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THE MAIN PRINCIPLES OF INSULIN THERAPY

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The article describes the main indications for insulin therapy, insulin agents and their characteristics depending on the origin, methods of producing and action duration. The article elucidates the methods of insulin injection and injection technique. Also, this article presents the insulin therapy regimen: the conventional and basal-bolus therapy, the daily insulin demand depending on the DM period and its distribution throughout a day. Besides, the article deals with the morning hyperglycemia syndromes, their differential diagnostics and therapeutic approach.

KEY WORDS: diabetes mellitus type 1, insulin, Standard Medical therapy, basal-bolus therapy, insulin therapy regimen

ЗАГАЛЬНІ ПРИНЦИПИ ІНСУЛІНОТЕРАПІЇ

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У статті представлені основні показання до призначення інсулінотерапії, препарати інсуліна та їх характеристики залежно від походження, методу отримання і тривалості дії. Висвітлено питання способу введення інсуліну та техніки виконання ін'єкції. Описано режими інсулінотерапії: традиційна і базисно - болюсна, визначення добової потреби в інсуліні в залежності від періоду перебігу цукрового діабету та його розподіл протягом дня. Розглянуто синдроми ранкової гіперглікемії, їх диференційна діагностика та тактика лікування.

КЛЮЧОВІ СЛОВА: цукровий діабет 1 типу, інсулін, стандартна терапія, базисно-болюсна терапія, режими інсулінотерапії

ОСНОВНЫЕ ПРИНЦИПЫ ИНСУЛИНОТЕРАПИИ

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В статье представлены основные показания к назначению инсулинотерапии, препараты инсулина и их характеристики в зависимости от происхождения, метода получения и длительности действия. Освещены вопросы способа введения инсулина и техники выполнения инъекции. Описаны режимы инсулинотерапии: традиционная и базисно-болюсная, определение суточной потребности в инсулине в зависимости от периода течения сахарного диабета и его распределение в течение дня. Рассмотрены синдромы утренней гипергликемии, их дифференциальная диагностика и тактика лечения.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 1 типа, инсулин, стандартная терапия, базисно-болюсная терапия, режимы инсулинотерапии

INSULIN THERAPY

100 % of patients with diabetes mellitus (DM) type 1 (DM-1) need insulin therapy, as hyperglycemia that was caused by absolute insulin deficit can be negated only with the help of replacement therapy institution. A diet and physical activity are considered only for insulin dose modification [1, 2].

Besides, up to 40 % of patients with DM type 2 (DM-2) are on the insulin [2, 3].

GENERAL INDICATIONS FOR INSULIN THERAPY [1-3]

1. DM-1.
2. DM-2, in such cases:
 - progressive weight loss and ketoacidosis expansion;
 - surgical intensive interference;

- acute macrovascular complications;
- serious virulent diseases;
- glycemia's level is more than 15-18 mmol/L;
- permanent lack of compensation in case of maximum daily dose administration of tableted antihyperglycemic drugs;
- advanced stages of the DM's chronic complications.

3. Ketoacidotic and hyperosmolar coma.
4. Gestational DM without compensation achievement.
5. Pancreatectomy.

INSULIN AGENTS' CLASSIFICATION

Insulin agents are divided by origin and action duration [3,4].

I. By origin:

1. Of animal origin:
 - a) Porcine,
 - b) Beef;
2. Of human origin:
 - a) Genetically engineered,
 - b) Semisynthetic;
3. Insulin human analogues - with fixed pharmacokinetics.

Porcine insulin is distinguished from human origin insulin by one amino acid and the beef one - by three amino acids, that leads to its greater antigenic specificity. Recently animal origin insulins are rarely used. There are two methods of producing human insulin: a semi-

synthetic (with the help of porcine insulin, by replacing one differ amino acid), and genetically engineered.

Genetically engineered human insulins are of the highest quality, as they are produced by the association of human genome's locus, responsible for insulin release ,with the yeast cultures genome or E.coli, that start to produce human insulin.

Genetically engineered insulins - are agents of choice in the course of the DM-1 treatment (especially for the youngsters under the age of eighteen) [4, 5].

Insulin analogues were obtained in the result of the amino acids' misplacement in order to get fixed pharmacokinetics agents (of ultrashort and long-act).

Insulin analogues are recommended in cases of intolerance to other types of insulin and during the labile DM with a tendency to severe hypoglycemia.

If the compensation of DM was achieved, it isn't recommended to switch to other insulin types [3].

II. By action duration:

1. Ultrashort-acting (insulin human analogues);
2. Short-acting (regular insulin);
3. Intermediate-acting (Neutral Protamine Hagedorn);
4. Long-acting (insulin human analogues).

Table 1 describes the characteristics of insulin agents.

