WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Phosphodiesterase Inhibitors: A Review

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Introduction:

Phosphodiesterase's (PDEs) constitute a large family of phosphohydrolytic enzymes; they were first identified around 50 years ago, and since then, research on PDEs has focused on a variety of topics. Phosphodiesterase (PDE) are enzymes found in the human body that help regulate the intra-cellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate which subsequently elicited a role in conducting multiple cellular functions in human body.[1] cAMP and cGMP are pivotal second messengers in signaling, involved in cell proliferation, cell-cycle regulation and metabolic functions.

The complex superfamily comprising 11 families is known as the cyclic nucleotide. PDEs are expressed by 21 genes and more than 100 gene variants. They are responsible for accelerating the hydrolysis of the 3'-cyclic phosphate link in cyclic nucleotide molecules, which results in the production of inert compounds.[2] Each of the individual PDE families is characterized by varying specificities towards the cyclic nucleotide substrate: the families 1, 2, 3, 10, and 11 hydrolyze both cAMP and cGMP with comparable affinity; the families 4, 7, and 8 exhibit higher affinities towards cAMP, while the families 5, 6, and 9 are more specific towards cGMP.[3]

In fact, the inhibition of PDE leads to an increase in cyclic nucleotide levels, which in turn play a prominent role as second messengers, in the regulation of a variety of cell functions, such as secretion, contraction, metabolism and growth.[4,5]

Till today, PDE 1-11 families have been found and 50 isoforms are noted. Isoforms of all PDEs are widespread in several organs with sole functional activities. Their activation is linked to pathophysiology, and their inactivation or inhibition is associated with disease recovery.[6]

PDE was classified based on its substrate, amino acid sequences, regulatory properties and tissue distribution. Some PDE are cAMP selective hydrolases, others are cGMP selective, while some are both cAMP and cGMP.

HISTORY:

The pioneering work on PDE started by Henry Hyde Salter in

1886. Salter was an asthmatic himself, he observed that on drinking a strong cup of coffee his breathing would ease out, this was probably an effect of caffeine's bronchodilator property.

Isolation of forms and subtypes of PDE was done by Uzunov and Weiss.In 1977, Weiss along with Hait predicted the therapeutic potential of PDE inhibitors. Xanthines act as PDE, an ingredient found in coffee, tea and cacao.

Table-:1. Phosphodiesterase Families:[7,8]

FAMILY	LOCATION	SUBSTRATE	INHIBITORS	CLINICAL USES
PDE-1	Brain, vascular smooth muscle	cAMP, cGMP	Vinpocetine Nicardipine Nimodipine	Alzheimer's disease Dementia Tinnitus
PDE-2	Brain, adrenal cortex, heart	cAMP, cGMP	EHNA (erythro-9-2-hydroxy-3-nonyladenine)	Malignant pleural mesothelioma

PDE-3	Vascular smooth muscle, platelets, cardiac myocytes, adipose tissue, pancreas	cAMP, cGMP	Cilostazol Dipyridamole Milrinone, Amrinone Anagrelide	Peripheral artery disease Prophylaxis of thromboembolism
PDE-4	Mast cells, bronchial smooth muscle	cAMP	Rolipram, Crisaborole Roflumilast, Apremilast Denbufylline	Organ transplantation COPD Glomerulonephritis
PDE-5	Smooth muscle of corpus cavernosum, esophagus	cGMP	Sildenafil Tadalafil Vardenafil Avanafil	Erectile dysfunction Chronic renal failure Pulmonary hypertension
PDE-6	retina	cGMP	Dipyridamole Zaprinast vardenafil	
PDE-7	T-cells	cAMP	Dipyridamole thiadiazole	Airway disease
PDE-8	thyroid	cAMP	Dipyridamole	Immune-system
PDE-9	Broadly expressed	cGMP	Zaprinast	Hypoglycemia effect
PDE-10	brain	cAMP, cGMP	Papaverine dipyridamole	Neuro-psychiatric treatment
PDE-11	Kidney, liver	cAMP, cGMP	Tadalafil dipyridamole	

