL
- ONCE DAILY DOSING – WITH OR WITHOUT FOOD
- MAIN SIDE EFFECTS : NAUSEA/VOMITING/SORE THROAT/RUNNY NOSE

ORAL DPP4 INHIBITORS

- **PLACE IN THERAPY :**

  - CAN BE USED AS MONOTHERAPY.

  - INDICATED AS A SECOND LINE TO IMPROVE GLYCAEMIC CONTROL IN COMBINATION WITH DIET AND METFORMIN WHEN METFORMIN ALONE DOES NOT PROVIDE ADEQUATE CONTROL.

  - AS AN ALTERNATIVE TO SULPHONYLUREAS WHERE HYPOGLYCAEMIA/WEIGHT GAIN IS A PROBLEM.

  - USEFUL ADDITION IN THE RANGE OF EXISTING TREATMENT FOR TYPE 2 DIABETES, TAKING INTO COSIDERATION RECENT PROBLEMS WITH GLITAZONES. SHOULD NOT BE USED IN TYPE 1 AS INEFFECTIVE.

- **APPROVED FOR USE IN MANY COUNTRIES.**
- **RECENT CASES OF ACUTE PANCREATITIS.**

INCRETIN MIMETICS
(GLP1 ANALOGUES/AGONISTS)

- **EXENATIDE**
- **LIRAGLUTIDE**

INCRETIN MIMETICS

EXENATIDE – AN INCRETIN MIMETIC

- EXENATIDE MIMICKS INCRETIN (MIMICKS GLP1)
- INJECTABLE FORM (S/C) – PEN DEVICE
- SYNTHETIC VERSION OF EXENDIN 4, A HORMONE FOUND IN THE SALIVA OF THE GLIA MONSTER, A POISONOUS LIZARD IN THE AMAZONIAN SOUTHWEST.
- SCIENTISTS HAVE NOTICED THAT GLIA MONSTER GO FOR LONG PERIOD OF TIME WITHOUT EATING. WHILE FASTING THE PANCREAS IS LITERALLY SWITCHED OFF. WHEN THEY DO EAT, EXENDIN 4 IS SECRETED WHICH FLIPS THE SWITCH ON, HENCE THE MEAL IS DIGESTED.

INCRETIN MIMETICS

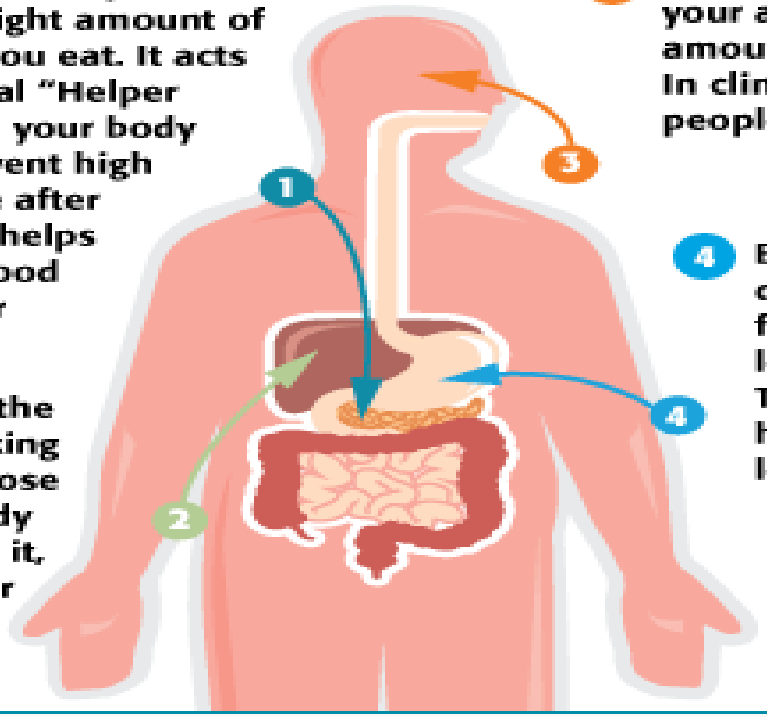
GLIA MONSTER LIZARD

INCRETIN MIMETICS

EXENATIDE CAN BE USED WITH METFORMIN, A SULFONYLUREA, OR A GLITAZONE TO HELP KEEP BLOOD GLUCOSE (BLOOD SUGAR) UNDER CONTROL IN AT LEAST FOUR WAYS:

HOW IT WORKS

1. BYETTA signals the pancreas to make the right amount of insulin after you eat. It acts like the natural "Helper Hormones" in your body that help prevent high blood glucose after meals, which helps lower your blood glucose closer to normal.
2. BYETTA stops the liver from making too much glucose when your body does not need it, especially after meals.
3. BYETTA may also reduce your appetite and the amount of food you eat. In clinical trials, most people lost weight.
4. BYETTA helps slow down how quickly food and glucose leave the stomach. This helps prevent high blood glucose levels after you eat.



EXENATIDE – *An incretin mimetic*

- IMPORTANT REDUCTION IN HBA1C
- MAIN SIDE EFFECTS ARE NAUSEA / VOMITING – WORST DURING THE FIRST TWO WEEKS, GETS BETTER WITH TIME.
- TWICE DAILY DOSING SC (WITHIN AN HOUR OF EATING BREAKFAST / DINNER)
- RISK OF HYPOGLYCAEMIA IS LOW ON ITS OWN. HYPOGLYCAEMIA MAY OCCUR WHEN IT IS FIRST ADDED TO ORAL MEDICATION.
- CAUSES WEIGHT LOSS. USEFUL IN OVERWEIGHT / OBESE PATIENTS WITH TYPE 2 DIABETES.
- POST MARKETING REPORTS : FEW CASES OF ACUTE PANCREATITIS.
- EASY TO USE AS PATIENTS NEVER HAVE TO ADJUST THE DOSE BASED ON THE SIZE OF THE MEAL OR HOW MUCH EXERCISE DONE.

