



MEDICAL UPDATE GROUP MEETING

WHAT'S NEW IN THERAPEUTICS ?

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SADECK VAWDA

WHAT'S NEW IN THERAPEUTICS ?

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**NEW ORAL ANTICOAGULANTS FOR
MANAGEMENT / PREVENTION OF VTE**

History of oral anticoagulation

- Warfarin was one of 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)**
&
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 risk involved
- Interpatient / inpatient 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
- Longer acting injectable : Under development is idraparinux – once weekly injection.
- New oral anticoagulants are rivaroxaban and dabigatran which are already marketed in the European Union

Novel Drugs

Idraparinux – as heparin, LMWH and fondaparinux, injectable

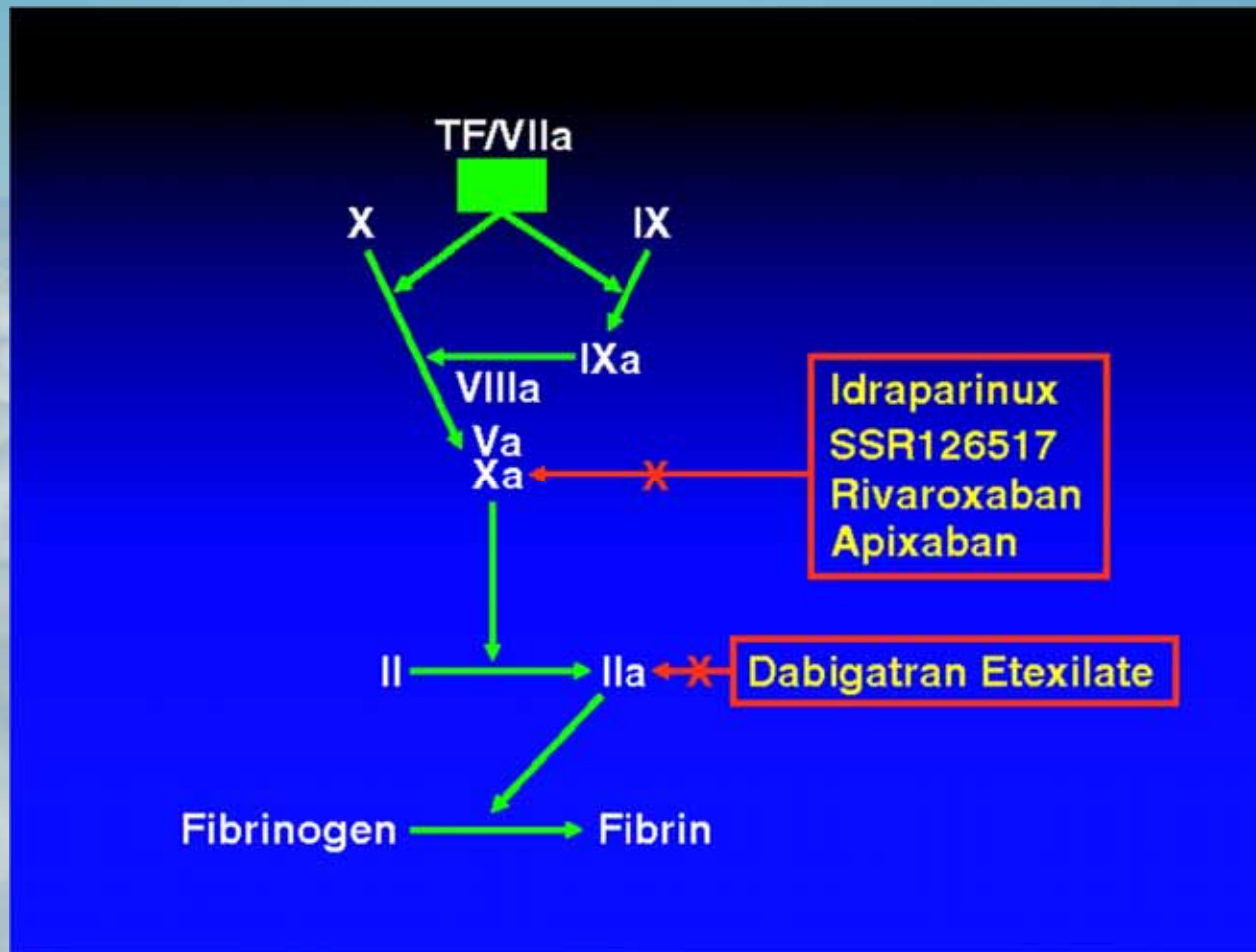
- Factor Xa inhibitor

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)

