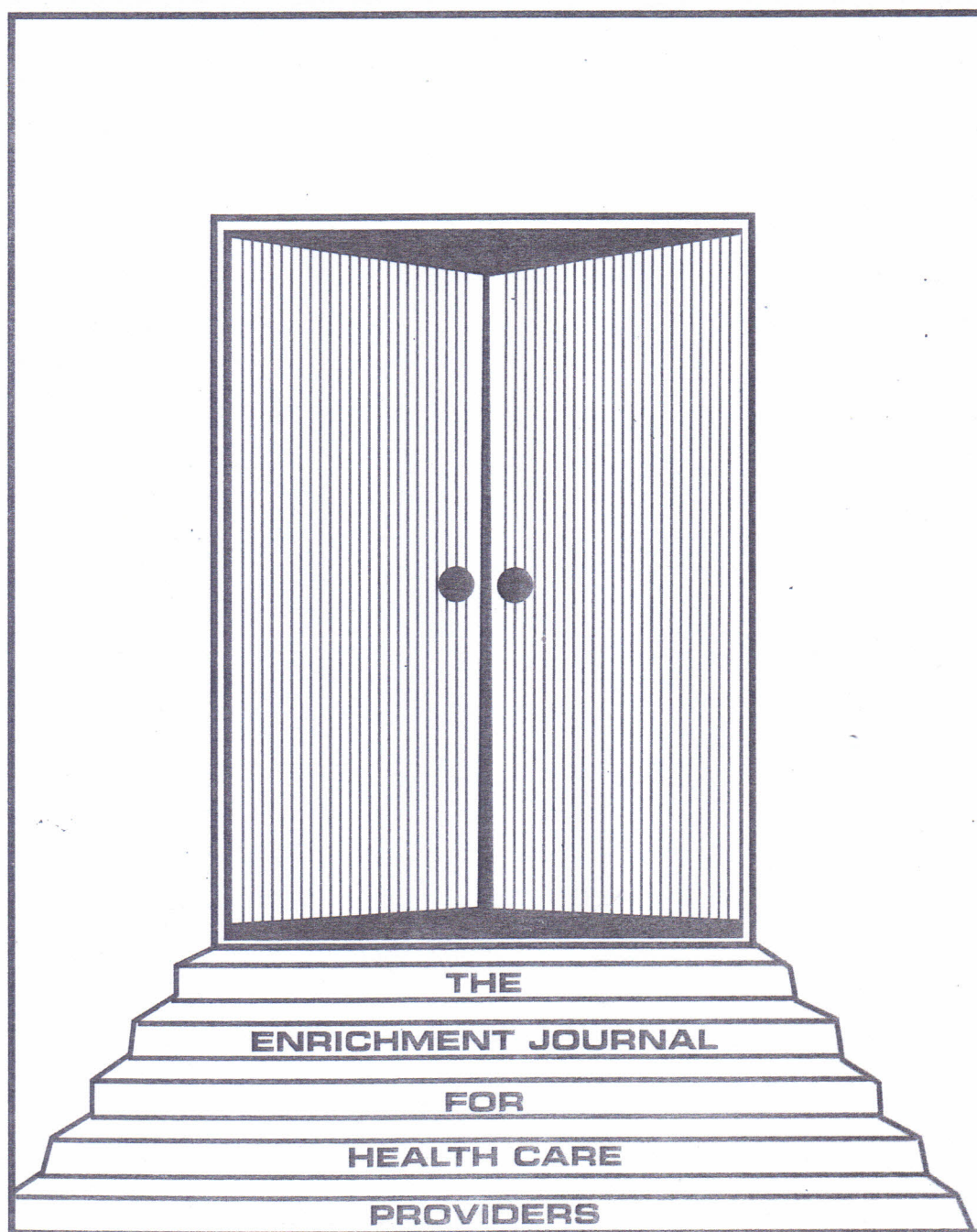


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Review of Pharmacology of Insulin and Guidelines for its Administration

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Abstract

The quest for insulin that could mimic the physiologic insulin continues to rise. This has led to the expansion of insulin therapy option for type 1 diabetes in particular. On this premise this paper presents the pharmacology and guidelines for insulin therapy for health care providers, particularly nurses.

