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A REVIEW ON PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTI DIABETIC MEDICATIONS IN CLINICAL PRACTICE

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ABSTRACT

It is a non-communicable prolong metabolic diseases marked by high glucose levels consequences from defects and inequality between insulin secretion and insulin action. The chronic condition of hyperglycemia in diabetes patients is associated with chronic destruction and improper retort of various vital organs. Pharmacokinetics accords with absorption, distribution, metabolism, elimination of the drugs. The Pharmacodynamic response pledged with therapeutic returned with nature of the drug. It is treated with several drugs includes sulfonyl ureas, biguanides, alpha glucosidase inhibitors, metaglinides, glucagon like peptides, sodium glucose transporters and insulin injections. Insulin is concealed by beta cells of the pancreatic islets. It consist of 51 amino acids arranged in two chains an A chain 21 amino acids and B chain 30 amino acids that are linked by two disulfide bonds. The insulin preparations consist of long acting, short acting, ultra short acting. The diabetic drugs possess the pharmacokinetic properties,it includes equivalent therapeutic dose of the drugs, plasma protein binding capability, half life ability, exact duration of action,mode of absorption,distribution,metabolism,excretion process. The diabetic drugs shows individual responses impact the insulin release and variations in pharmacokinetic parameters reverse from one drug classification to another drugs.The individual drugs will exert the multiple mechanisms with receptor interactions utilized towards secretion of insulin.

***Key Words:** Hormone, Pancreas, Autoimmune destruction, Hyperglycemia.*

INTRODUCTION

Diabetes mellitus associated with defective insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia.The early symptoms are related polydipsia, polyphagia, polyuria, and blurred vision. The chronic complications

include vascular disease, peripheral neuropathy, nephropathy, and predisposition to infection. Diagnosis is by measuring plasma glucose. Treatment is associated with modifying diet, exercise and using oral hyperglycemic agents **(Figure 1).**

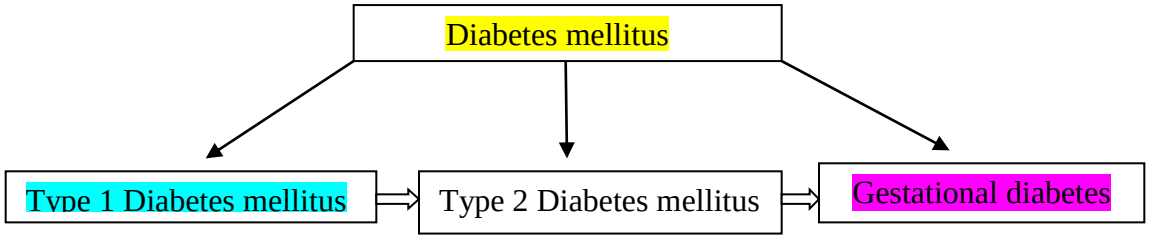

Figure 1. Types of Diabetes mellitus

Type 1 is an autoimmune disease in which the immune system attacks its own insulin producing cells so that insufficient amounts of insulin[1].Type 2 is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, high obesity and lack of exercise.Gestational diabetes mellitus affects the women who develop diabetes mellitus during gestation.

INTRODUCTION TO INSULIN

Insulin is a peptide hormone produced by beta cells of the pancreatic islets. It regulates the metabolism of carbohydrates, fats and proteins in the body. It composed of 51 amino acids, and has a molecular mass of 5808 Daltons and a dimer of an A-chain and a B-chain, which are linked together with disulfide bonds. These act primarily through cyclic AMP (cAMP) and protein kinase A. The insulin attached to N- and C-terminal helices of the A chain to the central helix of the B chain. Proinsulin is the insulin precursor that is transported to the golgi apparatus of the beta cell where it will be processed and packaged converted to granules[2] **(Table 1)**.

Mechanisms of Insulin secretion

Glucose entry into the β cell is sensed by glucokinase

⇩

phosphorylation of glucose to glucose-6-phosphate (G6P), generating ATP

⇩

closing of K+-ATP-dependent channels results in membrane depolarization and activation of voltage dependent calcium channels leading to an increase in intracellular calcium concentration

⇩

Activation of this response by K+-ATP channel independent Ca2+-dependent pathway and K+-ATP channel-independent Ca2+-independent pathways of glucose action.