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
- Dialysis is likely to clear but more studies needed
- 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

New oral anticoagulants

- Present indication is only in primary prevention of VTE and not in treatment
- Present indication is 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

- More studies / results awaited on
 1. Efficacy in VTE treatment
 2. Side effect profile
 3. Secondary prevention of VTE
 4. Comparison with LMWH / Warfarin
 5. Use in AF for stroke prevention
- Dabigatran has just obtained the indication in AF
- Rivaroxaban anticoagulant is expected to be the first new oral anticoagulant to have all the three indications (prevention / treatment of VTE / AF for stroke prevention) by end 2011 following a favourable recommendation by the European Committee for medicinal products
- A third oral anticoagulant: apixaban has just obtained approval in prevention of VTE

Does this mean the end for anticoagulation clinics?



BIOPHARMACEUTICALS / BIOSIMILARS

- Challenges ahead

BIOPHARMACEUTICALS / BIOSIMILARS

- Challenges ahead

- Few biopharmaceuticals have been around for a while
 - erythropoietin
 - beta interferons
 - recombinant insulin
 - interleukins
 - somatostatin
 - granulocyte colony stimulating factors
 - monoclonal antibodies
 - low molecular weight heparins
 - thrombolytic agents (alteplase)
- But as technology progresses, numbers will increase
- Similarly as patent expires, “biosimilars” are set to become available
- Biotech drugs account for around 10% of the world pharmaceutical market

History of evolution of drugs

- Beginning of the 20th century – Medicine market was dominated by preparations derived from natural sources of plants , animals or mineral origin.
- Later on the evolution led to the development of synthetic molecules discovered in the laboratory and manufactured in large scale chemical plants. Advantage was that they were consistent in their molecular structure and could easily be purified and characterised.
- By varying the molecules in a homologous series, they could be made more potent with less side effects.
- By the end of the 20th century , the synthetic molecules reaching the market decrease considerably.
- Recombinant DNA technology became available as a manufacturing tool and the age of biopharmaceuticals ushered in the 21st century

WHAT ARE BIOPHARMACEUTICALS ?

- Biopharmaceuticals are complex , high molecular weight proteins and peptides that are produced in living systems.
- Encoding of gene and insertion in DNA of host cells results in a master cell batch suitable for the production process.
- Master cell batch split in several aliquots which are stored in deep freeze to preserve their integrity.
- Each aliquot is used in cell culture to produce larger volumes.
- The culture produces a unique product that consists of several different variations on the original molecule (ex. Amino acid chains/ sugar residue can vary).
- Biopharmaceuticals produced by different manufacturing units / processes can never be identical, only similar.

WHAT ARE BIOPHARMACEUTICALS?

- The term “generics” should not be used for biopharmaceuticals but “biosimilars”
- Production of a biopharmaceutical is a much longer process than chemical manufacturing, hence high cost
- Culture medium includes hamster ovary cells (which secrete product in medium), yeast, or E.coli (needs to be lysed to release product)

WHAT ARE BIOPHARMACEUTICALS?

- Modification of biopharmaceuticals by glycosylation / pegylation
 - e.g. glycosylation of erythropoietin (given 3 times a week)
 - darbepoetin alfa → prolongs duration → given once weekly or every two weeks
 - pegylation → e.g. pegylated interferons
- Peptides, hence can only be given by injectable route (S/C / IV)

BIOPHARMACEUTICALS

- Carry a warning that it should not be shaken vigorously
→ to prevent aggregation. Aggregates are known to produce an immune response and to alter pharmacokinetic profile.
- Most should be stored between 2-8 degree Celsius
- As product purification and formulation has improved, some (insulin in pens) can be stored at room temperature
- Although biopharmaceuticals closely resemble the endogenous proteins, it can elicit an immune response : can vary from no perceptible effect to significant clinical effects.
- Product related factors that can influence immunogenicity are amino acid sequence variation / glycosylation / host cell / contaminants / formulation / handling and storage.

BIOSIMILARS

- The worldwide biopharmaceuticals market is worth more than 45 billion Euros annually.
- Copies of these products have been made worldwide in non regulated markets and in regulated markets where patents have expired, other companies other than the originators have been quick to enter this market
e.g. – Biosimilar Insulin
 - Omnitrope is a biosimilar brand of genotropin, using it as a reference
- Advantages :
 - As more suppliers enter the market this will lead to fall in prices with more funds released for the treatment of more patients.