EXENATIDE – *An incretin mimetic*

- **PLACE IN THERAPY**
  - IN COMBINATION WITH ORAL MEDICATIONS/INSULIN IN TYPE 2 DIABETES.
  - CANNOT BE USED IN TYPE 1 DIABETES.
  - MAIN DISADVANTAGE IS INJECTABLE FORM.
  - APPROVED FOR USE IN USA AND IN MANY COUNTRIES.
  - WEIGHT LOSS IS A MAJOR ADVANTAGE

- **EXENATIDE LAR (ONCE WEEKLY INJECTION)**

  NOW AVAILABLE

LIRAGLUTIDE *(An incretin mimetic)*

- A LONG ACTING GLP1 ANALOGUE (INCRETIN MIMETIC) PARTLY RESISTANT TO DPP4.
- HALF LIFE OF 10-14 HOURS
- S/C USE
- ONCE DAILY INJECTION
- REDUCES FASTING AND POST PRANDIAL GLUCOSE AND HB1AC LEVELS BY UP TO 1.75%.
- INDUCES SIGNIFICANT WEIGHT LOSS.
- STUDIES SHOW THAT ONCE DAILY LIRAGLUTIDE SHOWS BETTER GLYCAEMIC CONTROL THAN TWICE DAILY EXENATIDE.
- INCIDENCE OF HYPOGLYCAEMIA IS LOW.
- A THIRD GLP1 ANALOGUE – LIXISENATIDE HAS BEEN LAUNCHED IN 2013. ONCE DAILY ADMINISTRATION.

Future developments

- Animal studies and in vitro studies have shown that GLP1 analogues/ agonists and to a lesser extent oral DPP4 inhibitors prevent beta cell apoptosis and induces beta cells regeneration. An important finding which if confirmed by more clinical research would revolutionize the treatment for type 2 diabetes.
- Improvement of Pharmacokinetic parameters of GLP1 analogues
  - Minimize peak levels to reduce nausea
  - Long acting- for better control and to improve compliance
- Long term mortality / morbidity studies awaited to situate their exact places in the therapy of Type 2 diabetes.

DAPAGLIFLOZIN

A NEW CLASS OF ANTIDIABETIC AGENT

DAPAGLIFLOZIN

- **FIRST SODIUM – GLUCOSE CO-TRANSPORTER 2 INHIBITOR**

- **NOVEL INSULIN – INDEPENDENT MODE OF ACTION THAT TARGETS THE KIDNEY**

DAPAGLIFLOZIN

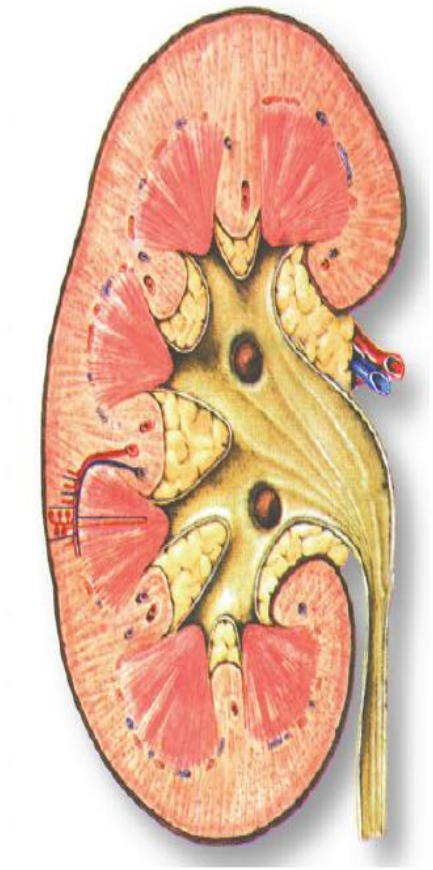
MECHANISM OF ACTION

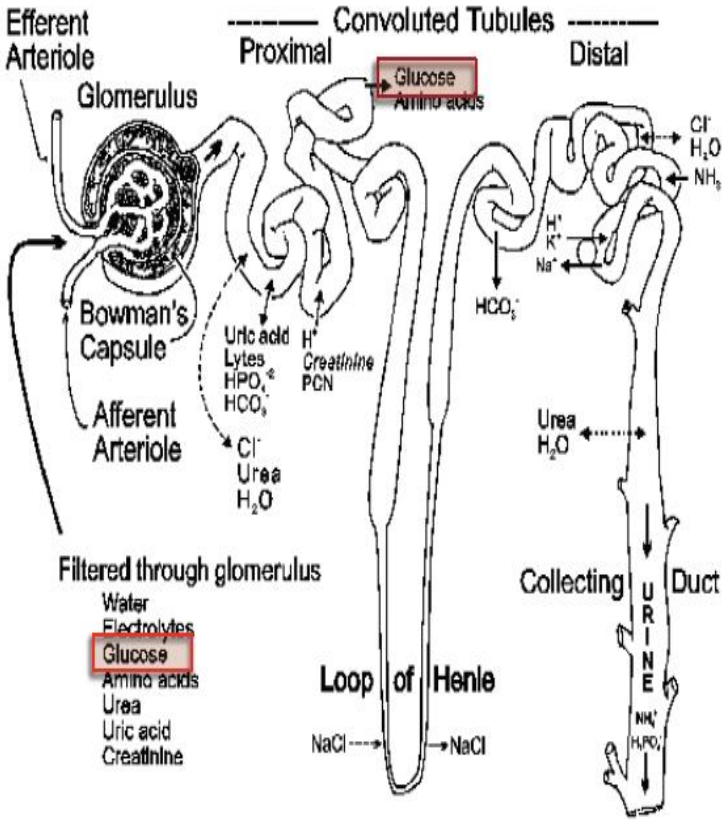
- THE POSSIBILITY OF ALTERING PLASMA GLUCOSE BY MODIFYING RENAL EXCRETION ORIGINATED FROM THE DISCOVERY OF PHLORIZIN.