⇩

Activation of adenyl cyclase response

⇩

activation of β cell protein kinase A path ways results in insulin secretion[3].

Table 1: Risk factors for type 2 diabetes include

S.No	Person with age more than 45
1	more obesity Patients
2	Family history of diabetes mellitus
3	History of impaired glucose regulation
4	Gestational diabetes mellitus
5	Family history of hypertension
6	Dyslipidemia
7	Polycystic ovary syndrome

EPIDEMOLOGY

The increasing prevalence of diabetes worldwide has led to a situation where approximately 360 million people had diabetes in 2011.It is estimated to high upto 552 million by 2030[4].

CLINICAL SYMPTOMS

The symptoms associated with diabetes related to high blood and urine glucose levels and include **(Table 2,3).**

Table 2: Symptoms of Type 1 and Type 2 Diabetes

blurred vision	weight loss	dryness mouth
hunger	fatigue	slow-healing wounds, cuts, or sores
dehydration	slow capability of healing	itching skin and skin infections

Complications of diabetes mellitus

Table 3: Acute complications includes

Acute complications	Other complications
Hypoglycemia	Impaired growth

Diabetes Ketoacidosis	Lipodystrophy
Chronic complications	Hypothyroidism
Diabetic neuropathy	Hyperthyroidism
Micro vascular complications	Celiac disease
Diabetic retinopathy	Vitiligo
Diabetic nephropathy	Addison's disease
Necrobiosis lipoidica diabeticorum	Non-alcoholic fatty liver disease
Infections	Edema

The management plan for a person with diabetes includes

- Diabetes education: The structured education and self-management and promoting awareness to the community[4].
- Diet and life style: Modification of healthy diet practices will benefit for the patients controlling diabetes.
- Educating the patients about the health problems associated with smoking and promoting cessation practices[5].
- Proper guidelines for regular physical exercise helpful for preventing diabetes complications.
- Monitoring and providing the early intervention for complications of diabetes and there prevention practices.

Introduction to Pharmacokinetics

Pharmacokinetics: The study of absorption,distribution,metabolism,excretion process in the body.

Pharmacodynamics: The study of the effect of the drug on the body interact with receptors in the body.

Absorption : The process of movement of substance from the site of administration into the systemic circulation.

Distribution : The dispersion of substances throughout the biological fluids and tissues of the body.

Metabolism : The process of irreversible transformation of parent compounds into daughter metabolites.

Excretion : It is the process in which removal of the substances from the body through urine, fecal, sweat, salivary and tears [6] **(Figure 2) (Table 4)**.

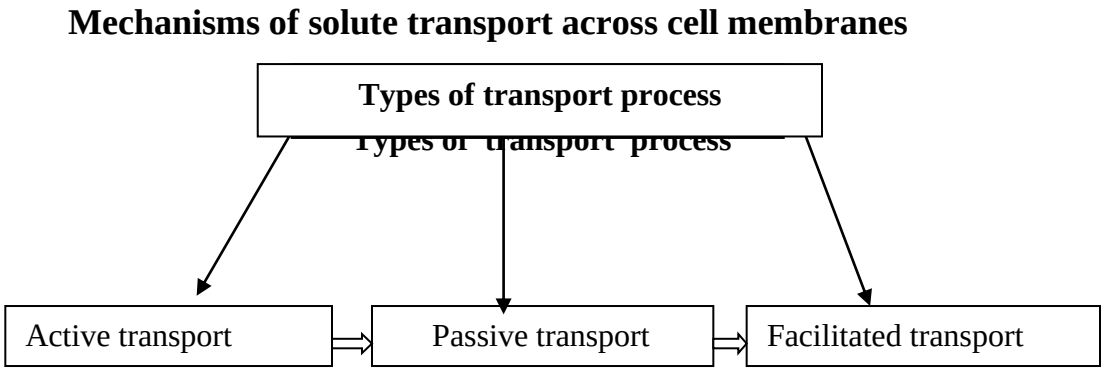

Figure 2: Types of transport process

Table 4: Factors affecting pharmacokinetics

Physicochemical properties of drug molecules	**Factors related to body**
Lipid water solubility	Area of absorptive surface[7].
Molecular size	*Vascular nature*
Particle size	*pH*
Degree of Ionization	*Presence of other Substances*
Physical Forms	*Gastrointestinal Mobility*
Chemical Nature	*Functional Integrity of Absorptive Surface*
Dosage Forms	Presence of diseases
Disintegration	Renal diseases
solubility	Endocrine disorders
Dissolution	Cardiac diseases
Surface area, type of formulation	Hepatic diseases

Introduction to Pharmacodynamics

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects.