BIOSIMILARS

Disadvantages:

- cannot make exact copy of originator, hence no true generics
- produced all over the world but to different qualities and standards
- Gel electrophoresis is starting point to compare profile → products showing similar patterns are likely to have similar activity and half life

BIOSIMILARS

- To get into regulated market, biosimilars have to provide a full evaluation comparing them to a reference compound
- European medicine agency (EMA) has produced specific guidelines on biosimilars
- Unlike generics which need to show only bioequivalence, biosimilars need to undergo phase I / phase III clinical trials to show similarity to reference compound, in terms of safety, quality and efficacy
 - e.g. epoietin alpha , epoietin beta & epoietin zeta produced by different manufacturing processes
- Cost difference will not be as important as it is the case with generics as manufacturers need to perform trials to show similarity

BIOSIMILARS

Substitution or clinical interchange

- As more and more biosimilars are inevitable, can they be safely interchanged ?
 - for clinical reasons
 - for cost reasons
- Insulin provides a good analogy
 - switching require clinical monitoring
- Some biopharmaceuticals can be interchanged but prescriber must be involved and patient must be transferred under monitored conditions
- Simple substitution at dispensing level is not acceptable
- BNF recommends to use brand names when prescribing biopharmaceuticals

BIOSIMILARS

The Future

- Several hundred biopharmaceuticals in pipeline, outnumbering new chemical entities
- Moving now into the concept of “biobetters”
e.g. increase in half life , improved efficacy with less side effects
- Use in gene therapy – 70 % of trials are in cancer
- At present many of the products in use are administered in hospitals / clinics but just like insulin they shall find their way increasingly into common practice.

AGOMELATINE – A NOVEL ANTIDEPRESSANT

Depression

- Is a common and recurrent illness accounting for significant morbidity worldwide
- Untreated depression increases the risk of death from suicides, accidents, heart disease, respiratory disorders and strokes
- The effective treatment and management of depression is a challenge for all healthcare professionals
- On a biochemical level, a variety of neurotransmitter abnormalities have been hypothesised to contribute to depression. These include deficiencies in serotonin, noradrenaline, GABA and peptide neurotransmitters

Depression

Treatment Options

- Non drug treatment: Psychotherapy / Cognitive Behavioural Therapy (CBT)
- Pharmacotherapy:
 1. Selective Serotonin Reuptake Inhibitors (SSRI's) e.g fluoxetine, paroxetine
 2. Selective Serotonin and Noradrenaline Reuptake Inhibitors (SNRI's) e.g venlafaxine, duloxetine
 3. Tricyclic Antidepressants (TCA's) e.g amitriptyline, imipramine
 4. Monoamine Oxidase Inhibitors (MAOI's) e.g moclobemide
 5. Agomelatine – a melatonergic agonist
 6. ECT (Electroconvulsive Therapy)

AGOMELATINE

- The first melatonergic antidepressant
- Melatonin plays a key role in synchronising circadian rhythms which are known to be perturbed in depressed states. Mood disorders are closely linked to circadian rhythm disturbances.
- There is clear evidence that there are strong links between circadian disturbance and symptoms of clinical depression including delayed sleep onset, non-restful sleep, early morning wakening, daytime fatigue and blunting or reversal of normal morning peaks in subjective energy, mood and alertness.
- Agomelatine was approved in 2010 for the treatment of major depression in Europe, thereby becoming the first approved antidepressant to incorporate a non-monoaminergic mechanism of action.
- The restoration of disturbed circadian rhythms is an innovative approach in depression treatment.

AGOMELATINE

Mode of action

- Is a melatonergic agonist (MT₁ / MT₂ receptors), and 5HTC_{2C} antagonist
- No effect on monoamine reuptake and no affinity for cholinergic, histamine, dopamine, adrenergic and GABA receptors
- Resynchronises circadian rhythms
- No influence on extracellular levels of serotonin
- Has demonstrated efficacy in the acute phase, in the short term and in maintenance phase of depression and both in moderate / severe depression.
- Significant effect on core symptoms: depressed mood, anxiety symptoms, sleep-wake disturbances
- No abuse potential shown
- Onset and quality of sleep significantly improved without daytime clumsiness

Agomelatine – IN PRACTICE

- Is hailed as a major advance in the management of depression through the restoration of circadian rhythms
- Indicated in adults > 18 years of age
- Patient improvement within the first week of treatment
- Preserves sexual functioning, weight neutral
- Easy to use – one tablet of 25mg at bedtime without discontinuation symptoms at end of treatment
- Can be increased to 50mg if no improvement of symptoms in 2 weeks