Table 1

Insulin agents'characteristics

Insulin types	International nonproprietary name	Effect		
		Onset	Peakttime	Duration
Ultrashort-acting	Insulin lispro Insulin aspart Insulin glulisine	5-15 min	1-2 h	4-5 h
Short-acting	Soluble genetically engineered human insulin	20-30 min	2-4 h	5-6 h
Intermediate-acting	Isophane genetically engineered human insulin	2 h	6-10 h	12-16 h
Long-acting	Insulin glargine Insulin detemir	1-2 h	-	Up to 24 h

Ultrashort-acting agent should be injected immediately preprandial, short-acting - a 30 minute before meals. A short duration effect of ultrashort acting insulin reduces the hypoglycemia risk [6]. Ultrashort- and short-acting agents can be injected in a subdermic, intramuscular and endovenous way [3-7].

Among the intermediate-acting insulin the most popular agents are those that include Neutral Protamine Hagedorn (NPH), which adsorbates insulin noncovalently, reducing its subcutaneous fat absorption [3].

NPH doesn't bind insulin's additional amounts and as a result it is possible to create standard mixtures with short-acting insulin (diphasic genetically engineered human insulin) and ultrashort insulin analogues (diphasic insulin lispro and aspart) [7]. It is possible to combine short- and ultrashort-acting insulins with protamined insulin in different proportions such as 25/75, 30/70 or 50/50. Usually only the first digit is on the product name and it indicates the percentage of regular insulin, the second one - attends to NPH insulin.

The advantage of insulin's standard mixtures is a substitution of two injections for one, the downside - inability to separate the individual dosing components out of the mixture [3, 7].

Long-acting insulin analogues provide more uniform and prolonged agent's admission from subdermal repository, than NPH insulin, that can be injected once a day, regardless of the time of day. [8].

THE INJECTION TECHNIQUE

In general the success of insulin therapy depends on strict implementation of injection technique.

The simplest and the most reliable method is insulin injection using an insulin syringe. The method of insulin injection using an automatic syringe device, which consists of the insulin cartridge, dose delivery system and skin wheel needle with the pressure infusor, is more convenient for patients. For maintenance therapy insulin should be administered subcutaneously: short-acting insulin - to the subcutaneous fat of the abdomen, prolonged - to the pectoral of the shoulder or hip. The needle is to be located at an angle of 45° to the skin fold, if the thickness of subcutaneous fat layer exceeds the length of the needle - of 90°. At the same time, in order to prevent lipodystrophy, the injection site within the same zone should be daily changed [3-5, 9].

Daily-used insulin vials or injection pens can be stored at indoor temperature during one month; insulin is to be of indoor temperature before being injected. Intermediate-acting insulins (NPH insulins) and ready-made insulin mixtures should be mixed meticulously before the injection [9].

The insulin pump usage is one of the insulin injection methods. It allows to make the basal insulin injection at the rate of 0.5-1.0 U/h with the additional insulin injection before meals, depending on the consumed carbohydrate and glycemia [3, 7]. The positive aspect of insulin pump usage is the ability to inject only short-acting or ultrashort-acting insulin. It is more physiological, because prolonged insulin absorption is exposed to large fluctuations [10]. The disadvantages of insulin pump injection are: inconvenience caused by constant wearing of a device on the body and long-term presence of the injection needle in the subcutaneous tissue. The indications for insulin pump usage are: decompensated or refractory DM, the dawn phenomenon patients, pregnant or planning pregnancy women with DM-1 [9, 10].

INSULIN THERAPY REGIMEN

In arriving at a DM-1 diagnosis, short-acting insulin is prescribed subcutaneously 4-6 times a day before meals. A few days later it is necessary to start the combined insulin injection. The average daily insulin demand in patients with DM-1 is 40 - 60 units.

In early disease the required amount of insulin is 0.5-0.6 U/kg.

After insulin therapy initiation the insulin requirement may even decrease (0.3-0.4 U/kg) - the «honeymoon period». This period can last from several weeks to several years (on average for several months), but the autoimmune destruction of the rest of endocrine pancreas will inevitably lead to increasing insulin requirement up to 0.7-0.8 U/kg [3, 4].

The DM-1 decompensation will lead to even greater insulin demand - 1.0-1.5 U/kg [3, 4].

Insulin therapy must be individualized in order to achieve the best control of DM progression in the setting of the absence of severe hypoglycemia.

Normally the pancreas secretes 35-50 units of (0.6-1.2 U per 1 kg body mass) insulin per day. This secretion is divided into *nutritional* or *bolus* (50-70 % of daily output) and *basal*.

The neutralization of postprandial hyperglycemia occurs at the expense of food insulin secretion - about 1-2.5 U per 10-12 g of carbohydrates (= 1 bread unit -BU). 2.0-2.5 units of insulin are secreted at 1 BU during breakfast, 1.0-1.5 units at lunch and 1.0 unit at dinner. It is connected with the greatest activity of counter-insulin hormones in the morning [3, 4].