Receptors: Receptor proteins can be categorized into their specific location. It includes ion channel-linked receptors, G protein-linked receptors, enzyme-linked hormone receptors, cytoplasmic receptors and nuclear receptors [8].

Enzymes: It is a protein created by a living organism that acts as a catalyst to bring about life sustaining biochemical reactions.

Ion channels

Ion channels are pore creating membrane proteins creates a resting membrane potential and control and allow the flow of ions across the cell membrane [9] **(Table 5)**.

Table 5: Pharmacokinetics of sulfonyl urea derivatives

Agent	Equivalent therapeutic dose (mg)	Serum protein binding (%)	Half-life (h)	Duration of action (h)	Mode of metabolism (conjugation)
Tolbutamide	1000 mg	95 - 97	4.5-6.5	6-12 hours	Carboxylation
Chlorpropamide	250 mg	88 - 96	36	60 hours	Hydroxylation
Tolazamide	250 mg	94	7	12-14 hours	Hydroxylation
Acetohexamide	500 mg	65 - 88	6-8	12 – 18 hours	Reduction
Glyburide	5 mg	99	1.5-3.0	24 hours	Hydroxylation
Glipizide	5 mg	92 - 97	4	24 hours	Hydroxylation

Sulfonyl urea derivatives mechanism

It is proposed that the sulfonyl ureas enhances the insulin release through after binding to specific receptors on cell membrane that are linked to closure of the channels that facilitate the passive efflux of K^+ from the cell[10]. These K+ channels are responsive to ATP and ADP ratio and close when the ratio increases because of an increase in glucose metabolism. Binding of sulfonyl ureas to their receptor leads to the closure of the potassium channels which opens calcium channels for influx of Ca^{+2} ions into the respective cytoplasm. The increase in cytosolic calcium activates the effector system that leads to the translocation of the secretory granules to the exocytotic sites at the plasma membrane at which insulin is released[11].

Biguanides Dose: 2.5/250 mg and 500mg and 5 mg and 50 mg.

Mechanism: The drug acts on the liver to minimize the gluconeogenesis and causes a decrease in insulin resistance associated problems.The process is transpire with increasing signaling mechanism.

Advantages

- The drugs won't exhibit associated weight gain
- Low the risk of hypoglycemia problems when compared to other alternatives
- Better effect on LDL cholesterol
- It is very less inexpensive [12].

Phenformin

Phenformin is well absorbed after oral administration. The major metabolic reaction is aromatic hydroxylation to form 4–hydroxyphenformin, which is then conjugated with glucuronic acid. Up to about 50% of a dose is excreted in the urine in 24 h, about two thirds in the form of unchanged drug and one–third as the hydroxy metabolite[13].

Metformin: Metformin has an oral bioavailability of 50–60% under fasting conditions and is absorbed slowly. The plasma protein binding of metformin is negligible.

Thiazolidinediones: The drugs bind to PPARγ receptors and promotes the transcription of genes regulating glucose and fat metabolism. These PPARs acts on peroxysome proliferator responsive elements (PPRE). The peripheral peroxysome proliferative receptors impact the insulin-sensitive genes further higher the production of mRNAs of insulin dependent enzymes **(Table 6)**.

Advantages

- It is having lower risk of hypoglycemia in diabetic community
- Slight increase in high density lipoprotein levels in the cells
- It is convenient convenient dose to the community

Table 6: Pharmacokinetic parameters of Thiazolidinediones

Parameter	**Rosiglitazone**	**Pioglitazone**
Bioavailability	99%	81-94% (Minimal)
T_{max}	1 hour	2 hours
PPB	99.8%	>99%
Vd	0.2	0.63
Plasma t1/2	100-160 hours	3-7 hours
Metabolism	Sulfate conjugation	CYP2C8,CYP3A4 enzyme
Elimination half-live	3-4 hours	16-24 hours
Total renal Elimination	64%	15-30%
Total Fecal Elimination	23%	>60%

Metaglinides: Repaglinide (Brand name: Prandin): It is Food and drug administration approved for monotherapy and for combination therapy with metformin or thiazolidinediones.