The pharmacology, sources, properties, preparation, storage, adverse effects of insulins are critically reviewed in this paper. The comparison among the various insulin types and their merits/demerits are clearly highlighted. Moreover, factors influencing its absorption and conditions that determine the mixing of insulin types are considered in detail as well.

This paper has been able to provide useful information capable of equipping healthcare providers, particularly nurses with valid knowledge of insulin therapy, its pharmacologic properties, its administration and relevant nursing implications. The teaching-role of nurses regarding insulin therapy will be of great benefit to patients living with diabetes.

Key words: Pharmacology, Insulin, Immunogenic, Peptides, Hypoglycaemia, Pancreas.

Introduction

Health care providers have been looking forward to obtaining an insulin therapy that could mimic the physiologic insulin secreted by the pancreas and thus achieve better glycaemic control in patients living with Diabetes mellitus. The quest for this insulin type has led to the introduction of several new insulins since 1996 and more are on the way. Thus, insulin therapy option for type I and type II diabetes has expanded considerably [1]. Therefore, it is quite imperative that nurses and other relevant health care providers acquaint themselves constantly with the various types of insulins, their administrations, effects and nursing implications as they emerge in order to ensure patients' safety during therapy. The physiologic response to injected animal insulin in a patient with

type 1 diabetes was first demonstrated by a Canadian researcher in 1922. In 1955, insulin became the first protein to be sequenced [1, 2, 3]. This paper reviews the pharmacology and guidelines for administration of insulin with the view of providing an update for health care workers who have the responsibility to provide patients with accurate and correct information on their illness and insulin therapy.

Pharmacology of Insulin

Insulin is a hormone produced in the beta cells of pancreas. It is known to have actions that affect the transmembrane transport of different substances, particularly glucose, into numerous different kinds of cells. Insulin is a large poly-

peptide molecule having 5808 molecular weight [1, 2, 4].

Structurally, insulin is made up of 51 amino acids arranged into A and B chains. The two chains are connected together by two disulfide bridges. There are 21 and 30 amino acids in A and B chains respectively [fig. 1] [1]. A rise in the blood glucose concentration is the stimulus for its secretion [1, 2, 3, 4]. Insulin is processed from a precursor called proinsulin, which consists of a single-chain 86 amino acid peptide. The proinsulin is first produced in the Golgi apparatus of beta cells, where it is

packaged into granules. Upon stimulation from glucose and other insulin secretagogues, the proinsulin is segregated into insulin and C-peptide. Both are secreted in equimolar proportions from the beta cells upon stimulation. Although, the physiologic function of the C-peptide is yet unknown but it can be measured. Thus, its presence indicates that a person has functioning beta cells [1, 2].

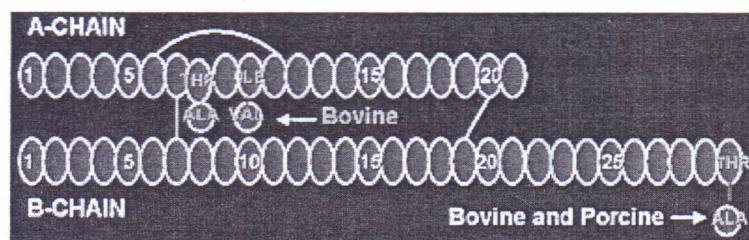


Fig. 1: Structure of insulin (Courtesy of Sinan Tanyolac *et al*, 2008)

Functions of Insulin

Insulin is responsible for the membrane transport of glucose, regulation of transport of some amino acids, some fatty acids, potassium, magnesium and certain other monosaccharide. Besides, it mediates the formation of macromolecules in cells, which are used in cell structure, energy stores and in the regulation of many cell functions. Insulin stimulates glycogenolysis, lipogenesis, proteogenesis and nucleic acid synthesis [3, 5].

All these biological effects exerted by insulin involve insulin-insulin receptor interactions [3, 5]. Upon binding, insulin promotes the cellular uptake of glucose into fat and skeletal muscle and inhibits hepatic glucose output, thus lowering the blood glucose [1, 2].