PDE1: is a multifunctional enzyme that is essential for preserving the equilibrium of two important second messengers in the brain: cAMP and cGMP, or 3C,5′-cyclic guanosine monophosphate and cAMP, respectively.[9] PDE1 has three isoforms: PDE1A, PDE1B, and PDE1C. PDE1B has been found to have the highest expression in specific areas of the brain.[10] PDE1C is often synthesized in the cerebellum.

Moreover, more than 90% of the total brain activity depends on PDE1B, which is linked to memory and learning processes, thus making this isotype a desired drug target for protection against AD.

PDE1 Blockers: Vinpocetine: which is extracted from the periwinkle plant cross the blood-brain barrier (BBB). Vinpocetine inhibits phosphodiesterase (PDE) enzymes, particularly PDE1. By doing so, it increases cyclic nucleotide levels (such as cAMP and cGMP) within neurons. Elevated cyclic nucleotides can influence various cellular processes, including neurotransmitter release and neuronal excitability. Vinpocetine protect the neuronal cell from cytotoxic effects of inflammation, oxidative stress and ion influx. Vinpocetine's multifaceted effects include antioxidant and anti-inflammatory activity.[11]

PK: Vinpocetine is absorbed from the small intestine and its active metabolites are apovincaminic acid absorbed from the stomach. It is rapidly absorbed from the gastrointestinal tract and peak plasma level is reached at about 1 hour after oral administration. It is more soluble in gastric pH (1.2) and intestinal PH (6.8).

Vinpocetine was eliminated with a mean half-life of 2.12± 0.51 h. Protein binding is about 86.6 ±99.99%.[12,13]

Uses: Alzheimer's disease, Epilepsy, Dementia for memory, Breast cancer, Acute Cerebro-Vascular Accidents (Strokes), Meniere's disease and Aging process

S/E: flushing, nausea, dizziness, dry mouth, transient hypo- and hypertension, headaches, heartburn.

PD3: PDE3 can hydrolyze cGMP but has a strong affinity for cAMP. But because it hydrolyzes cAMP ten times faster than it does cGMP, cGMP effectively works as a competitive inhibitor for both cAMP and PDE3.

PDE3 was discovered as a possible therapeutic target in asthma and cardiovascular illness because of its high expression in the airways and vasculature.

PDE3 inhibitors: have subsequently been shown to relax vascular and airway smooth muscle, inhibit platelet aggregation and induce lipolysis. This group of drugs works well as a positive inotropic effect on the cardiac system which in turn helps reduce preload and afterload of the heart.

CILOSTAZOL: PDE III inhibitor is a derivative of quinolone, works mainly on platelets and vascular smooth muscles, it inhibits PDE 3 enzyme present here which reduces degradation of cAMP hence increasing the cAMP level, cAMP subsequently increases protein kinase A, this facilitates anti-aggregatory action and vasodilator effect.

PK: Cilostazol is orally absorbed. A high-fat meal increases its absorption. 95% to 98% protein-bound, predominantly to albumin. Metabolism occurs extensively in the liver by hepatic cytochrome P450 enzymes CYP3A4 and CYP2C19. It's t1/2 is 12 hours. It is eliminated by urinary excretion of metabolites.[14]

USES: Peripheral artery disease, antianginal therapy

S/E: tachycardia, headache, drowsiness, nausea, vomit, weakness.

C/I: Heart failure, tissue necrosis.

