

Insulin Administration

AMERICAN DIABETES ASSOCIATION

Insulin is necessary for normal carbohydrate, protein, and fat metabolism. People with type 1 diabetes mellitus do not produce enough of this hormone to sustain life and therefore depend on exogenous insulin for survival. In contrast, individuals with type 2 diabetes are not dependent on exogenous insulin for survival. However, over time, many of these individuals will show decreased insulin production, therefore requiring supplemental insulin for adequate blood glucose control, especially during times of stress or illness.

An insulin regimen is often required in the treatment of gestational diabetes and diabetes associated with certain conditions or syndromes (e.g., pancreatic diseases, drug- or chemical-induced diabetes, endocrinopathies, insulin-receptor disorders, certain genetic syndromes). In all instances of insulin use, the insulin dosage must be individualized and balanced with medical nutrition therapy and exercise.

This position statement addresses issues regarding the use of conventional insulin administration (i.e., via syringe or pen with needle and cartridge) in the self-care of the individual with diabetes. It does not address the use of insulin pumps. (See the American Diabetes Association's position statement "Continuous Subcutaneous Insulin Infusion" for further discussion on this subject.)

INSULIN— Insulin is obtained from pork pancreas or is made chemically identical to human insulin by recombinant DNA technology or chemical modification of pork insulin. Insulin analogs have been developed by modifying the amino acid sequence of the insulin molecule.

Insulin is available in rapid-, short-, intermediate-, and long-acting types that may be injected separately or mixed in the same syringe. Rapid-acting insulin analogs (insulin lispro and insulin aspart) are available, and other analogs are in development. Regular is a short-acting insulin.

Intermediate-acting insulins include lente and NPH. Ultralente and insulin glargine are long-acting insulins. Insulin preparations with a predetermined proportion of intermediate-acting insulin mixed with short- or rapid-acting insulin (e.g., 70% NPH/30% regular, 50% NPH/50% regular, and 75% NPL/25% insulin lispro) are available.

Different companies have adopted different names for the same short-, intermediate-, or long-acting types of insulin or their mixture. Human insulins have a more rapid onset and shorter duration of activity than pork insulins.

Insulin is commercially available in concentrations of 100 or 500 units/ml (designated U-100 and U-500, respectively; 1 unit equals ~36 µg of insulin). U-500 is only used in rare cases of insulin resistance when the patient requires extremely large doses. U-500, insulin lispro, insulin aspart, insulin glargine, and 75% NPL/25% insulin lispro require a prescription. Insulin preparations are sometimes formulated individually for use in infants (e.g., U-10) with diluents provided by the manufacturer. In these instances, special care must be taken to ensure that the correct dose of the diluted insulin is administered with an ordinary insulin syringe.

Different types and species of insulin have different pharmacological properties. Human insulin is preferred for use in pregnant women, women considering pregnancy, individuals with allergies or immune resistance to animal-derived insulins, those initiating insulin therapy, and those expected to use insulin only intermittently. Insulin type and species, injection technique, insulin antibodies, site of injection, and individual patient response differences can all affect the onset, degree, and duration of insulin activity. Changing insulin species may affect blood glucose control and should only be done under the supervision of a health profes-

sional with expertise in diabetes. Human insulin manufactured using recombinant DNA technology is replacing insulin isolated from pigs. Future availability of animal insulin is uncertain.

Pharmacists and health care providers should not interchange insulin species or types without the approval of the prescribing physician and without informing the patient of the type of insulin change being made. If an individual is admitted to a hospital, the type of insulin he or she has been using should not be changed inadvertently. If there is doubt about the principal species, human insulin should be administered until adequate information is available. When purchasing insulin, the patient should make sure that the type and species are correct and that the insulin will be used before the expiration date.

In the event that a patient's specific brand of insulin is temporarily unavailable, the same insulin formulation from another manufacturer may be substituted. Changing insulin types (e.g., long, intermediate, short, and rapid acting) from one formulation to another should always be done under medical supervision. The patient should be fully informed as to the reason for any change in insulin and the potential need for additional glucose monitoring.