Mechanism: It will increases insulin secretion by blocking ATP potassium channels on beta islet cells of pancreas,which facilitates calcium entry through calcium channels increased intracellular calcium stimulates the insulin release from pancreatic beta cells [14] **(Table 7)**.

Table 7: Pharmacokinetics of Metaglinides

Parameter	Repaglinide	Nateglinide
Bioavailability	56%	72-75%
Duration	15-60 min	4 hours
Peak plasma time	Less than 1 hour	less than1 hour
Protein binding	More than 98%	97-99%
Volume of distribution	31 L	10 L
Metabolism	acyl glucuronide	Alpha glucosidase inhibitors
Excretion	urine (8%),Feces (90%)	Urine:83%,Feces: 10%
Half-life	1 hour	1.2-3 hour

Nateglinide (Brand name : Starlix)

Nateglinide acts as endogenous insulin patterns strengthen insulin secretion and controls mealtime glucose surges. It works by stimulating insulin release from pancreatic beta cells. It is indicated as monotherapy for type 2 diabetes or as combination therapy with metformin or a thiazolidinedione [15].

Dose: It is available in 60-mg and 120-mg tablets.

Mechanism of Action: Increases insulin secretion via binding K+ channels on beta islet cells. It reduces postprandial hyperglycemia. Amount of insulin released is dependent upon existing glucose levels.

Alpha glycosidase inhibitors: These agents slow the digestion of starch in the small intestine and influences the glucose from the starch of a meal enters the bloodstream more slowly and can be matched more effectively by an impaired insulin response or sensitivity [17].

Advantages

- Slightly decreased risk of hypoglycemia as compared to sulfonylurea
- Not associated with weight gain
- Decreases triglycerides

Acarbose (Precose): it is the alpha-glucosidase inhibitor.It is absorbed to a small degree so liver function abnormalities can occur rarely. It can be used as monotherapy and combination with other treatment modalities.

Mechanism: These drugs acting on intestinal brush border cells. The drug linked with pancreatic alpha-amylase and alpha glucosidases and results in delayed hydrolysis of ingested complex carbohydrates and helps for absorption of glucose. It stops the conversion of metabolic process of sucrose to glucose and fructose[16].

Miglitol (Glyset): *Miglitol is not absorbed so liver function abnormalities do not occur. It is used as monotherapy or in combination with sulfonylureas in practice.*

Mechanism of Action

Delays glucose absorption by delaying digestion of ingested carbohydrates. Inhibits hydrolysis of disacharides and oligosaccharides to gucose. It will reduces the postprandial hyperglycemia (Table 8).

Table 8: Comparison of pharmacokinetics of alpha glycosidase inhibitors

Acarbose	**Miglitol**
Onset of action : 1 hour	Half-Life : 2 hours
Peak Plasma Time : 1 hr,Half life : 2 hr	Absorption : saturable at 50-70% for 100 mg
Bioavailability : < 2 %	Bioavailability: 100%
Metabolism : It will happens in the intestine by bacterial and digestive enzymes	Protein Bounding : <4%
Excretion : Urine 34 % as inactive metabolites	Volume of distribution : 0.18 L/kg
Feces : 51% as unabsorbed drug	Metabolism: It will happens in the intestinal bacteria.Excretion: urine >95%

Insulin

In general practice there are three types of insulin, characterized by the rate which they are metabolized by the body. They are rapid acting insulin intermediate acting insulin and long acting insulin. Insulin is usually given subcutaneously,either by injections or by an insulin pump. In acute-care settings, insulin may also be given intravenously[18].

Examples of rapid acting insulin includes:

- Regular insulin (Brand name : Humulin R,Novolin R)
- Insulin lispro (Brand name : Humalog),Insulin aspart (Brand name : Novolog)
- Insulin glulisine (Brand name: Apidra),Prompt insulin zinc (Brand name : Semilente, Slightly slower acting).

Examples of intermediate acting insulin include: Isophane insulin, neutral protamine Hagedorn (NPH),(Brand name: Humulin N, Novolin N),Insulin zinc (Brand name : Lente).