Agomelatine – IN PRACTICE

- Contraindicated in patients with hepatic impairment / concomitant use of CYP1A2 inhibitors (e.g fluvoxamine / ciprofloxacin). In clinical studies, elevations of serum transaminases have been observed in patients (particularly with 50mg dose). On discontinuation, it reverts to normal (1.1% incidence). Liver function tests in all patients: initiation, after 6 weeks and around 12 and 24 weeks (end of maintenance phase). Therapy discontinued if serum transaminases exceed 3 X upper limit (repeated within 48 hours) / symptoms of hepatic dysfunction / jaundice observed. Caution in alcoholics.
- No cardiovascular precaution needed
- Common side effects: nausea / dizziness (transient)
- Taken at bedtime to maximise melatonergic effect
- Recommended duration of treatment: around 6 months

AGOMELATINE

NICE recommendation

- Aglomelatine may have a role for specialist initiation in those patients with severe depression who have failed to respond to, or cannot tolerate an adequate trial of at least two antidepressant drugs at maximally tolerated doses.

BOTOX: FROM SPECIALIST OPHTHALMOLOGY CLINICS TO SUBURBAN BOTOX PARTIES

- No other landmark drugs has such a high public profile as BOTULINUM TOXIN
- Its 20 year odyssey from orphan drugs to billion dollar blockbuster has seen botulinum toxin travel from specialist ophthalmology clinics to suburban botox parties, and its clientele extend from grateful patients with previously untreated muscle spasms to multi-millionaire in search of youthful skin

BOTULINUM TOXIN

- Produced by clostridium botulinum, an organism present in 90% of soil samples.
- There are seven different neurotoxins, A-G, although A, B and E account for most cases of botulism – the paralysing illness from eating food contaminated with toxin. The toxin blocks neuromuscular transmission.
- It is now known that botulinum toxins break up key proteins SNAP25, VAMP and syntaxin which are needed for synaptic vesicles filled with acetylcholine to bind to synaptic membrane.
- Unable to bind to the membrane, the vesicles cannot release acetylcholine, so no nerve impulse is transmitted to the muscle, and the result is paralysis.

BOTULINUM TOXIN

- Today, botulinum toxin A (Botox) is by far the most commonly used toxin in clinical practice, although botulinum toxin B is sometimes used for patients who fail to respond to type A.
- For clinical purposes, the toxin is extracted from the bacterium, purified and formulated as a dry powder for reconstitution.
- Botox has become the household name but it was Dysport, originally developed by scientists at Britain's chemical weapons centre that was used in early clinical studies. However, it was Botox that pursued the cosmetic indications and ensured the product's posterity.

BOTULINUM TOXIN

From squints to spasticity

- Idea of using tiny doses of botulinum toxin to modify neuromuscular function was first proposed by squint researchers in San Francisco in early 1970's
- Proposed as an alternative to surgery but it was not suitable to all types and the effect was temporary
- In the original paper, it was suggested that the technique could be extended to blepharospasm, and this was where it had its first major success
- By injecting the toxin in the orbicularis oculi of the eye, it proved possible to weaken the muscle sufficiently to restore blinking and visual function to normal in about a third of patients and achieve significant improvement in a further 50%
- Based on its effects on blepharospasm, experimenting started in patients with focal dystonia (cervical dystonia – spasmodic torticollis) which affects the neck / head. Significant improvements in morbidity / disability were noted

BOTULINUM TOXIN

- As a result, botulinum is now widely considered as the first line therapy for cervical dystonia and is commonly used for focal dystonia, essential tremor in the arms, laryngeal dystonia, hemifacial spasms, focal dystonia in the legs and motor tics.
- Injections need to be repeated every 3 months. Patients continue to benefit from treatment for many years.
- Failure occurs in only 2% of patients treated with Botulinum A (due to formation of antibodies against the toxin). 10% of patients will still respond to type B (but effect is not long lasting).
- Botulinum toxin also plays an important role in the management of spasticity related to MS, stroke, motor neurone disease and cerebral palsy
- The key to effective treatment is to ensure precise injection techniques, so that patients get the optimal amount of drug in the muscle where they need it, with lowest possible risk of spread to surrounding muscles resulting in unwanted weakness.

BOTULINUM TOXIN

Recent developments

- For severe sweating problems (hyperhidrosis), botulinum toxin has superseded surgery as first line therapy
- Growing role in overactive bladder (option for patients resistant to antimuscarinic drugs)
- Potential role in migraine?

