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(DIABIZ) SGLT2 INHIBITORS IN TYPE 2 DIABETES

Type 2 diabetes is a progressive disease typically requiring multiple medications in order to control blood glucose levels.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the latest class of anti-hyperglycemic agents to receive approval and get introduced in the market. SGLT2 inhibitors function through a novel mechanism of reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release.

The first SGLT2 inhibitor discovered was phlorizin, a naturally occurring compound derived from apple tree bark. Because of its non-selective nature, which caused severe gastrointestinal symptoms & poor oral bioavailability, its candidature wasn't considered further.

Glucosuria (i.e., the excretion of glucose through the kidneys) only occurs if the maximal capacity of various glucose transporter proteins is exceeded. Earlier, glucosuria was thought to be a pathological mechanism, or a marker of illness. However, one may approach this condition from a different view point. Persons with ambient hyperglycemia are at risk of endothelial dysfunction and resultant complications, due to the high levels of glucose in circulation. Kidneys try to prevent an excessive rise in blood glucose levels by excretion of glucose in the urine, thereby mitigating the adverse effects associated with high glucose levels.

Theoretically, compounds which promote this should help to reduce circulating glycemia, manage diabetes, and prevent long-term complications.

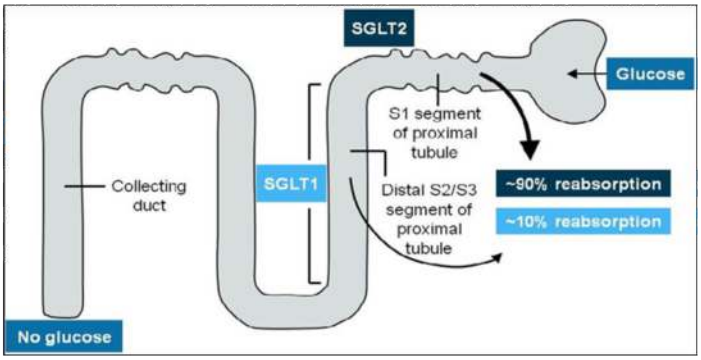
MECHANISM OF ACTION OF SGLT2 INHIBITORS

SGLT2 inhibitors function through a novel mechanism of reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release.

SGLT2 proteins are expressed in the proximal convoluted tubule (PCT) of the kidneys & are responsible for roughly 90% of filtered glucose reabsorption thus making them an ideal target. The normal renal threshold for reabsorption of glucose corresponds to a serum glucose concentration of 180 mg/dL. In patients with type 2 diabetes, this threshold can increase and the expression of the SGLT2 can be up-regulated causing a maladaptive response that worsens hyperglycaemia.

SGLT2 inhibitors work by inhibiting SGLT2 in the PCT, to prevent reabsorption of glucose and facilitate its excretion in urine. As glucose is excreted, its plasma levels fall leading to an improvement in all glycaemic parameters.

This mechanism of action is dependent on blood glucose levels and, unlike the actions of thiazolidinediones (mediated through GLUTs), is independent of the actions of insulin. Thus, there is minimal potential for hypoglycaemia, & no risk of overstimulation or fatigue of the β cells.



WHAT ARE THE OTHER BENEFITS OF SGLT2 INHIBITORS?

Apart from effective glucose control in type 2 diabetes, SGLT2 inhibitors present various other effects like weight-loss, reduction in blood pressure, especially cardiovascular and reno protective benefits.

WHAT ARE THE ADVERSE EFFECTS OF SGLT2 INHIBITORS?

The most common adverse side effect to SGLT2 inhibitors appears to be genital infections. Detectable concentrations of glucose in the urine can facilitate the onset of mycotic infections, as observed in patients who experience severe glycosuria.

Because of the osmotic diuresis induced by glycosuria resulting from SGLT2 inhibition, volume depletion is a possibility. This is usually accompanied by increased urinary frequency, thirst, and rarely orthostatic hypotension.