- ALTHOUGH THE MOLECULE COULD NOT BE DEVELOPED AS A MEDICINE, IT WAS SHOWN TO NORMALISE FASTING AND FED GLUCOSE LEVELS IN DIABETIC RATS.

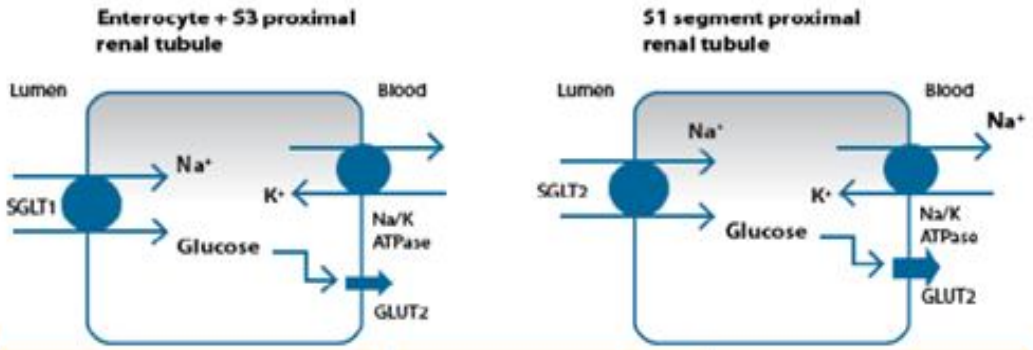
- GLUCOSE IS USUALLY FILTERED IN THE KIDNEY AND REABSORBED VIA ACTIVE TRANSPORT BY SGLT1 AND SGLT2. THE LATTER IS A HIGH CAPACITY, LOW AFFINITY CARRIER RESPONSIBLE FOR 90% OF REABSORBED GLUCOSE.

DAPAGLIFLOZIN





DAPAGLIFLOZIN



Récepteur	SGLT1	SGLT2
Localisation	Intestin Rein Coeur	Rein
Segment rénal	Fin de Tube contourné proximal	Début de Tube contourné proximal
Affinité pour le Glucose	Km = 0,4mM	Km = 2mM
Capacité de transport de glucose	Faible	Elevée
Taux de réabsorption du Glucose	10%	90%

- SGLT3: joue le rôle de glucose sensor au niveau de la membrane plasmique des neurones cholinergiques.
- SGLT4,5,6: non spécifique du transport du D-glucose. Rôle moins établit.

DAPAGLIFLOZIN

MECHANISM OF ACTION

- WHEN SGLT2 IS BLOCKED BY DAPAGLIFLOZIN, SOME OF THE FILTERED GLUCOSE IS EXCRETED IN THE URINE
- AS WELL AS DECREASING BLOOD GLUCOSE LEVELS, THIS MAY CAUSE MODERATE WEIGHT LOSS AND A SLIGHT DECREASE IN BLOOD PRESSURE
- OSMOTIC DIURESIS IS BELIEVED TO CONTRIBUTE TO THESE SECONDARY EFFECTS, ALTHOUGH THE WEIGHT LOSS IS POSSIBLY MAINTAINED BY FAT MASS REDUCTION DUE TO GLUCOSURIA

DAPAGLIFLOZIN

LICENSING

- IS APPROVED IN THE EUROPEAN UNION FOR TYPE 2 DIABETES AS MONOTHERAPY IN PATIENT INTOLERANT OF METFORMIN AND IN COMBINATION WITH SEVERAL OTHER ANTIDIABETIC AGENTS INCLUDING INSULIN

- RECOMMENDED DOSE IS 10mg ONCE DAILY WITH OR WITHOUT FOOD (MEANING IT CAN BE TAKEN AT A TIME THAT SUITS THE PATIENT).

DAPAGLIFLOZIN

EVIDENCE

- MARKETING AUTHORISATION WAS GRANTED BASED ON AN EXTENSIVE CLINICAL DEVELOPMENT PROGRAMME CONSISTING OF 12 PHASE III TRIALS

- THE MEAN REDUCTION IN HBAIC THROUGHOUT THE DEVELOPMENT PROGRAMME WAS CONSISTENTLY SIGNIFICANT AND RANGE FROM 0.4% TO 0.8% (AT 24 WEEKS)