Examples of long acting insulins include :

- Extended insulin zinc insulin (Brand name: Ultralente),Insulin glargine (Brand name : Lantus),Insulin detemir (Brand name :Levemir).

Injectable Glucagon-like peptide analogs and agonists

The drug bind to GLP receptor in the cell membrane. The insulin release from the pancreatic beta cells is raised.

- Exenatide (Exendin-4, marketed as Byetta) is the first GLP-1 agonist approved for the treatment of type 2 diabetes.
- Liraglutide , a once-daily Victoza.

- Lixisenatide (Lyxumia)

Exenatide (brand names : Byetta, Bydureon) ***Dose:*** *250mcg/mL (1.2mL, 2.4mL vial)*

Mechanism of Action: A glucagon like peptide-1 (GLP-1) that mimics incretin and promotes insulin secretion, suppresses glucagon, and slows gastric emptying [19] **(Table 9a, 9b)**.

Table 9 a: Pharmacokinetics of Exenatide

Peak plasma time: 2.1 hour
Peak plasma concentration: 211 pg/mL
AUC: 1036 pg hour/mL
Vd: 28.3 L
Half-life: 2.4 hour (immediate release); 2 weeks (extended release)
Renal clearance: 9.1 L /hour
Excretion: Urine

Liraglutide (Victoza): Dose: **0.6mg, 1.2mg.**

Mechanism of Action: *It acts on the G-protein in pancreatic beta cells. The optimization of intracellular cyclic adenosine monophosphate (cAMP) leading to insulin release.[20-21].*

Table 9 b: Pharmacokinetics of Liraglutide

Absolute bioavailability: 55%
Peak plasma time: 8-12 hr
Average steady state concentration over 24 hr: 128 ng/mL (at 1.8 mg dose)
Pharmacokinetics
Protein bound : > 98%
Vd: 13 L (SC) : 0.07 L/kg (IV)
Half-life : 13 hr
Mean apparent clearance : 1.2 L/hr (SC)
Excretion (metabolites) : 5% feces, 6% urine

Albiglutide (Tanzeum) *Dose:* ***30mg/pen***

Mechanism of Action: Incretin mimetic and analogue of human glucagon like peptide-1 and acts as GLP-1 receptor agonist to augment glucose dependent insulin secretion **(Table 10)**.

Table 10: Pharmacokinetics of Liraglutide

Peak plasma time: 3-5 days

Peak plasma concentration: 1.74 mcg/mL
AUC: 465 mcg /mL
Steady-state concentration: 4-5 weeks
Vd: 11 L
Half-life: 5 days

Dulaglutide (Trulicity): Dosage Forms: 0.75mg, 1.5mg.

Mechanism of Action: Incretin mimetic analogue of human glucagonlike peptide-1 (GLP-1) acts as GLP-1 receptor agonist to raising insulin secretion in the presence of elevated blood glucose and delays gastric emptying to decrease postprandial glucose and decreases glucagon secretion [22] **(Table 11)**.

Table 11: Pharmacokinetics of Dulaglutide

Absolute bioavailability : 65%
Peak plasma concentration: 114 ng/mL
AUC : 14,000 ngh/mL
Vd: 19.2 L
Half-life: 5 days

Antidiabetics, Dipeptidyl Peptidase IV Inhibitors

They increase insulin release and decrease glucagon levels in the circulation in a glucose-dependent manner. DPP-4 degrades numerous biologically active peptides including the endogenous incretins GLP-1 and glucose-dependent insulinotropic peptide (GIP).

Sitagliptin (Januvia) : *Dosage Forms:* ***25mg,50mg,100mg.***

Mechanism of Action: DPP-4 inhibitor prolongs incretin hormone activity which is inactivated by DPP-4 enzyme. Incretins increase insulin release and synthesis from pancreatic beta cells and reduce glucagon secretion from pancreatic alpha cells [22] **(Table 12)**.

Table 12: Pharmacokinetics

Bioavailability: 87%
Peak plasma time: 1-4 hr
Protein bound: 38%
Vd: 198 L
Half-life : 12.4 hr
Excretion: Urine (87%), feces (13%)

Saxagliptin (Onglyza): Dose: 2.5mg, 5mg

Mechanism of Action: Dipeptidyl peptidase IV (DPP-4) inhibition that results in increased incretin hormones and enhanced glycemic control [23] (Table 13).