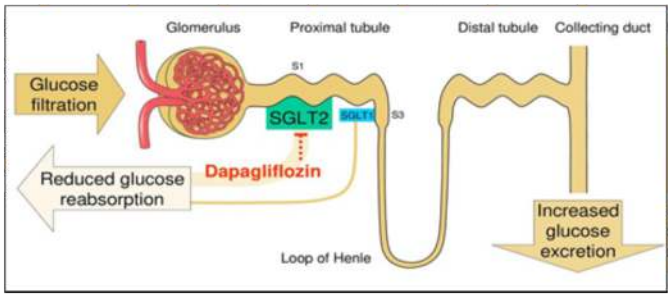
Because their mode of action relies upon normal renal glomerular-tubular function, the efficacy of SGLT2 inhibitors is reduced in persons with renal impairment. However, the risk of hypoglycaemia is minimal with SGLT2 inhibitors, as they have a non-insulin-based mechanism of action.

WHAT ARE THE CURRENT SGLT2 INHIBITORS?

A handful of SGLT2 inhibitors have been approved for the treatment of type 2 diabetes namely Canagliflozin, Dapagliflozin, & Empagliflozin.

DAPAGLIFLOZIN

Dapagliflozin is a highly potent, reversible and selective SGLT-2 inhibitor indicated worldwide for the treatment of T2DM. The selectivity of dapagliflozin for SGLT2 is >1,400- fold greater than that for SGLT1.Dapagliflozin as monotherapy and combination therapy with other anti-hyperglycaemic agents provided effective glycaemic control and reduced bodyweight and blood pressure (BP) across a broad spectrum of patients. Dapagliflozin reduced the rate of cardiovascular (CV) death or hospitalization for heart failure (HHF), did not adversely affect major adverse CV events (MACE) and possibly reduced progression of renal disease relative to placebo in patients with established atherosclerotic CV disease (CVD) or multiple risk factors for CVD.



CONCLUSION

The SGLT2 inhibitors represent a novel class of drugs which will certainly help a large number of people with diabetes achieve target control in a safe and well-tolerated manner. Their unique mechanism of action, coupled with pleiotropic benefits on weight and blood pressure, should make them attractive choices for initiation of monotherapy and/ or add-on therapy to

persons not controlled on other medications. They complement very well with other oral anti-diabetic agents and Insulin.

Source: Kalra S. Diabetes Ther 2014; 5(2): 355-366; Hsia DS et al. Curr Opin Endocrinol Diabetes Obes 2017; 24(1): 73-79.

DICYCLOMINE versus DOTAVERINE: Which one to prefer?

Muscle spasms (muscle cramps) are painful contractions and tightening of muscles. They're common, involuntary and unpredictable. Various anti-spasmodic/analgesic pharmacological interventions are available that may help alleviate the symptoms. The visceral mucosal receptors respond primarily to the chemical stimuli which include kinins (bradykinin), biogenic amines (histamine), & prostanoids (PGs) which lead to contraction of smooth muscles and spasm. Acetyl choline (Ach) is the key neurotransmitter mediating smooth muscle spasm especially colicky pain. [Dysmenorrhea, Colicky pain (Intestinal/Biliary/Renal)].

Dicyclomine relieves smooth muscle spasm with its dual mechanisms. It achieves its action partially through direct antimuscarinic activity of the M1 and M2 receptors, and partially through antagonism of bradykinin & histamine as direct musclotropic action.

Drotaverine, mainly acts by inhibiting type IV phosphodiesterase [PDE], leading to an increase in intracellular cyclic AMP and cyclic GMP leading to smooth muscle relaxation. (Ca influx into the cells is restricted leading to relaxation), however it has no anticholinergic effects & therefore does not have any action on the key neurotransmitter acetylcholine.