Future directions

- Migraine / headaches and other forms of pain
- Genetic engineering of neurotoxins is aimed at separating the muscle relaxing and analgesic effects of the toxin, so that improved pain control can be achieved without problems of muscle weakness
- Longer lasting formulations to reduce the frequency of injections

PRUCALOPRIDE

- A novel enterokinetic agent
- Symptomatic treatment of constipation for women in whom laxatives fail to provide adequate relief
- Targets underlying impaired gut motility by increasing colon motility and transit

CHRONIC CONSTIPATION

- Can have a substantial impact on patient's quality of life and affects two to three times as many women as men and prevalence rates are around 10% in women under 65 years of age and around 20% in women over 65 years of age in UK
- Symptoms include infrequent defecation, excessive straining, lumpy / hard stools, sensation of incomplete evacuation, abdominal bloating / pain / discomfort
- Currently treatment focuses on the use of laxatives to relieve symptoms. One or a combination of laxatives from different pharmacological groups (e.g osmotic, bulk forming or stimulant laxatives) may be required
- For some patients chronic constipation can become intractable requiring relatively invasive procedures (such as enema, rectal irrigation or manual removal). Quality of life is substantially affected in such patients

PRUCALOPRIDE

Mode of action

- First in class selective 5HT₄ (serotonin) receptor agonist
- This results in increased acetylcholine release in the GIT which in turn stimulates colonic motility, thereby restoring bowel function
- Structurally different from other non-selective prokinetic agents such as cisapride. These drugs are less selective for 5HT₄ receptors and interact with other serotonin receptors such as 5HT₃, 5HT_{1B} and 5HT_{1D} which are suggested to account for adverse cardiac effects.

PRUCALOPRIDE – In Practice

- Recommended dose: 2mg once daily for adult women < 65 years old and 1mg daily for adult women > 65 years old (can be increased if needed)
1mg dose for patients with severe renal and hepatic dysfunction
- The drug is contraindicated in patients with intestinal perforation, obstruction or severe inflammatory disease of the GIT

PRUCALOPRIDE

Clinical Evidence

- 3 pivotal studies for prucalopride that demonstrated efficacy compared to placebo
- Approximately 90% of patients in the trials were female, hence the drug is only licensed for women
- Patients had a history of chronic constipation and one or more of the following criteria for at least 6 months before the screening visit:
 - Straining during at least 25% of bowel movements
 - Very hard / hard stools in at least 25% of bowel movements
 - A sensation of incomplete evacuation for at least 25% of bowel movements
- Patients excluded if constipation was drug induced or as a result of endocrine / metabolic / neurological disorders
- Primary outcome was achieving three or more spontaneous complete bowel movements (SCBM) per week. Response evaluated at 4 / 12 weeks
- The product was found to be better than placebo in each of the 3 studies with around a third of patients responding to treatment

PRUCALOPRIDE

Place in Therapy

- NICE has issued guidance for the use of prucalopride in December 2010

“It is recommended as an option in women who have failed to obtain adequate relief for at least 6 months of treatment with laxatives from at least two different classes at maximally tolerated doses and for whom invasive treatment for constipation is being considered.”

- Clinical trials have demonstrated that most patients who respond will do so within 4 weeks
- Should be prescribed by a clinician who has supervised the woman's previous courses of laxatives
- There are currently no other pharmacological options for the treatment of laxative resistant chronic constipation. Non-pharmacological options have a high failure rate, are costly, provide short-term relief and are associated with a risk of complications

PRUCALOPRIDE

Safety considerations

- Some categories of patients were excluded from the studies, namely those suffering from:
 - Drug induced constipation
 - Constipation caused by endocrine / metabolic / neurologic disorder
 - Renal failure
 - Liver failure
 - Cardiovascular diseases
- Unclear how safe / effective it will be for women with above conditions, hence not recommended for use or use with caution in such patients

PRUCALOPRIDE

Interactions

- Low interaction potential (excreted without extensive hepatic metabolism)
- Therapeutic concentrations are not expected to affect the metabolism of other medicines via cytochrome P450 pathways
- Should be used with caution among patients receiving concomitant drugs known to cause QT interval prolongation (amiodarone, clarithromycin, erythromycin)

Adverse Effects

- Most common are headache / gastrointestinal symptoms (abdominal pain, diarrhoea / nausea)
- Most adverse effects subside after a few days
- More long term data to evaluate the cardiac side effect profile (QT prolongation has not occurred yet in doses up to 20mg)

Conclusion

- Prucalopride is a useful treatment option for women with laxative resistant chronic constipation.
- Chronic constipation, though not life threatening, can have a significant effect on quality of life, often accompanied by a host of unpleasant symptoms like irritability, lethargy and painful bloating, hence the availability of prucalopride is a clinically valuable treatment option for chronic constipation resistant to standard laxatives.