Table 13: *Pharmacokinetics of saxagliptin*

Peak plasma time: 2hr
Hepatic by CYP450 3A4/5 to active metabolite.
Half-life (elimination): 2.5 hr (saxagliptin); 3.1 hr (5-hydroxy saxagliptin)
Renal clearance: 7.2 L/hr
Excretion: Urine (75%); feces (22%)

Linagliptin (Tradjenta), *Dose: 5mg*

Mechanism of Action: Dipeptidyl peptidase 4 (DPP-4) inhibitor increases and prolongs incretin hormone activity which is inactivated by DPP-4 enzyme Incretins regulate glucose homeostasis by increasing insulin synthesis and release from pancreatic beta cells and reducing glucagon secretion from pancreatic alpha [24] **(Table 14)**.

Table 14: *Pharmacokinetics of Lingagliptin*

Bioavailability: 30%
Peak Plasma Time: 1.5 hr
Peak Plasma Concentration : 8.9 nmol/L
AUC: 139 nmol/L
Protein Bound: 75-99%
Volume of distribution : 110 L
Small fraction metabolized to inactive metabolite[22]
Half-Life : 12 hr
Terminal Half-Life : >100 hr
Enterohepatic system (80%), urine (5%)
Renal clearance: 70 mL/min

Alogliptin (Nesina): *Dose : 6.25mg, 12.5mg, 25mg*

Mechanism of Action: Selective dipeptidyl peptidase-4 (DPP-4) inhibitor and slows inactivation of incretin hormones thereby reducing fasting and postprandial glucose concentrations in a glucose-dependent manner **(Table 15,16)**.

Table 15: *Pharmacokinetics of Alogliptin*

Bioavailability : 100%
Peak plasma time : 1-2 hr
Protein bound : 20%
Volume of distribution : 417 L
Active metabolite : N-demethylated
Inactive metabolite : N-acetylated alogliptin

Half-life : 21 hr
Renal clearance : 9.6 L/hr
Total body clearance : 14 L/hr
Excretion : 76% urine ; 13% feces

Table 16: Types of Insulin preparations

Insulin	**Categories**	**Generic (Brand)**	**Effect**
Rapid Acting	insulin lispro	Humalog	Prandial
Short Acting	insulin regular	Novolin R	Prandial
Intermediate	Acting	insulin NPH	Basal
Long Acting	insulin glargine,detemir (Levemir®) insulin degludec (Tresiba®)		Basal
Premixed insulin	Insulin lispro 75/25 (Humalog Mix 75/25 Insulin lispro 50/50 (Humalog Mix50/50®) **Insulin aspart** NPH/regular 70/30 (Humulin or Novolin Mix 70/30®) NPH/regular 50/50	20 to 60 minutes	Prandial + basal

Antidiabetics, Intermediate-Acting Insulins

These drugs have a slow onset of action and a longer duration of action.

Insulin NPH (Humulin N, Novolin N) *Insulin neutral protamine Hagedorn (NPH) has an onset of action of 3-4 hours[25].*

Dose: ***100units/mL (3mL),100units/mL (10mL)***

Mechanism of Action : It diminishes the blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat and by inhibiting hepatic glucose production insulin inhibits lipolysis and proteolysis and enhances Protein synthesis targets include skeletal muscle liver, and adipose tissue **(Table 17)**.

Table 17: Pharmacokinetics

Onset: 1-1.5
Duration: 14-24 hr
Peak plasma time: 6-10 hr
Protein bound[24] : 5%
Vd: 0.15 L/kg
Excretion: Urine
Onset: 1-1.5

Short-Acting Insulins : Regular insulin (Humulin R, Novolin R)

Dose: 100 units/mL (3mL vial),100units/mL.

Mechanism of Action: Insulin and its analogues lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production; insulin inhibits lipolysis and proteolysis and enhances protein synthesis; targets include skeletal muscle, liver, and adipose tissue [26] **(Table 18)**.