DIPYRIDAMOLE: it is a derivative of pyrimido pyrimidine. This drug has its effect as coronary dilator but does not have action on large conducting coronary vessels and hence shows "Coronary steal phenomenon" hence has no effect on cardiac output. dipyridamole inhibits PDE 3 enzyme by which level of cAMP is increased reflecting on its antithrombotic action. Besides having inhibitory action on PDE 3 enzyme, this drug also inhibits uptake of adenosine leading to additional inhibition of platelet aggregation owing to this there is enhancement of nitric oxide expression helping in reduction of proteinuria and improves renal function progression in patients with kidney disease.[15]

USES: prevention and prophylaxis of thromboembolism in patients with prosthetic heart valves and are on warfarin, reduces risk of long-term hemodialysis in chronic kidney disease, potential for protecting tissue from oxidative and metabolic stress.[16,17]

S/E: coronary steal phenomenon, tachycardia, gastrointestinal distress, postural hypotension.

C/I: Thrombocytopenia, hypersensitivity reaction

D/I: Coadministration of dabigatran with dipyridamole may potentiate the risk of bleeding due to additive or synergistic effects on hemostasis. Theophylline consumers need a higher dose of dipyridamole.

MILRINONE: this drug again works on PDE 3 enzyme, mainly the ones present in cardiac myocytes. On inhibition of PDE3 enzyme, degradation of cAMP is reduced, increasing cellular cAMP level causing increasing in dilation of blood vessels and increasing cardiac output.

PK: Well, absorbed orally; 92% oral bioavailability, 70% protein bound, Half-life is 2.3 hours in patients with heart failure, slightly less in normal healthy adults and longer in patients with renal dysfunction, Onset of action is usually within 5-15minutes, 85% really excreted: unchanged in the urine, 15% excreted as an inactive o-glucuronide.

USES: Cardiogenic shock, Diastolic heart failure

S/E: Tachycardia

C/I: renal disease

D/I: Riociguat is a stimulator of soluble guanylate cyclase, which (in combination with milrinone) would cause catastrophic vasoplegia and hemodynamic collapse.

AMRINONE: is a nonglycosidic noncatecholamine, again works on PDE 3 enzyme, increases cAMP level helps to increase transmembrane influx of calcium resulting in positive inotropic effect, causing decrease in preload and afterload on the cardiac system, rise in cardiac output is noted with mild (non-significant) hypotension. This drug has a high record of mortality hence is abandoned.

PD/PK: rapid iv onset, duration of action:2-3 hours, t ½: 2-4 hours

USES: congestive heart failure, plastic surgery by clinically assessing its ability to enhance flap blood flow after reconstructive surgery.[18]

S/E: include thrombocytopenia hypotension, tachydysrhythmias (sometimes resulting in syncope and death) worsening cardiac ischemia, worsening heart failure, gastrointestinal disturbances, neurological complications , liver damage, fever , nephrogenic diabetes insipidus, hyperuricemia, flaking of the skin, brown discoloration of the nails and reduced tear secretions.

C/I: hypersensitivity

ANAGRELIDE: It is an Imidazoquinolinone having an antithrombotic and platelet reducing activity. Inhibits maturation of platelets from megakaryocytes. Inhibits PDE2, PDE3 and phospholipase A2 as well.[19]

PK/PD: Anagrelide has a large volume of distribution and is extensively metabolized; less than 1% is recovered unchanged in the urine. Plasma half-life is 1.3 hours. [20,21]

USES: Initial mgmt. of essential thrombocythemia in myeloproliferative neoplasm

S/E: Hypotension, headache, hair loss, dizziness, fatigue, palpitations, tachyarrhythmias, cardiomyopathy, angina, and heart failure.

C/I: acute renal injury

Newer PD-3 Inhibitor: levosimendan: phase III clinical trial, U.S.FDA approval pending, calcium sensitizer, used in CHF. (U.S.FDA APPROVAL PENDING: to attain reduction morbidity in patients with Pulmonary HTN from Heart Failure.)