- THIS IS SIMILAR TO THAT ACHIEVED BY PROGLITAZONE AND DPP4 INHIBITORS

DAPAGLIFLOZIN

Box 1: Summary of key trials

STUDY	DESCRIPTION	LIMITATIONS	KEY FINDINGS	CLINICAL SIGNIFICANCE/PRACTICAL NOTES
Nauck *et al*[3]	Add-on to metformin; dapagliflozin (2.5–10mg) versus sulphonylurea (glipizide 5–20mg/day)	Non-inferiority design therefore unable to prove that it is clinically better than sulphonylurea Patients were allowed treatment with another oral antidiabetic at half maximal dose (triple therapy) but no further details given	Both dapagliflozin and glipizide reduced HbA_{1c} by 0.52% but with different profiles of glucose alteration	Equivalent efficacy to glipizide as second-line therapy Showed weight loss versus weight gain with sulphonylurea, which may indicate a place in therapy for patients with higher BMI Significant reduction in hypoglycaemic events compared with sulphonylurea
Jabbour *et al*[5]	Add-on to dipeptidyl peptidase-4 inhibitor (sitagliptin) with or without metformin; dapagliflozin (10mg) versus placebo	Trial yet to be published and there are limited details on study design	Greater reduction in HbA_{1c} at 24 weeks seen with dapagliflozin treatment compared with placebo in dual and triple therapy; results maintained at week 48	Significant HbA_{1c} reduction seen for triple therapy compared with placebo Only trial that looks at use with DPP-4 inhibitor, so shows this combination could have potential if sulphonylurea cannot be used This is not a common drug combination used in the UK and is not recommended by current NICE guidance
Wilding *et al*[7]	Add-on to insulin ≥30 units ± up to two oral antidiabetics; dapagliflozin (2.5mg, 5mg or 10mg) versus placebo	Insulin doses not titrated to target, although this was to enable interpretation of the effect of dapagliflozin No details given of the original oral antidiabetic therapy Most patients enrolled were Caucasian and effects may vary in other ethnic groups	HbA_{1c} reduction was statistically higher for all doses compared with placebo; these were sustained to week 104	Demonstrated statistically significant benefit over placebo Higher rates of hypoglycaemia in comparison with placebo demonstrating a possible need for insulin dose reduction
Bolinder *et al*[8]	Body composition measurement; dapagliflozin (10mg) versus placebo in patients inadequately controlled on metformin	Significant differences between male and female populations studied Patients with body weight over 120kg were excluded which means those with the highest BMI cannot be included in the conclusions The study did not determine precise mechanism of dapagliflozin weight loss, and its effects on food intake and satiety are unknown	Mean weight loss of 2kg above placebo; proportion of patients achieving weight reduction of at least 5% was 26.2%	Greater effect seen in men than women; weight loss was mainly accounted for by fat loss rather than water Although this does not indicate significant benefits over other therapies (eg, glucagon-like peptide-1 agonists) it does offer weight loss benefits at an earlier stage in therapy and without the restrictions placed on GLP-1 agonists

DAPAGLIFLOZIN

SPECIAL GROUPS

RENAL IMPAIRMENT

- DAPAGLIFLOZIN REQUIRES A GOOD LEVEL OF RENAL FUNCTION TO WORK
- EFFICACY IS REDUCED IN PATIENTS WHO HAVE MODERATE RENAL IMPAIRMENT AND IS PROBABLY ABSENT IN PATIENTS WITH SEVERE RENAL IMPAIRMENT
- IT IS NOT LICENSED FOR USE IN PATIENTS WITH A CREATININE CLEARANCE BELOW 60ml/mins
- HOWEVER NO DOSE ADJUSTMENT IS NEEDED FOR PATIENTS WITH MILD RENAL IMPAIREMENT

DAPAGLIFLOZIN

SPECIAL GROUPS

HEPATIC IMPAIRMENT – DOSE ADJUSTMENT UNNECESSARY EXCEPT THOSE WITH SEVERE IMPAIRMENT (WHERE A STARTING DOSE OF 5mg IS RECOMMENDED)

OLD AGE – NO DOSE ADJUSTMENT BASED ON AGE. DUE TO LACK OF EXPOSURE IN PATIENTS ≥ 65 YRS, DAPAGLIFLOZIN IS NOT CURRENTLY RECOMMENDED IN THIS AGE GROUP.

DAPAGLIFLOZIN

SIDE EFFECTS

- **URINARY AND GENITAL TRACT INFECTIONS**
  - **COMMON FINDING IN CLINICAL TRIALS**
  - **INCIDENCE OF GTI DOSE RELATED**
  - **INFECTIONS APPEAR TO BE MILD AND RESPONDED TO STANDARD THERAPY**
- **HYPOGLYCAEMIA**
  - **INCIDENCE WAS LOW BUT INCREASED WITH CONCURRENT SULPHONYLUREA OR INSULIN**

DAPAGLIFLOZIN

SIDE EFFECTS

- MALIGNANCY
  - AN ANALYSIS OF THE ADVERSE EFFECTS THAT OCCURED DURING CLINICAL TRIALS SUGGESTED THAT THERE WAS AN IMBALANCE IN THE OCCURENCE OF BOTH BLADDER CANCER (10 CASES) AND BREAST CANCER (9 CASES)
  - THE TRIALS WERE NOT OF ADEQUATE DESIGN, SIZE OR SCOPE TO DETECT A SIGNIFICANT RISK DIFFERENCE BETWEEN DAPAGLIFLOZIN AND COMPARATORS FOR THESE TYPES OF CANCER
  - HOWEVER THE FDA DETERMINED THAT THE NUMBER OF OBSERVED BREAST AND BLADDER CANCERS IN THE DAPAGLIFLOZIN TREATED GROUP EXCEEDED THE NUMBER OF CASES IN THE GENERAL DIABETIC POPULATION

DAPAGLIFLOZIN

SIDE EFFECTS

- **HEPATIC IMPAIRMENT**
  - **THERE WERE AT LEAST 8 CASES OF DERANGED LIVER FUNCTION DURING THE PHASE 3 TRIALS WHICH INCLUDED RAISED SERUM ALANINE TRANSMINASE AND BILRUBIN TEST RESULTS. ONLY ONE CASE WAS THOUGHT TO BE RELATED TO DAPAGLIFLOZIN.**

DAPAGLIFLOZIN

INTERACTIONS

- FEW INTERACTIONS REPORTED DURING THE PHARMACOKINETIC STUDIES CARRIED OUT

- LACK OF EFFECT ON CYTOCHROME P450 → INTERACTIONS ARE NOT EXPECTED WITH DRUGS METABOLISED BY THESE ENZYMES

- PATIENTS TREATED WITH MEDICINES THAT AFFECT RENAL FUNCTION SUCH AS ACE INHIBITORS/LOOP DURETICS SHOULD BE STARTED ON DAPAGLIFLOZIN CAUTIOUSLY