Storage

Vials of insulin not in use should be refrigerated. Extreme temperatures (<36 or >86°F, <2 or >30°C) and excess agitation should be avoided to prevent loss of potency, clumping, frosting, or precipitation. Specific storage guidelines provided by the manufacturer should be followed. Insulin in use may be kept at room temperature to limit local irritation at the injection site, which may occur when cold insulin is used.

The patient should always have available a spare bottle of each type of insulin used. Although an expiration date is stamped on each vial of insulin, a loss in potency may occur after the bottle has been in use for >1 month, especially if it was stored at room temperature.

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Abbreviations: SMBG, self-monitoring of blood glucose.

The person administering insulin should inspect the bottle before each use for changes (i.e., clumping, frosting, precipitation, or change in clarity or color) that may signify a loss in potency. Visual examination should reveal rapid- and short-acting insulins as well as insulin glargine to be clear and all other insulin types to be uniformly cloudy. The person with diabetes should always try to relate any unexplained increase in blood glucose to possible reductions in insulin potency. If uncertain about the potency of a vial of insulin, the individual should replace the vial in question with another of the same type.

Mixing insulin

Administration of mixtures of rapid- or short- and intermediate- or long-acting insulins will produce a more normal glycemia in some patients than use of a single insulin. The formulations and particle size distributions of insulin products vary. On mixing, physicochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately. When rapid-acting and ultralente insulins are mixed, there is no blunting of the onset of action of the rapid-acting insulin. A slight decrease in the absorption rate, but not the total bioavailability, is seen when rapid-acting and protamine-stabilized insulin (NPH) are mixed. In clinical trials, however, the postprandial blood glucose response was similar when rapid-acting insulin was mixed with either NPH or ultralente. Mixing of short-acting and lente insulins is not recommended, except for patients already adequately controlled on such a mixture. Upon mixing, Zn^{2+} present in lente insulins (e.g., lente and ultralente) will bind with the short-acting insulin and delay its onset of action. The degree and rate of binding varies with the ratio and species of the two insulins; binding equilibrium may not be reached for 24 h. Phosphate-buffered insulins (e.g., NPH insulin) should not be mixed with lente insulins. Zinc phosphate may precipitate, and the longer-acting insulin will convert to a short-acting insulin to an unpredictable extent. Mixing of insulins should follow these guidelines:

- Patients who are well controlled on a particular mixed-insulin regimen should

maintain their standard procedure for preparing their insulin doses.

- No other medication or diluent should be mixed with any insulin product unless approved by the prescribing physician.
- Insulin glargine should not be mixed with other forms of insulin due to the low pH of its diluent.
- Use of commercially available pre-mixed insulins may be used if the insulin ratio is appropriate to the patient's insulin requirements.
- Currently available NPH and short-acting insulin formulations when mixed may be used immediately or stored for future use.
- Rapid-acting insulin can be mixed with NPH, lente, and ultralente.
- When rapid-acting insulin is mixed with either an intermediate- or long-acting insulin, the mixture should be injected within 15 min before a meal.
- Mixing of short-acting and lente insulins is not recommended except for patients already adequately controlled on such a mixture. If short-acting and lente mixtures are to be used, the patient should standardize the interval between mixing and injection.
- Phosphate-buffered insulins (e.g., NPH) should not be mixed with lente insulins.
- Insulin formulations may change; therefore, the manufacturer should be consulted in cases where its recommendations appear to conflict with the American Diabetes Association guidelines.

SYRINGES — Conventional insulin administration involves subcutaneous injection with syringes marked in insulin units. There may be differences in the way units are indicated, depending on the size of the syringe and the manufacturer. Insulin syringes are manufactured with 0.3-, 0.5-, 1-, and 2-ml capacities. Several lengths of needles are available. Blood glucose should be monitored when changing from one length to another to assess for variability of insulin absorption. Regulations governing the purchase of syringes vary greatly from one state to another.