PDE-4 INHIBITORS: PDE 4 enzymes are predominantly present in mast cells and bronchial smooth muscles, this enzyme tends to hydrolyse cAMP, causing insufficient level of cAMP which signals release of inflammatory cells resulting in relaxation of smooth muscles. PDE 4 inhibitors inhibit hydrolysis of cAMP by which there is no drop in cAMP level hence no inflammatory cell stimulation is noted.

ROFLUMILAST: it majorly inhibits PDE4D enzyme associated with vomiting and inhibits PDE4B enzyme to display its anti-inflammatory property. active principle of roflumilast is dichloropyridyl N-oxide metabolite.[22]

PK/PD: oral bioavailability: 80%, topical administration was 1.5% is metabolized by CYP3A4 and CYP1A2, inhaled form of PDE 4 inhibitors is better but uncertain efficacy.[23]

USES: Chronic obstructive pulmonary disease (has anti-inflammatory action on bronchial smooth muscle by reducing eosinophil infiltration), bronchitis.

S/E: Headache, GI disorders, dizziness, Palpitations, light headedness

C/I: Child-Pugh Grade B/C disease, liver impairment

D/I: if used with rifampicin efficacy of roflumilast is reduced. No role in treatment of bronchospasm.

APREMILAST: it is as well a PDE 4 inhibitor, when cAMP is degraded by PDE-4 enzyme, there is increase in levels of cytokines like TNF alpha, IFR gamma in causing diseases like psoriasis and forming lesions on skin.

Apremilast inhibits PDE-4 enzyme effect in turn reducing the production of inflammatory cytokines, hence considered as a treatment for psoriasis.[24,25]

USES: psoriatic arthritis, moderate to severe case of plaque psoriasis, atopic dermatitis, alopecia areata, lichen planus and sometimes in oral ulcerations in Behcet disease cases.

S/E: weight loss and depression

CRISABOROLE: it is a boron containing benzoxaborole, mimics phosphate of cAMP and has competitive activity to inhibit PDE-4 enzyme. Boron in this drug helps facilitate effective drug penetration through the skin layer.

USES: topical application for cases of mild to moderate atopic dermatitis.[26,27] in adults and pediatric age group over 2 year. SIDE EFFECTS: burning or stinging sensation of skin on application and not very often hypersensitivity reaction.

Newer PDE4B Inhibitor: BI 1015550: Idiopathic pulmonary fibrosis

PDE4 Inhibitor Roflumilast: used in COVID-19

PDE-4B/D Inhibitor: Orismilast: uses: atopic dermatitis, chronic inflammatory skin disease, U.S FDA approved Fast Track for oral orismilast.

PDE-5 INHIBITORS: naturally by name we understand that this group of drugs inhibit PDE-5 enzyme which is present in smooth muscles of corpus cavernosum and esophagus. In general, nitric oxide enters the vascular smooth muscle and stimulates soluble guanylyl cyclase which brings out the conversion of GTP to cAMP, cAMP levels help in stimulation of protein kinase G which results in protein phosphorylation and decrease in intracellular calcium too, culminating to smooth muscle relaxation which enhances blood flow and the end result having an penile erection. But PDE-5 enzyme tends to break down the cAMP to 5'GMP affecting the erection. Our drug inhibits the enzyme allowing the continuation of cAMP levels to be sufficient to result in a penile erection in presences of sexual arousal.[28]

SILDENAFIL: structurally it mimics the purine ring of cGMP, is an competitive and selective PDE-5 inhibitor.

PD/PK: oral bioavailability is 40% and is rapidly absorbed, 95% plasma protein bound, it's active metabolite N-desmethyl-sildenafil, biliary route for elimination and metabolized by CYP3A4.

USES: erectile dysfunction, pulmonary hypertension, acute hypoxemic respiratory failure, intravenous route is used as intracavernosal injection therapy but best avoided due to risk of fibrosis development.[29]

S/E: hypotension, priapism, headache, visual color disturbances (cyanopsia), visual loss and hearing loss, increase risk of non-arteritic anterior ischemic optic neuropathy (NAION) in males over age 50.[30]

C/I: retinitis pigmentosa, myocardial infarct, hypertension, anginal pain, pulmonary hypertension secondary to sickle cell disease, renal and hepatic impairment. Avoid fatty meals.