DAPAGLIFLOZIN

MARKETING AUTHORISATION

- IT HAS BEEN GRANTED EUROPEAN MARKETING AUTHORISATION (EMEA)
- IT WAS NOT RECOMMENDED FOR APPROVAL BY FDA BECAUSE OF CONCERNS OVER ITS ADVERSE EFFECTS PROFILE. FURTHER CLINICAL DATA HAVE BEEN REQUESTED BY THE FDA TO ALLOW BETTER ASSESSMENT OF RISKS
- THE EUROPEAN MEDICINES AGENCY'S COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE, HOWEVER BELIEVES THAT THE COMMONLY SEEN SIDE EFFECTS ARE MANAGEABLE
- IT HAS RECOMMENDED THOUGH THAT FURTHER STUDIES INVESTIGATING THE POTENTIAL CANCER RISKS BE CARRIED OUT
- THE MANUFACTURER PLANS TO CONDUCT POST-MARKETING TRIALS TO EVALUATE THE SAFETY PROFILE

DAPAGLIFLOZIN

PLACE IN THERAPY

- DAPAGLIFLOZIN WILL PROBABLY BE A THIRD LINE THERAPY OPTION FOR DIABETES, ALONGSIDE DPP4 INHIBITORS AND GLP-I AGONISTS
- HOWEVER WITH THE GROWING CONCERN REGARDING THE HYPOGLYCAEMIA RISK OF SULPHONYLUREAS, IT WILL PROBABLY BE PROMOTED TO BE USED EARLIER IN THE COURSE OF DIABETES AS AN ALTERNATIVE FOR PATIENTS IN WHOM SULPHONYLUREAS ARE CONTRAINDICATED
- FURTHERMORE THE WEIGHT LOSS SEEN DURING TRIALS WOULD BE AN ADDED BENEFIT
- AT THE MOMENT, DAPAGLIFLOZIN DOES NOT HAVE THE STRENGTH OF EVIDENCE TO SUPPORT IT REPLACING METFORMIN OR SULPHONYLUREAS AS FIRST AND SECOND LINE OPTIONS

DAPAGLIFLOZIN

PLACE IN THERAPY

- NONETHELESS, ITS NEW MODE OF ACTION ALLOW PRESCRIBERS ANOTHER OPTION TO TAILOR THERAPY TO MEET INDIVIDUAL NEEDS
- IT ALSO PRESENTS AN OPPORTUNITY TO PRESCRIBE WITH INSULIN DUE TO ITS INSULIN-DEPENDENT MECHANISM AND INSULIN SPARING EFFECTS

NICE GUIDANCE

- IS RECOMMENDED IN COMBINATION WITH METFORMIN AS AN OPTION FOR TYPE 2 DIABETES
- ALSO RECOMMENDS DAPAGLIFLOZIN IN COMBINATION WITH INSULIN FOR TREATING TYPE 2 DIABETES
- TRIPLE THERAPY REGIMEN IN COMBINATION WITH METFORMIN AND SULPHONYLUREA IS NOT RECOMMENDED

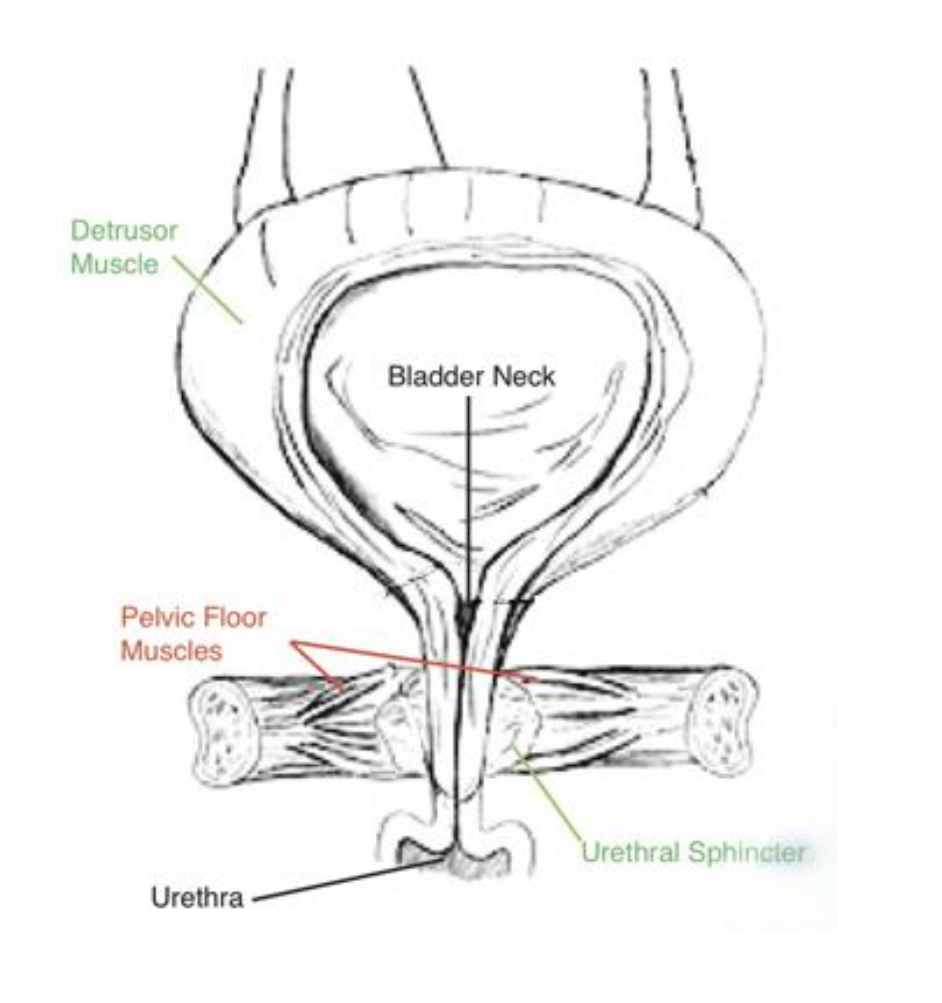
MANAGEMENT OF URINARY INCONTINENCE

MIRABEGRON A NEW DRUG FOR OVERACTIVE BLADDER

TYPES OF URINARY INCONTINENCE

- STRESS INCONTINENCE
- URGE INCONTINENCE
- OVERFLOW INCONTINENCE
- MIXED INCONTINENCE (A COMBINATION OF URGE/STRESS INCONTINENCE)
- OTHER FORMS (E.G NOCTURNAL ENURESIS)