PHOSPHODIESTERASE INHIBITORS

A phosphodiesterase inhibitor is a drug that blocks one or more of the five subtypes of the enzyme phosphodiesterase (PDE), therefore preventing the inactivation of intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by the respective PDE subtype(s).

- Different forms or subtypes of phosphodiesterase (PDE 1-5) were initially isolated in 1972
- Potential for selective phosphodiesterase inhibitors as therapeutic agents were predicted as early as 1977
- Prediction has proved to be true in a variety of fields

PHOSPHODIESTERASE INHIBITORS

Classification

- Non selective (Methylxanthines and Derivatives)
 - Caffeine, a minor stimulant
 - Aminophylline / Theophylline (Bronchodilators)
 - Pentoxifylline, a drug used to enhance circulation in intermittent claudication, microvascular injuries, etc.
- PDE₁ selective inhibitors
 - Vinpocetine – vasodilator and nootropic for memory enhancement
- PDE₂ selective inhibitors
 - Anagrelide – a drug used for the treatment of essential thrombocytosis (overproduction of blood platelets)

PHOSPHODIESTERASE INHIBITORS

- PDE₃ selective inhibitors
 - Enoximone, cilostazol and milrinone, used clinically for short term treatment of heart failure. These drugs mimic sympathetic stimulation and increase cardiac output
- PDE₄ selective inhibitors
 - Drotaverine – used to alleviate smooth muscle spasms and renal colic
 - Roflumilast – a new drug indicated for people with severe COPD
 - Rolipram in Alzheimer's Disease?
- PDE₅ inhibitors
 - Sildenafil, vardenafil and tadalafil used in erectile dysfunction and pulmonary hypertension
 - Dipyridamole, an antiplatelet agent

ROFLUMILAST

- A new add on therapy for COPD
- A phosphodiesterase 4 inhibitor
- Add on to existing bronchodilator treatment
- Indicated for maintenance treatment of severe COPD associated with chronic bronchitis in adults with a history of frequent exacerbations
- Roflumilast targets inflammatory processes in COPD, with beneficial effects on tobacco-induced lung inflammation, lung fibrosis and remodeling, mucociliary malfunction and oxidative stress
- Many phase III trials have demonstrated the beneficial effects of roflumilast in patients already receiving long acting β_2 agonist or muscarinic antagonist ipratropium