Sources of Insulin

Insulins are obtained from beef, pork and human (table 1). With the availability of

human insulin by recombinant DNA technology in the 1980's, the use of animal insulin has declined drastically. In fact, beef and beef-pork insulin are no longer commercially available. The FDA may allow for personal importation of beef insulin from foreign countries, if a patient cannot be treated with human or pork insulin. Pork insulin is still available in some countries. Beef insulin differs from human insulin by 3 amino acids and pork insulin differs by one amino acid (1).

Table 1: Insulin Amino Acids (Courtesy of Sinan Tanyolac *et al*, 2008)

Sources of insulin	A – chain		B – chain
	Position 8	Position 10	Position 30
Beef	Alanine	Valine	Alanine
Pork	Threonine	Isoleucine	Alanine
Human	Threonine	Isoleucine	Threonine

Human insulin and or analogue of human insulin are currently in use. The production of human insulin is achieved through the recombinant DNA technique. This involves insertion of the human pro-insulin gene into either *saccharomyces cerevisiae* (baker's yeast) or a non-pathogenic laboratory strain of *Escherichia coli* (E. coli), which serves as the production organism. The human insulin is subsequently isolated and then purified [1, 3].

Insulin Analogue

The development and production of analogue to human insulin has been made while figure 3 shows that of insulin glargine.

Immunogenicity

The difference of pork and beef insulin from human insulin by 1 and 3 amino acids respectively makes them to be more immunogenic than exogenous human insulin. The high proportion of impurities containing islet-cell peptides, proinsulin, C-peptide, pancreatic polypeptides, glucagons and somatostatin present in the older formulation contributed to immunogenicity of insulin [1, 7, 8, 9]. Besides, components of insulin preparation (e.g. zinc and protamine) and subcutaneous insulin aggregates are considered to contribute to antibody formation [1, 9, 10]. Commercially available human insulins are now free from contaminants relatively [1]. Thus, insulin side effects such as local or

possible by the recombinant DNA technology. The pharmacokinetic properties of insulin, primarily affecting the absorption have been altered by the slight modification of the insulin molecules. Thus, the amino acids are substituted at the B26 – B30 region of the insulin molecules because this region is not critical for insulin receptor recognition (1, 7). Therefore, the insulin analogues are still recognized by and can still bind to the insulin receptors. The three insulin analogues currently available are: insulin aspart, lispro and insulin glargine. Figure 2 shows the structure of insulin aspart and lispro, systemic hyper-sensitivity lipodystrophy, and antibody production causing insulin resistance, are now rarely seen with exogenous human insulin [1, 11]. The availability of human insulin and the increased immunogenic potential inherent in animal source insulin, have led to the rare use of insulins from the later source. Therefore, people with diabetes should be intimated with the human insulin.

The rare hypersensitivity responses to insulin can either be immediate reaction (local or systemic) or delayed local reaction. Studies [9, 12] have shown that patients who experience a true allergic reaction to insulin often have received insulin in the past, and subsequently experience the allergic reaction after insulin is re-commenced. The delayed local reaction from animal insulins is that IgG-mediated [9, 10]. Insulin therapy can result in the production of insulin

antibodies of the IgG class, which neutralizes insulin. This can occur in patients with a very high titre IgG-antibodies.

Lipodystrophy common with insulin administration can either be lipoatrophy or lipohypertrophy. Lipoatrophy is an immune-mediated condition in which there is loss of fat at the insulin injection sites [9]. It occurs much less frequently with purified human insulins. Injection of human insulin at the atrophied site is the treatment for patients, who were on animal insulin. Lipohypertrophy is a non-immunological side effect of insulin resulting from repeated administration of insulin at the same site.

Preparation and Properties of Insulin: Insulin Concentration

In the United States, all insulins are in the concentration of 100 units /ml (signified as U-100) [1]. Insulin syringes are designed to accommodate this concentration of insulin. Regular human insulin (Humulin R, Lilly) is available in more concentrated insulin, U-500 (500 units/ml) however, this preparation is used primarily in a specialized institutional setting or for rare cases of extreme insulin resistance, where very large doses of insulin are required.