Table 18: Pharmacokinetics

Bioavailability: 55-77% (SC)
Onset: 0.5 hr
Duration: 4-12 hr (U-100)
Peak plasma time: 0.8-2 hr (SC)
Vd: 0.26-0.36 L/kg
Metabolized by liver
Excretion: Urine

Antidiabetics, Rapid-Acting Insulins: **Insulin aspart (NovoLog)** *Dose:* ***100 units/mL***

Mechanism of Action*:* Insulin and its analogues lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis and enhances protein synthesis targets include skeletal muscle, liver, and adipose tissue [27] **(Table 19)**.

Table 19: Pharmacokinetics

Onset: 0.2-0.3 hr; 1-3 hr (peak effect)
Duration of action: 3-5 hr
Peak plasma time: 40-50 minutes

Peak plasma concentration: 82 microunits/L
Protein bound: <10%,
Vd: 0.26-0.36 L/kg
Metabolism ***:*** *Liver (>50%); kidney (30%); adipose tissue/muscle (20%).*
Elimination ***:****Half-life: 81 min (SC).*
Excretion: Urine[27]

Insulin glulisine (Apidra),*Dose :* ***100 units/mL***

Mechanism of Action: Insulin lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production [28] **(Table 20)**.

Table 20: Pharmacokinetics

Bioavailability: 70%
Onset of action : 20 minutes
Peak Plasma Time : 1 hr
Peak Plasma oncentration: 83 microUnits/mL
Duration of action: 5 hr
Plasma protein bound : 5%
Volume of distribution : 13 L
Elimination : urine

Insulin lispro (Humalog)*, Dose: 100units/mL (10mL vial)*

Mechanism of Action**:** Regulates glucose metabolism insulin lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat and by inhibiting hepatic glucose production [29] **(Table 21)**.

Table 21: Pharmacokinetics

Bioavailability: 55-77%
Onset: 0.5-5 hr (initial): 0.5-2.5 hr
Duration of action: ≤5 hr
Peak plasma time: 0.5-1.5 hours
Distribution Vd: 0.26-0.36 L/kg
Metabolism ***:*** *Liver (>50%),kidney (30%)*
Half-life: 1 hr (SC); 0.5-1 hour (IV)

Insulin inhaled (Afrezza) ***Dose:*** *4 units/cartridge.*

Mechanism of action : It reduces the blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat and by inhibiting hepatic glucose production[30] **(Table 22)**.

Table 22: Pharmacokinetics

Peak plasma time : 12-15 minutes
Median time to maximum effect : ~53 minutes
Return to baseline levels : 160 minutes
39% of dose distributed to the lungs
7% of dose swallowed
Half-life : 28-39 minutes

Conclusion

Diabetes is a recurrent disorder characterized by the presence of hyperglycemia condition. The severe diabetes condition will affects the physiology of essential organs in the body and it is associated with various macrovascular and microvascular complications.The pharmaceutical industries should discover the formulations methods in diabetic drugs towards beneficial of the community. It is available in the form of oral and injections. The article targets the absorption and distribution metabolism and excretion process and its pharmacological responses in clinical level. The better outcomes of the diabetic treatment depends on individual dosage regimen.

Oral hypoglycaemic drugs have contrasting pharmacokinetic properties. Clinical level of sulphonylureas and biguanides engage crucial role. The high aggregation of the drug in the body will affects the pharmacokinetic parameters within the cellular stage. Oral hypoglycaemic drugs, sulphonylureas and biguanides should available in combinations and having immersed role in management of diabetes mellitus. The biguanides demonstrates the altered metabolism due to the the drug mechanism interacted with genes. Gliclazide is rapidly absorbed in all species, with a plasma peak observed between 1 and 6 hours. Gliclazide reduces blood glucose levels in patients with Type 2 diabetes mellitus by correcting both defective insulin secretion and peripheral insulin resistance. The gliclazide have a low extent of side effects and efficacy longer on compared with other sulphonylureas. Metformin is high effective than sulfonylureas. Combination therapy may exhibits good glycemic control in patients with type 2 diabetes.

The newer class of drugs are reaching to the market for treating diabetes mellitus but metformin is the first line therapy still leading in the market because of its beneficial effects [30].

The pharmacokinetic and pharmacodynamic characteristics of anti diabetic drugs plays a essential role in design of individualization of optimization of dosage regimen for anti diabetic patients.which leads to better patient care towards the disease.

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