Many different medical devices have been developed to reduce the risk of needle sticks and other sharps injuries using current OSHA standards. These devices incorporate features designed to reduce injury. Use of some currently available

insulin syringes with engineered sharps injury protection (ESIP) may present barriers to effective insulin self-administration training. Use of a device for training that is different from the device to be used in practice is inconsistent with teaching/learning principles, and may compromise the success of the training process. Individualized patient assessment should guide the use of an ESIP insulin syringe during insulin self-administration instruction. (See AADE, *Diabetes Educ* 28: 730, 2000).

Syringes must never be shared with another person because of the risk of acquiring a blood-borne viral infection (e.g., acquired immune deficiency syndrome or hepatitis).

Travelers should be aware that insulin is available in a strength of U-40 outside of the U.S. To avoid dosing errors, syringes that match the concentration of U-40 insulin must be used.

Disposal

Recapping, bending, or breaking a needle increases the risk of needle-stick injury and should be avoided. Insulin syringes and pens, needles, and lancets should be disposed of according to local regulations. Some areas may have special needle disposal programs to prevent sharps from being in the main waste disposal stream. When community disposal programs are unavailable, used sharps should be placed in a puncture-resistant container. Local trash authorities should be contacted for proper disposal of filled containers. Care should be taken to keep these filled containers away from containers to be recycled. In areas with container-recycling programs, placement of containers of used syringes, needles, and lancets with materials to be recycled is prohibited.

Needle reuse

Manufacturers of disposable syringes and pen needles recommend that they only be used once. One potential issue, which arises with reuse of syringes or needles, is the inability to guarantee sterility. Most insulin preparations have bacteriostatic additives that inhibit growth of bacteria commonly found on the skin. Nevertheless, syringe/needle reuse may carry an increased risk of infection for some individuals. Patients with poor personal hygiene, an acute concurrent illness, open wounds on the hands, or decreased resistance to infection for any reason should not reuse a syringe or pen needle.

Another issue has arisen with the advent of newer, smaller (30 and 31 gauge) needles. Even with one injection, the needle tip can become bent to form a hook which can lacerate tissue or break off to leave needle fragments within the skin. The medical consequences of these findings are unknown but may increase lipodystrophy or have other adverse effects.

Some patients find it practical to reuse needles. Certainly, a needle should be discarded if it is noticeably dull or deformed or if it has come into contact with any surface other than skin. If needle reuse is planned, the needle must be recapped after each use. Patients reusing needles should inspect injection sites for redness or swelling and should consult their healthcare provider before initiating the practice and if signs of skin inflammation are detected.

Before syringe reuse is considered, it should be determined that the patient is capable of safely recapping a syringe. Proper recapping requires adequate vision, manual dexterity, and no obvious tremor. The patient should be instructed in a recapping technique that supports the syringe in the hand and replaces the cap with a straight motion of the thumb and forefinger. The technique of guiding both the needle and cap to meet in midair should be discouraged, because this frequently results in needle-stick injury.

The syringe being reused may be stored at room temperature. The potential benefits or risks, if any, of refrigerating the syringe in use or of using alcohol to cleanse the needle of a syringe are unknown. Cleansing the needle with alcohol may not be desirable, because it may remove the silicon coating that makes for less painful skin puncture.

SYRINGE ALTERNATIVES — Insulin can be given with jet injectors that inject insulin as a fine stream into the skin. These injectors offer an advantage for patients unable to use syringes or those with needle phobias. A potential advantage may be a more rapid absorption of short-acting insulin. However, the initial cost of these injectors is relatively high, and they may traumatize the skin. They should not be viewed as a routine option for use in patients with diabetes.

Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle. In many patients (e.g., especially

those who are neurologically impaired and those using multiple daily injection regimens), these devices have been demonstrated to improve accuracy of insulin administration and/or adherence.

Low-dose pens that can deliver insulin in half-unit increments are also available.

Insulin delivery aids (e.g., nonvisual insulin measurement devices, syringe magnifiers, needle guides, and vial stabilizers) are available for people with visual impairments. Information about these products is available in the American Diabetes Association's annual diabetes resource guide.