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

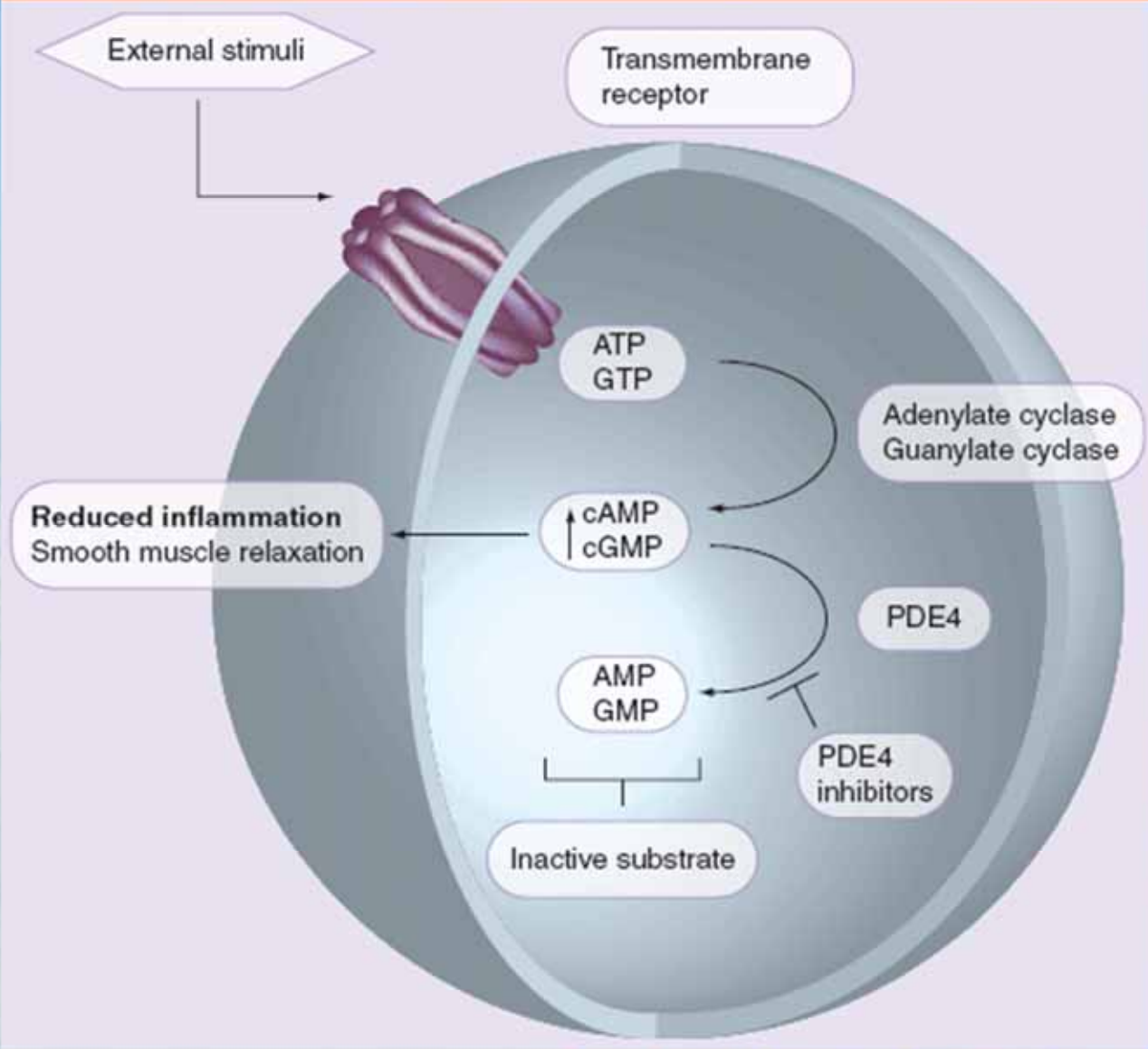
- A chronic inflammatory disease of the airways / lungs is a major cause of morbidity / mortality worldwide
- The disease characterised by progressive airway limitation that is not fully reversible
- Primarily caused by cigarette smoking although occupational and environmental pollution might have a role in some cases
- Nearly always associated with complex co-morbidities such as heart failure and metabolic syndrome

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- At present, no approved drugs to slow or halt the progression of COPD
- Current pharmacotherapy provides symptomatic relief with bronchodilator drugs e.g inhaled short acting / long acting β_2 agonist, and anticholinergic agents
- Patients with severe disease and a history of exacerbations are also prescribed inhaled corticosteroids with long acting β_2 agonists which can help reduce frequency of exacerbations
- Theophylline has been used to treat COPD, but its narrow therapeutic window and interactions limit its use

ROFLUMILAST

- A PDE₄ inhibitor
- PDE₄ – catalyse the breakdown of signaling pathways cAMP / cGMP
- Is the main cAMP-metabolising enzyme in inflammatory and immune cells
- PDE₄ inhibitors cause an accumulation of cAMP
- PDE₄ inhibitors have a range of anti-inflammatory properties including inhibition of the release of inflammatory mediators and inhibition of immune cell activation
- Roflumilast is the first PDE₄ inhibitor to receive marketing approval



ROFLUMILAST – IN PRACTICE

- Once daily dosing (oral tablets)
- The drug might take several weeks to achieve its effects
- Has been associated with an increased risk of psychiatric disorders such as insomnia, anxiety, depression and nervousness
- Adverse effects include diarrhoea, nausea, abdominal pain and headache. Occur in the first weeks of treatment and most resolve with continued treatment
- Patients should check their weight regularly and if an unexplained weight loss occurs, treatment should be stopped

ROFLUMILAST

Place in Therapy

- The most unmet need in COPD is for prevention in patients with frequent exacerbations
- Existing therapy has limited effects in severe COPD, on pulmonary and systemic inflammation associated with COPD, and do not affect chronic co-morbidities of COPD
- Roflumilast has an important role to play in maintenance treatment of patients with severe COPD associated with frequent exacerbations

ROFLUMILAST

- Has an important effect on the pulmonary and systemic chronic inflammation associated with COPD (inhibits chemotaxis, leucocyte infiltration, cytokine production and reduces neutrophils and eosinophils in airways of patients with COPD)
- Several innovative aspects of roflumilast might help address some of the unmet needs of patients with COPD
- As COPD exacerbations are associated with progression of disease and may increase mortality, the effect of roflumilast on disease exacerbations is particularly important
- Oral administration can improve compliance and could result in systemic effects that also influence chronic comorbidities

ROFLUMILAST

- The future
- Use in management of COPD, not only as a maintenance treatment
- Asthma

Are We Closer To CVD Treatment With POLYPILLS?