THE BLADDER MECHANISM



STRESS INCONTINENCE

- CAUSED BY AN INCOMPETENT URETHRAL SPHINCTER THAT ALLOWS LEAKAGE OF URINE WHEN PRESSURE IS RAISED IN BLADDER SUDDENLY (E.G EXERCISING, LIFTING, COUGHING, ETC)

- CAUSES OF URETHRAL SPHINCTER INCOMPETENCE INCLUDE DIRECT DAMAGE TO THE PELVIC FLOOR MUSCLES (OFTEN ASSOCIATED WITH CHILDBIRTH), POST MENOPAUSAL OESTROGEN DEFICIENCY AND IN MEN PROSTATECTOMY OPERATIONS

- AGGRAVATED BY WEAK PELVIC FLOOR MUSCLES, OBESITY, CHRONIC COUGHS, ALPHA BLOCKING DRUGS (WHICH RELAX THE URETHRAL SPHINCTER), PREMENSTRUAL HORMONE FLUCTUATIONS AND EXERCISE

URGE INCONTINENCE

- CAUSED BY OVERACTIVITY OF THE DETRUSOR MUSCLE (BLADDER WALL)
- MANIFESTED AS URINARY URGENCY AND/OR FREQUENCY WITH OR WITHOUT INCONTINENCE, AND AS NOCTURIA
- DETRUSOR HYPERACTIVITY MAY BE IDIOPATHIC BUT IT MAY HAVE A NEUROPATHIC ORIGIN SUCH AS BRAIN INJURY OR CEREBROVASCULAR ACCIDENT
- CAN BE AGGRAVATED BY ANXIETY, ALCOHOL, ETC