INJECTION TECHNIQUE

Dose preparation

Before each injection, the insulin label should be verified to avoid injecting an incorrect insulin. The hands and the injection site should be clean. For all insulin preparations, except rapid- and short-acting insulin and insulin glargine, the vial or pen should be gently rolled in the palms of the hands (or shaken gently) to resuspend the insulin. An amount of air equal to the dose of insulin required should first be drawn up and injected into the vial to avoid creating a vacuum. For a mixed dose, putting sufficient air into both bottles before drawing up the dose is important. When mixing rapid- or short-acting insulin with intermediate- or long-acting insulin, the clear rapid- or short-acting insulin should be drawn into the syringe first.

After the insulin is drawn into the syringe, the fluid should be inspected for air bubbles. One or two quick flicks of the forefinger against the upright syringe should allow the bubbles to escape. Air bubbles themselves are not dangerous but can cause the injected dose to be decreased.

Injection procedures

Injections are made into the subcutaneous tissue. Most individuals are able to lightly grasp a fold of skin, release the pinch, then inject at a 90° angle. Thin individuals or children can use short needles or may need to pinch the skin and inject at a 45° angle to avoid intramuscular injection, especially in the thigh area. Routine aspiration (drawing back on the injected syringe to check for blood) is not necessary. Particularly with the use of insulin pens, the needle should be embedded within the skin for 5 s after complete

depression of the plunger to ensure complete delivery of the insulin dose.

Patients should be aware that air bubbles in an insulin pen can reduce the rate of insulin flow from the pen; underdelivery of insulin can occur when air bubbles are present, even if the needle remains under the skin for as long as 10 s after depressing the plunger. Air can enter the insulin pen reservoir during either manufacture or filling if the needle is left on the pen between injections. To prevent this potential problem, avoid leaving a needle on a pen between injections and prime the needle with 2 units of insulin before injection.

If an injection seems especially painful or if blood or clear fluid is seen after withdrawing the needle, the patient should apply pressure for 5–8 s without rubbing. Blood glucose monitoring should be done more frequently on a day when this occurs. If the patient suspects that a significant portion of the insulin dose was not administered, blood glucose should be checked within a few hours of the injection. If bruising, soreness, welts, redness, or pain occur at the injection site, the patient's injection technique should be reviewed by a physician or diabetes educator. Painful injections may be minimized by the following:

- Injecting insulin at room temperature.
- Making sure no air bubbles remain in the syringe before injection.
- Waiting until topical alcohol (if used) has evaporated completely before injection.
- Keeping muscles in the injection area relaxed, not tense, when injecting.
- Penetrating the skin quickly.
- Not changing direction of the needle during insertion or withdrawal.
- Not reusing needles.

Some individuals may benefit from the use of prefilled syringes (e.g., the visually impaired, those dependent on others for drawing their insulin, or those traveling or eating in restaurants). Prefilled syringes are stable for up to 30 days when kept in a refrigerator. If possible, the syringes should be stored in a vertical position, with the needle pointing upward, so that suspended insulin particles do not clog the needle. The predrawn syringe should be rolled between the hands before administration. A quantity of syringes may be premixed and stored. The effect of premixing of insulins on glycemic control

should be assessed by a physician, based on blood glucose results obtained by the patient. When premixing is required, consistency of technique and careful blood glucose monitoring are especially important.

Injection site

Insulin may be injected into the subcutaneous tissue of the upper arm and the anterior and lateral aspects of the thigh, buttocks, and abdomen (with the exception of a circle with a 2-inch radius around the navel). Intramuscular injection is not recommended for routine injections. Rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Rotating within one area is recommended (e.g., rotating injections systematically within the abdomen) rather than rotating to a different area with each injection. This practice may decrease variability in absorption from day to day. Site selection should take into consideration the variable absorption between sites. The abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks. Exercise increases the rate of absorption from injection sites, probably by increasing blood flow to the skin and perhaps also by local actions. Areas of lipohypertrophy usually show slower absorption. The rate of absorption also differs between subcutaneous and intramuscular sites. The latter is faster and, although not recommended for routine use, can be given under other circumstances (e.g., diabetic ketoacidosis or dehydration).