	DICYCLOMINE	DROTAVERINE
In India	Since 1950	After 1963
US fda	Approved	Not approved
Marketed Area	Marketed in US,UK & Europe (Regulated)	Marketed in Asian, African & East European countries (Not so regulated)
Absorption	Rapidly absorbed Peak 60-90 min	Rapidly absorbed but inadequate absorption
Bioavailability	67%	24.5 % to 58% (Highly Variable), significant inter-individual differences
T ½	9-10 hours	7-12 hours
Metabolism	*Not well defined but likely to be metabolized by liver	(Extensive First pass) Hepatic metabolism
Elimination	Renal ~ 80% Faeces ~10%	Biliary
Hepatic /Renal Impaired cases	No dosage adjustments required (Hepatic /renal impaired cases)	Dose reduction in hepatic impaired cases (since extensively metabolised)
Children	Infants > 6 months	Children > 1 year
Pregnancy	Category B	Unclassified
Dosage	Adults :10 mg / 20 mg tid Children > 6 months: 5 mg tid	Adults:40 mg / 80 mg t.i.d Children > one year: 20 mg tid

Dicyclomine also inhibits propulsive motility and decreases gastric acid secretions and these additional actions may offer more benefit in GI colicky conditions. Dicyclomine has been indicated in monotherapy as well as combination in the treatment of infantile colic as well as in children especially with GI motility disorders. Dicyclomine showed inhibitory action against several pathogenic bacteria which may be beneficial to intestinal colic.

With the dual mechanism of action and pleiotropic effects dicyclomine carries the advantages of using in wider age groups including pregnancy and has well established efficacy in all the colicky conditions including dysmenorrhea, supporting wider indications.

Sources:Pubchem.ncbi.nlm.nih.gov/compound/Dicyclomine; Tronnes JN et al. Pharamacoepidemiol Drug Safety 2017; 26: 802-811;drugs.com/pregnancy/dicyclomine.html.; Karak P et al. Ind J Med Res 2003; 118: 192-196.;Mc Grath WR et al. The J of Pharmacology & Exp Therapeutics 1964; 146(3): 354-358;Therapeutics drugs Dollery C (2nd) Ed.Vol 2,1999;Martindale,The complete drug reference,sweetman SC 37th Ed.2011.

Review on LEVOSALBUTAMOL

Cough is one of the most common symptoms that is presented in the clinical practice. It is not only a physiological defense reaction but a symptom of a disease. Considering the contents, cough can be productive-with secretions from the respiratory tract or unproductive-dry without secretions.

Levosalbutamol is β2 adrenoceptor agonist, & is the R-enantiomer of Salbutamol. It binds to the β2 adrenergic receptor to regulate bronchial smooth muscle relaxation or bronchodilation. Clinical studies have demonstrated better therapeutic index as compared to Salbutamol.

Productive cough can be treated with the combination of bronchodilators, expectorants and mucolytics. A combination of Levosalbutamol, Ambroxol and Guaiphenesin is indicated in acute or chronic conditions or infections for the treatment of productive cough which is associated with bronchospasm such as bronchitis and bronchial asthma as well as all conditions associated with tenacious mucous, wheezing and chest congestion.

In a trial conducted on 325 pediatric patients in the age group of < 1year and 2-12 years, it was observed that the combination of Levosalbutamol, Ambroxol and Guaiphenesin was safe and efficacious for the treatment of productive cough.

Another β2 adrenoceptor agonist also used in pediatric patients is Terbutaline. However, unlike Levosalbutamol, Terbutaline may cause side effects like wheezing, choking and other breathing problems and in some cases even seizures, making Levosalbutamol a safer choice than Terbutaline in the treatment of productive cough.

Levosalbutamol in combination with an expectorant and a mucolytic can be safely and effectively used to treat productive cough in pediatric patients. The usual dose of levosalbutamol is 0.05 mg per kg per dose to be repeated three times daily.

Source: Begic E et al. Med Arch 2017; 71(1): 66-68.

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