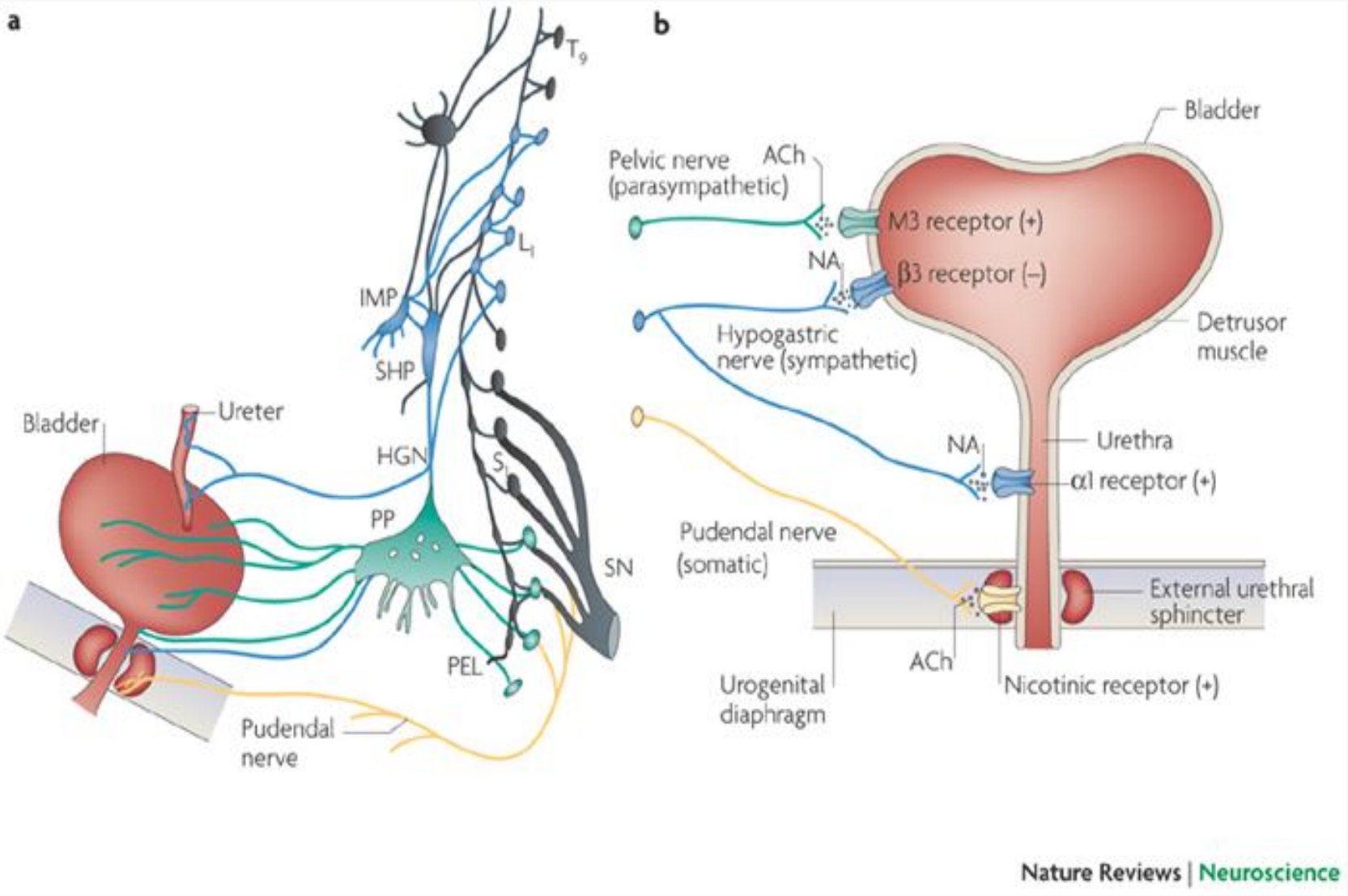
OVERFLOW INCONTINENCE

- PATIENT WILL PROBABLY HAVE NOCTURIA AND REPORT PASSIVE DRIBBLING OF URINE, FREQUENCY, INCOMPLETE BLADDER EMPTYING

- A COMMON CAUSE IS OUTFLOW OBSTRUCTION DUE TO BENIGN PROSTATIC HYPERTROPHY (BPH) OR CANCER OF THE PROSTATE

PHARMACOLOGICAL CAUSES

- ANY INCONTINENT PATIENT SHOULD HAVE THEIR MEDICATION REVIEWED TO CHECK WHETHER SIDE EFFECTS OF DRUGS ARE A CONTRIBUTING FACTOR TO THEIR PROBLEM
- THESE INCLUDE FOR EXAMPLE ALPHA BLOCKERS, DIURETICS
- CAFFEINE MAY AGGRAVATE DETRUSOR OVERACTIVITY AND ALCOHOL CAN CAUSE DIURESIS, BOTH LEADING TO URGE INCONTINENCE



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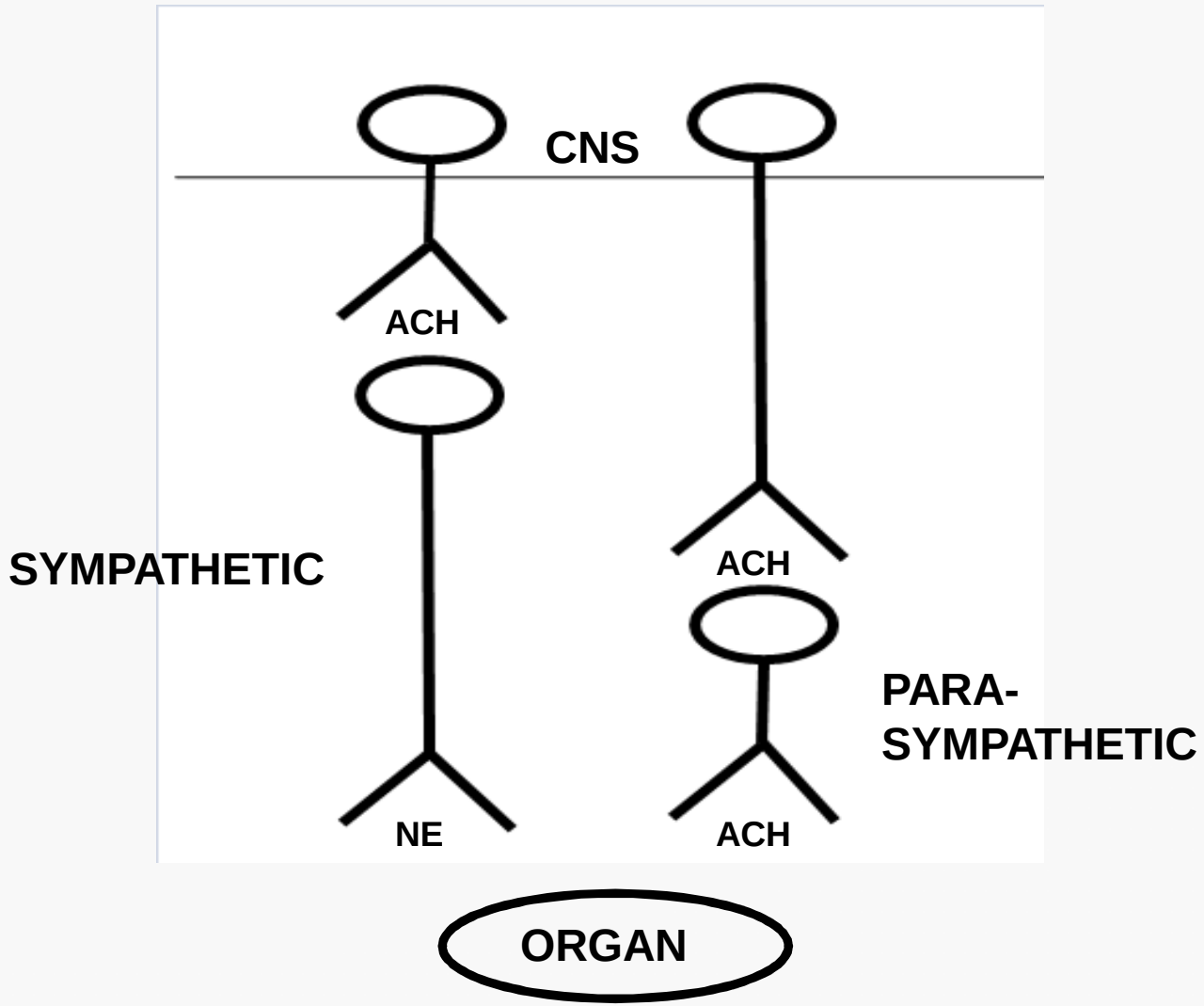
DUAL INNERVATION OF URINARY BLADDER