Other considerations

Whenever possible, insulin should be self-administered by the patient. In the case of children, the proper age for initiating this depends on the individual developmental level of the child as well as family and social circumstances. It should not be delayed beyond adolescence. In the case of the visually impaired, mechanical aids are available to ensure accuracy. Where this is insufficient, the syringes may be prefilled periodically by a relative, friend, home health aide, or visiting nurse and the dose may be self-injected. The latter strategy can also be applied to some individuals with borderline dexterity or arithmetical skills. For patients who are completely independent in insulin administration, it is still advisable to have a family member knowledgeable in the technique in case of emergency.

PATIENT MANAGEMENT

Dosing

The appropriate insulin dosage is dependent on the glycemic response of the individual to food intake and exercise regimens. For virtually all type 1 patients and many type 2 patients, the time course of insulin action requires three or more injections per day to meet glycemic goals. Type 1 patients and some type 2 patients may also require both rapid- or short- and longer-acting insulins. A dosage algorithm suited to the individual's needs and treatment goals should be developed with the cooperation of the patient. The timing of the injection depends on blood glucose levels, food consumption, exercise, and types of insulin used. Variables in insulin action (e.g., onset, peak, and duration) must be considered.

Rapid-acting insulin analogs should be injected within 15 min before a meal or immediately after a meal. The most commonly recommended interval between injection of short-acting (regular) insulin and a meal is 30 min. Eating within a few minutes after (or before) injecting short-acting insulin is discouraged because it substantially reduces the ability of that insulin to prevent a rapid rise in blood glucose and may increase the risk of delayed hypoglycemia. Guidelines should be set by the physician for the suggested interval between insulin injection and meal time based on factors such as blood glucose levels, site of injection, and anticipated activity during the interval.

Self-monitoring

Whenever possible, self-monitoring of blood glucose (SMBG). Insulin dosage adjustments should be based on blood glucose measurements. SMBG is extremely valuable in patients who take insulin because they experience day-to-day variability in blood glucose levels. This variability is influenced by differences in insulin absorption rates, insulin sensitivity, exercise, stress, rates of food absorption, and hormonal changes (e.g., puberty, the menstrual cycle, menopause, and pregnancy). Illness, traveling, and any change in routine (e.g., increased exercise and a different diet during vacation) may require more frequent SMBG under the guidance of a physician. Travel through three or more time zones requires special advice regarding insulin administration. During illness, it is im-

portant that insulin be continued even if the patient is unable to eat or is vomiting. When accompanied by hyperglycemia, a positive urine or blood test for ketones during illness indicates a need for extra, not less, insulin. Health professionals should obtain information regarding blood glucose values whenever patients need assistance in handling illness or stress.

Hypoglycemia

Excess insulin is a common cause of hypoglycemia. Hypoglycemia may also result from a delayed or missed meal, decreased carbohydrate content of a meal, increased physical activity, or increased insulin absorption rates (e.g., as a result of increased skin temperature due to sunbathing or exposure to hot water). All insulin-requiring individuals should be instructed to carry at least 15 g carbohydrate to be eaten or taken in liquid form in the event of a hypoglycemic reaction. Family members, roommates, school personnel, and coworkers should be instructed in the use of glucagon in those with type 1 for situations when the individual cannot be given carbohydrate orally. All insulin users should carry medical identification (e.g., a bracelet or wallet card) that alerts others to the fact that the wearer uses insulin.

SUMMARY — The injection of insulin is essential for management of patients with type 1 diabetes and may be needed by patients with type 2 diabetes for intermittent or continuous glycemic control. The species and dosage of insulin used should be consistent, and the patient's injection technique should be reviewed periodically with the diabetes care team. The effective use of insulin to obtain the best metabolic control requires an understanding of the duration of action of the various types of insulin and the relationship of blood glucose levels to exercise, food intake, intercurrent illness, certain medications, and stress; SMBG; and learning to adjust insulin dosage to achieve the individualized target goals established between the patient, family, and diabetes care team.

Bibliography

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