- The polypill concept involves combining several drugs used to treat cardiovascular disease into a once-daily pill
- Such an approach for CVD has been discussed for 20 years or so
- Debates as to which constituents would be optimal and trials have involved different formulations
- Many clinicians believe a polypill could increase compliance and reduce overall cost of treatment. There could also be significant health benefits in terms of primary prevention
- However, in prevention there is some debate about who should be treated: some proponents suggest everyone aged over 55 years; others favour targeting based on cardiovascular risk

POLYPILLS

WHAT TRIALS HAVE SHOWN?

- The Indian Polycap Study (TIPS) involved 2053 people without CVD but with one risk factor
Polypill treatment (simvastatin 20mg, HCZ 12.5mg, atenolol 50mg, ramipril 5mg, aspirin 100mg) reduced BP by 7.4/5.6 mmHg and LDL-cholesterol by 0.7mmol/L
The estimated proportional risk reduction was 62% for CHD and 48% for stroke
- Another trial involved 475 participants without CVD, hypertension or hyperlipidemia treated with atorvastatin 10mg, enalapril 2.5mg, HCZ 12.5mg, aspirin 81mg for 12 months. Polypill treatment gave estimated proportional risk reductions of 34% for CHD and 21% for stroke

POLYPILLS

WHAT TRIALS HAVE SHOWN?

- Another study involving 378 people with an estimated 5 year CVD risk greater than 7.5% showed that polypill treatment (simvastatin 20mg, HCZ 12.5mg, lisinopril 10mg and aspirin 75mg) gave an estimated risk reduction of 60% for CHD and 56% for stroke. BP was reduced by 9.9/5 mmHg and LDL-cholesterol by 0.8mmol/L
- More side effects were experienced in the polypill participants than those taking placebo. Side effects were sufficient to stop treatment in around 1 in 20 participants
- Most of the side effects (and virtually all of the more serious ones) are due to the aspirin content

POLYPILLS

PLACE IN THERAPY AND THE FUTURE

- The risk factor reductions in the trials, together with previous findings from systematic reviews of the component medicines, indicate that the polypill would more than halve people's cardiovascular risks. However, this is a moderately lower risk reduction than previous estimates.
- Larger trials are needed to test whether these medicines are best provided in the form of a polypill or as separate medicines, and whether this combination strategy improves adherence to cardiovascular medication.

POLYPILLS

- Treating lower risk individuals with aspirin is “slightly contentious” due to the side effect profile.

Since aspirin is protective against cancer the scene changes somewhat and it makes sense to include it to look at a broader preventive scenario.

- Long term trials are needed to assess the effect on clinical outcomes such as reduction in death, MI and stroke.
- It is possible to envisage a range of polypills with different dosing regimens, including stronger statins or different combinations of antihypertensive and antiplatelet medicines.

POLYPILLS

- Cost will not be an issue as most components are off-patent
- Minimal costs of implementing a general prevention strategy when compared to a more conventional “test all and treat those at risk” strategy
- Research indicates that it will take at least 10 years before a public interest-focused public health policy based on primary prevention is accepted
- Polypill in patients with existing CHD?

MISCELLANEOUS BREAKTHROUGHS

- Cardiovascular
 - New antiplatelet agents (ticagrelor / prasugrel)
 - Aliskiren - the first direct renin inhibitor for hypertension
- GI
 - Dronedarone – use in AF (under review for side effects)
 - Methylnatrexone – an opioid antagonist for opioid induced constipation without affecting analgesia
- Women's health / Men's health
 - Ulipristal – a new morning after pill that can be taken up to 5 days after an unprotected intercourse
 - Dapoxetine – a new drug for premature ejaculation

MISCELLANEOUS BREAKTHROUGHS

- Malignancy
 - Evrolimus / pazopanib – protein kinase inhibitors for advanced kidney disease
 - Azacitidine – an epigenetic therapy altering gene expression for use in certain forms of leukaemia
- AIDS/HIV
 - Raltegravir – an integrase inhibitor
- Neurology
 - Buccal midazolam for status epilepticus
- Hyperuricaemia
 - Febuxostat – for chronic hyperuricaemia



THANK YOU