In some countries, a less concentrated insulin preparation, U-40 (40 units/ml) is still available and sometimes used. Specific U-40 syringes are used with this insulin [1]. This implies that patients travelling from one country to the next should be aware of the concentration of insulin they use and that appropriate syringe is used.

Properties of Insulins

Regular human insulin is crystalline zinc insulin dissolved in a clear solution. Its administration may be through any of the parenteral routes: subcutaneous, intramuscular or intravenous. Similarly, insulin lispro and aspart are soluble crystalline zinc insulins, but they are intended for

subcutaneous administration. NPH, lente and ultralente insulins are suspensions with the regular insulin in them either complexed with protamine (NPH, Neutral protamine hagedorn or isophane meaning stoichiometric proportions) or mixed with excess amounts of zinc ions (Lente insulin or ultralente insulin) to delay their absorption and thus extend their actions [1, 11, 12]. Insulin suspensions should not be administered intravenously. Insulin glargine is a soluble clear insulin with a P^H of 4.0. All other insulins have neutral P^H . The insulin glargine should only be administered subcutaneously [1, 12, 13].

Pharmacokinetics

Absorption

Insulin administered via subcutaneous injection is absorbed directly into the blood stream, with the lymphatic system playing a minor role in transport (1). Insulin absorption rates vary and dependent on blood flow at various sites of injection (abdomen, deltoid, gluteus and thigh) [1]. For instance the absorption rate of regular insulin is twice faster from the abdomen than other subcutaneous sites [1]. Therefore, patients should avoid random use of different body regions for their injections. However, abdomen is often recommended as the preferred site of injection because, it is the least susceptible to factors affecting insulin absorption (see table 2).

Table 2: Factors affecting insulin absorption
(adapted and modified from
Sinan Tanyolac *et al*, 2008)

Factors influencing insulin absorption	Explanation
Local massage	Vigorous rubbing or massage will increase rate of absorption. Therefore, just press on the site to prevent seepage
Temperature	Heat increases rate of absorption, avoid hot application or bath soon after injection. Cold has contrast effect
Site of injection	Absorption of insulin is faster at the abdomen. This is however, less relevant with rapid-acting insulins and glargines
Lipohypertrophy	Injecting insulin in the area of lipohypertrophy will delay its absorption
Jet injectors	This injection device accelerate rate of absorption of insulin
Insulin mixtures	Regular insulin may lose its short-acting property when mixed with lente and resuspension of insulin suspension may be impaired as well
Insulin dose	Larger dose causes delayed absorption but prolongs duration of action
Physical status (whether soluble or suspension)	Insulin suspension must sufficiently be resuspended prior to injection to limit variability
Exercise of the injected part	Strenuous exercise of the part of injection increases absorption rate. This is clinically relevant with regular insulins

Distribution

Insulin is distributed equally between free insulin and insulin bound to IgG antibodies on getting to the bloodstream [1]. Presence of insulin antibodies can delay the onset of insulin action, reduce the peak concentration of free insulin and prolong the biologic half-life of insulin (1, 4).

Elimination

Larger amounts of insulin are metabolized by the liver and kidneys. Naturally $\approx 60\%$ of insulin released by the pancreas is degraded by the liver while about 35 - 45% is degraded by the kidneys [1, 4]. The portal vein is bypassed when insulin is injected exogenously. Thus, the degradation profile is altered. In this case, the kidney degrades up to 60% while the liver degrades about 30-40% of subcutaneous insulin. Therefore, renal dysfunction will reduce the clearance of insulin (both endogenous and exogenous) and prolong its effect.

Pharmacodynamics

Insulin pharmacodynamics refers to the metabolic effect of insulin i.e. what the insulin does to the body. Considering insulin pharmacodynamics (onset, peak and duration), intra/inter-patient variability accounts for the ranges of onset. Accurate specific time-action profile of specific insulin can be better determined through patient self-monitoring of blood glucose.