VARDENAFIL: Structurally similar to Sildenafil[31]

PK/PD: t1/2: 4-5 hours, metabolized by CYP3A4

S/E: Q-T interval prolongation

TADANAFIL: structurally it is different compared to Sildenafil,

PD/PK: it is long acting and more potent too, t1/2:18 hours while it's duration of action is 24-36 hours.[32]

USES: pulmonary artery HTN, obesity, erectile dysfunction, prostate cancer.[33]

C/I: hepatic or renal impairment, along with Guanylate cyclase stimulators like praliciguat as it causes toxic skin reactions: steven-johnson syndrome, exfoliative dermatitis.[34]

Newer PDE-5 Inhibitors:

sildenafil: adipogenesis: obesity, diabetes **udenafil**: weight loss. **lodenafil:**

phase III clinical trial, U.S.FDA approval pending.

sulindac sulfone: augments apoptosis and blocks tumor cell proliferation in

urinary bladder tumour, metastatic breast cancer, non-small-cell lung cancer, and colon tumour cell lines

PDE-10 INHIBITORS: PAPAVERINE: it is a non-xanthine inhibitor that works on PDE-10 enzyme majorly present in the brain but also helps with penile dysfunction.

USES: antispasmodic effect: chest pain, heart attack, abdominal pain, hypertension (vasodilator), erectile dysfunction, peripheral and cerebral ischemia[35]

S/E: Tachycardia, jaundice, skin rash, drowsiness, constipation, weight loss.

NON-SPECIFIC PDE INHIBITORS:

Theophylline: is a methylxanthine group of drugs. Available substitutes are enprofylline, doxofylline. Currently theophylline has a narrow therapeutic window.[36]

PD/PK: Orally well absorbed, it crosses placenta and is secreted in milk, 50% plasma protein bound, metabolized in liver by CYP1A2

t1/2: 7-12 hours (adults), 24-36 hours (premature infant)

It is recommended to administer the drug in a prone position only because the drug has delayed absorption at supine position.[37]

Additional mechanism of Theophylline are:

i. adenosine receptor antagonism

ii. interleukin-10 release

iii. effect on gene transcription

iv. histone deacetylase activation

USES: COPD, bronchial asthma, apnea in premature infant

S/E: CNS toxicity in children, ventricular tachycardia, arrhythmias, hypotension, avoid rapid iv administration as it results in precordial pain, syncope attack or death. has irritant property, diuresis, behavioral changes, seizures, headache, nausea, nervousness.

Limitations: Low tolerance, low efficacy, narrow safety margin

Drug interactions: Smokers, increase plasma conc Theophylline when given along with OC pills, erythromycin, allopurinol, reduces phenytoin effect hence need caution to give theophylline in seizures, convulsion case.

AMINOPHYLLINE: Aminophylline is a nonselective adenosine receptor antagonist and phosphodiesterase inhibitor.

PD/PK: Aminophylline is less potent and shorter-acting compared to theophylline. It is more soluble in water than theophylline.

a drug combination that contains theophylline and ethylenediamine in a 2:1 ratio. 60% PPB

USES: acute exacerbation of COPD, chronic bronchitis, bronchial asthma, bronchospasm

CAFFEINE: Is a non-selective PDE inhibitor and a non-specific adenosine receptor (AR) antagonist.

Mechanism of action: caffeine inhibits hydrolysis of cAMP and raised cAMP level reduces inflammatory markers like T-cell proliferation, IL-2, IL-4, IL-10 production, antibody production.

USES: apnea in preterm infants below 34 weeks of gestation, bronchopulmonary dysplasia, improved neurodevelopmental outcome in extremely premature infants

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