MANAGEMENT OF URGE INCONTINENCE

- DECREASING CAFFEINE AND ALCOHOL INTAKE
- PELVIC FLOOR EXERCISES
- BLADDER RETAINING (PATIENTS ENCOURAGED TO KEEP A BLADDER RECORD CHART WHICH RECORDS WHEN URINE IS PASSED NORMALLY AND ANY LEAKAGE) – AIM IS TO INCREASE TIME BETWEEN VISITS OR VOLUME PASSED EACH TIME
- DRUG THERAPY: MOST EFFECTIVE DRUGS ARE ANTICHOLINERGICS WHICH RELAXES DETRUSOR MUSCLES
- OPTIONS INCLUDE: OXYBUTYNIN, TOLTERODINE, SOLIFENACIN AND TROSPIUM
- MANY PATIENTS BENEFIT WITH A LOW DOSE, TO FACILITATE TOLERANCE AND GRADUALLY INCREASING UNTIL MAXIMUM EFFECT IS ACHIEVED
- SIDE EFFECTS INCLUDE RETENTION, DRY MOUTH, CONSTIPATION, ETC
- NEWER DRUGS SUCH AS TOLTERODINE, TROSPIUM, SOLIFENACIN ARE MORE SPECIFIC FOR THE BLADDER. HENCE LESS SYSTEMIC SIDE EFFECTS

MANAGEMENT OF OVERFLOW INCONTINENCE (OUTFLOW OBSTRUCTION)

- **ENLARGED PROSTATE (BPH) CAN BE TREATED BY DRUGS**

  1. **ALPHA BLOCKERS (ALFUZOSIN), TAMSULOSIN, ETC)**
  2. **5-ALPHA REDUCTASE INHIBITORS (FINASTERIDE, DUTASTERIDE)**

- **SURGERY**

MANAGEMENT OF STRESS INCONTINENCE

- PELVIC FLOOR EXERCISES (FOR WOMEN AND FOR MEN POST-PROSTATECTOMY)
- ELECTROTHERAPY ADMINISTERED BY A COMPETENT CONTINENCE NURSE
- SURGERY
- DRUG THERAPY
  1. ORAL OR TOPICAL OESTROGEN REPLACEMENT IN POST MENOPAUSAL WOMEN
  2. DULOXETINE – NOVEL AND FIRST AGENT IN THE MANAGEMENT OF URINARY STRESS INCONTINENCE

DULOXETINE

- SEROTONIN AND NORADRENALINE REUPTAKE INHIBITOR BLOCKING THE UPTAKE OF THESE NEUROTRANSMITTERS IN THE SPINAL CORD
- THIS INCREASE IN THE NEUROTRANSMITTERS STIMULATES INCREASED ACTIVITY OF THE NERVE THAT STIMULATES THE URETHRAL SPHINCTER
- CONTRACTION OF THE SPHINCTER AT THE OPENING OF THE BLADDER, PREVENTING LEAKAGE OF THE URINE DUE TO PHYSICAL EXERTION

MIRABEGRON

A NEW DRUG FOR OVERACTIVE BLADDER (URGE INCONTINENCE)

"HOW IT WORKS"

- MIRABEGRON IS THE FIRST B_3 ADENOCEPTOR AGONIST TO BE MARKETED
- IT'S LIKELY THAT MIRABEGRON EXERTS ITS EFFECTS VIA A DUAL MECHANISM BOTH DIRECTLY ON THE BLADDER SMOOTH MUSCLE AND ALSO VIA THE SENSORY NERVOUS SYSTEM
- BY STIMULATING B_3 RECEPTORS, IT INCREASES LEVEL OF CYCLIC AMP AND LEADS TO RELAXATION OF DETRUSOR MUSCLE
- MAIN ADVANTAGE IS LACK OF MUSCARINIC SIDE EFFECTS

MIRABEGRON

EVIDENCE

MIRABEGRON APPEARS TO BE MORE EFFECTIVE THAN PLACEBO IN TRIALS IN TERMS OF REDUCTION OF INCONTINENCE EPISODES AND MICTURITIONS BUT THE DIFFERENCE IS NOT STATISTICALLY SIGNIFICANT COMPARED TO TOLTERODINE

MIRABEGRON

ADMINISTRATION

- ONCE DAILY WITH OR WITHOUT FOOD
- 50mg DAILY RECOMMENDED FOR MOST ADULT PATIENTS

SIDE EFFECTS (IN TRIALS)

- URINARY TRACT INFECTION (5.9%)
- HEADACHE (4%)

MIRABEGRON

MARKETING AUTHORISATION

- AVAILABLE IN JAPAN AND US FOR OVER A YEAR
- RECENTLY REGISTERED IN UK
- SO FAR, IT APPEARS TO HAVE VERY FEW SIDE EFFECTS
- PRACTICALLY NO ANTIMUSCARINIC SIDE EFFECTS
- THE SUMMARY OF PRODUCT CHARACTERISTICS LISTS URINARY TRACT INFECTIONS AND TACHYCARDIA AS THE MOST COMMON SIDE EFFECTS (THE LATTER AFFECTING 1.2% OF PATIENTS)

MIRABEGRON

PLACE IN THERAPY

- IT IS LIKELY THAT MIRABEGRON WILL START AS AN ALTERNATIVE TO PATIENTS WHO FAIL OR CANNOT TOLERATE ANTIMUSCARINIC TREATMENT

- WITH MORE EXPERIENCE OF ITS USE, IT COULD BE USED FIRST LINE BUT IT IS NOT A CANDIDATE YET

- IT MIGHT ALSO BE USED IN THE FUTURE IN COMBINATION WITH ANTIMUSCARINIC (BUT FURTHER STUDIES AWAITED)

MIRABEGRON

NICE RECOMMENDS MIRABEGRON AS A POSSIBLE TREATMENT FOR SYMPTOMS OF OVERACTIVE BLADDER IN SOME PEOPLE FOR WHOM THE "ANTIMUSCARINIC DRUGS" DO NOT WORK, ARE NOT SUITABLE FOR, OR HAVE UNACCEPTABLE SIDE EFFECTS.

(TYPICALLY 30% OF PATIENTS CANNOT TOLERATE THE SIDE EFFECTS OF ANTIMUSCARINIC DRUGS OR FIND TREATMENT TO BE INEFFECTIVE)

THANK YOU