Storage

All insulin products have expiration date. The expiration date labelled on the product applies when they are intact (unopened) and refrigerated. Intact (i.e. insulin not currently in use) insulin should be stored in the refrigerator at $2^{\circ}\text{C} - 8^{\circ}\text{C}$ ($36^{\circ}\text{F} - 46^{\circ}\text{F}$). An insulin vial in use may be kept at room temperature $15^{\circ}\text{C} - 30^{\circ}\text{C}$ ($59^{\circ}\text{F} - 86^{\circ}\text{F}$) for about 1 month. Insulin cartridges, profiled disposable pens and other devices can have different storage recommendations for room temperature (table 5). Insulin should never be frozen or stored in an ambient temperature greater than 30°C (86°F) [1, 4].

Adverse Effects

Hypoglycaemia is the most significant adverse effect of insulin [1, 2, 4]. Therefore, it is imperative for all patients

receiving insulin to recognize the symptoms of hypoglycaemia and how to manage it. To pass this knowledge to the patients is the teaching role of nurses. Another significant side-effect of insulin therapy is weight gain [1, 2]. Over-treating/overeating in response to hunger may be responsible for this. Besides, insulin being an anabolic hormone also promotes the uptake of fatty acids into adipose tissue [1]. Injection sites should be rotated to avoid lipohypertrophy. Preferably, rotate within one area (e.g. abdomens, avoid 2-inch radius around navel) and do not reuse for one week. True allergic reactions and cutaneous reaction are rare (see immunogenicity).

Mixing

Mixing of two different insulins is dependent on the type of insulins and the duration the insulins are kept in the same syringe. Regular insulin and NPH insulin can be mixed in the same syringe for up to 3 months refrigerated without changing the pharmacodynamic profiles of the insulin [1]. Manufacturers have recommended that regular insulin should only be mixed with lente insulin or ultralente insulin immediately before injection, otherwise the excess zinc used in the formulation of lente insulin or ultralente insulin will bind regular insulin and thus impair the effect of the regular insulin. Insulin lispro may be mixed with NPH and ultralente insulin without significantly changing the peak or total bioavailability of insulin lispro [1, 3, 4]. Insulin aspart may be mixed with NPH insulin immediately before injection. While this may cause some attenuation of the peak concentration of insulin aspart, the time to peak and total bioavailability are not significantly affected. When mixing two types of insulins, the clear insulin is first drawn into the syringe then, the cloudy insulin. This prevents the cloudy insulin from being injected into the clear insulin vial, which could affect

the pharmacodynamic properties of the clear insulin. Insulin glargine with P^H 4.0 is the only clear insulin that cannot be mixed with any other insulin because of its low P^H . Mixing it with any other insulin will alter its absorption. Therefore, patients who reuse their syringes should particularly label one that is used only for insulin glargine [1]. The nurse should ensure that the client can demonstrate ability to accurately mix their insulin. Patients who have difficulty mixing insulins in the same syringe should avoid it or can use fixed or prefixed insulin (if appropriate).

Nursing Implications

The nurses and other relevant health care providers have the responsibility of providing useful information on the benefits of human insulin with less immunologic effects. However, the side-effects that patients can experience during the course of their insulin therapy must be communicated to them before its commencement. It is also very important that nurses acquaint themselves with the concentration which insulin preparation comes with, and the appropriate syringes designed for that particular insulin concentration to be used for its administration. Similarly, the appropriate route for each insulin type must be at the finger tips of nurses, as this will help in professional practice. It is imperative for nurses to know the onset, peak and duration of action of all insulin types and the various factors that influence these properties. In order to maintain insulin potency and prevent adverse effect that may occur as a result of expiration of the product, insulin should be stored at correct temperature ranges and expiration dates checked before administration. More importantly, patients on insulin therapy must be taught how to recognise symptoms of hypoglycaemia and how to prevent and manage it.

Conclusion

Nurses and other relevant health care providers must have a working knowledge of diabetes, types of diabetes, blood glucose monitoring, insulin therapy, hypoglycaemia and hyperglycaemia. It is believed this paper will be able to contribute to knowledge acquisition of nurses, other relevant health care providers and by extension patients with diabetes.

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