Basal insulin secretion (with a rate of 1 U/h) provides an optimal level of glycemia between meals and during a sleep.

The conventional insulin therapy involves the usage of standard mixtures with a fixed dose of insulin, which is more preferable for patients with DM- 2 [3, 4, 7].

Intensive insulin therapy with flexible choice of the dose which depends on glycemia and on the amount of carbohydrates in food is more approximated to a physiological insulin secretion [11]. The need for basal insulin secretion is provided by two intermediate-

acting insulin injections ($\frac{2}{3}$ in the morning and $\frac{1}{3}$ in the evening) or a single injection of long-acting insulin (does not matter in what time of day). A daily dose of basal insulin should not be more than a half of agent's total daily requirement ($\frac{1}{3}$ - $\frac{1}{2}$). *Food insulin secretion* is replaced by short-acting or ultra short-acting insulin before each meal ($\frac{1}{4}$ at dinner, the remaining dose is divided roughly in two parts between breakfast and lunch), taking into account the amount of carbohydrates which the patient is going to take during the meal. Not all carbohydrates are taken into account, but only «carb counting», such as: fruits, potatoes, grains, sweet and liquid milk products. You can count a matching insulin dose with the help of special exchange tables that were developed for the patients' convenience (tab. 2). For each BU, that is planned to be eaten, 2 U of insulin should be injected in the morning, 1,5 U at lunch and 1U at dinner [3, 4, 7].

Table 2

The exchange table of products containing 1 BU

Product description	Portion size	Dimension
Milk, kefir, curdled milk, whey	1 cup	250 ml
Cheesecake (medium-sized)	1	75 g
Ice-cream	$\frac{2}{3}$ of portion	65 g
Boiled groats (porridge)	2 tablespoons	50 g
Vermicelli, noodles, elbows	1,5 tablespoons	
Bread, small loaves except buns	1	25-30 g
Pancakes with cheese	1	
Sand sugar	1 tablespoon	12 g
Refined sugar	2-2,5 pcs	12 g
Mashed potatoes	1-1,5 tablespoons	
Fried potatoes	1,5-2 tablespoons	
Carrot (large)	3	
Kidney bean	7 tablespoons	120 g
Beetroot (large)	1	
Banana (with peel weight)	0,5	90 g
Pear	1	90-100g
Melon		300 g
Watermelon		400 g
Peach (medium-sized)	1	120 g
Apricots, blue plums (medium-sized)	3	120 g
Mandarines, oranges	1	170 g
Apples (medium-sized)	1	100-120 g
Strawberries (medium-sized)	10	120 g
Cherry (large)	15	120 g
Strawberries, blackberries, raspberries, black currants, gooseberries, cranberries	1 cup	100 g
Apple juice, grapefruit and orange juice	0,5 cup	100 g
Dumplings	4 pcs	
Cooked sausage, sausages		100 g
Cutlet (medium-sized)	1	

A short-acting and long-acting insulin dose depends on the amount of eaten carbohydrates (BU) and glucose level before the injection. While meal, containing 1 BU increases glycemia at 1.6-2.2 mmol/L, the injection of insulin (1U) reduces it to the same level. Short-acting insulin is injected with morning dose of NPH insulin. Evening dose of NPH insulin is prescribed for 22-23 hours. It is necessary to consider the probability of typical phenomena development during the selection of evening intermediate-acting insulin dose.

The *dawn phenomenon* is morning hyperglycemia associated with the lack of evening prolonged insulin dose, in the setting of increasing morning insulin requirement [3, 4, 12, 13].

The *Somogyi effect* also occurs through morning hyperglycemia and develops after the precursory hypoglycemia. The excessive evening dose of prolonged insulin leads to night hypoglycemia (between 2:00 and 4:00 a.m.), when the counter-insular hormones level is minimal and tissues are the most sensitive to insulin. During this period hypoglycemia stimulates the compensatory release of counter-

insular hormones (including glucagon) that leads to morning hyperglycemia. Clinically nocturnal hypoglycemia manifests as a poor sleep with nightmares, sweating, morning weakness and a headache. Choosing insulin therapy, glucose testing should be carried out at 3am in order to get proper diagnosis of morning hyperglycemia (the dawn phenomenon or the Somogyi effect) [3, 13].

The common rules of insulin therapy are [4]:

1. The regular insulin dose should not exceed 12 units in a single injection.
2. The total dose of a combined injection should not exceed 70-80 units.
3. The ratio of a daily and nightly insulin dose should be about 2:1.
4. The daily insulin dose cannot be changed more than 4 U/day.
5. Simultaneously a daily insulin dose should not be increased or decreased by more than 6-8 units.

And as conclusion I would like to quote the words of a German doctor Michel Berger: «Diabetes is not a disease but a way of life. Sick with diabetes – all the same that drive the car on a busy road – be aware traffic rules».

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