

Effect on Insulin upon Storage in Extreme Climatic Conditions (Temperature and Pressure) and Their Preventive Measures

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Abstract

Keywords

- insulin
- climatic changes
- therapeutic efficacy

Insulin is a naturally occurring hormone secreted by the pancreas. Insulin is required by the body cells to remove and use glucose from the blood. The insulin and its various analogues are essential in management of type 1 diabetes mellitus. This study has been done to analyze how variation in various storage conditions and climatic changes causes change in therapeutic efficacy. Storage condition affects the stability of insulin as observed in a study in which insulin stored at temperature between 32 and 37°C showed 14 to 18% decrease in its potency and could not cause a significant decrease in blood sugar level when compared with those receiving insulin stored at 5°C. This work was done with the aim of finding the effect of climatic changes and storage condition on efficacy of insulin.

Introduction

Insulin

Insulin is a naturally occurring hormone secreted by the pancreas. Insulin is required by the body cells to remove and use glucose from the blood. Cells use glucose to produce energy that they need to carry out their functions. Researchers first gave an active extract of the pancreas containing insulin to a young diabetic patient in 1922, and the Food and Drug Administration (FDA) first approved insulin in 1939. Currently, insulin used for treatment is derived from beef and pork pancreas as well as recombinant (human-made) technology. The first recombinant human insulin was approved by the FDA in 1982. People with diabetes mellitus (DM) have a reduced ability to take up and use glucose from the blood, and as a result, the glucose level in the blood rises. In type 1 diabetes, the pancreas cannot produce enough insulin. Therefore, insulin therapy is required. In type 2 diabetes, patients produce insulin, but cells throughout the body do not respond normally to the insulin. Nevertheless, insulin also may be used in type 2 diabetes to overcome the resistance of the cells to insulin. By increasing the uptake of glucose by cells and reducing the concentration of glucose in the blood, insulin prevents or reduces

the long-term complications of diabetes, including damage to the blood vessels, eyes, kidneys, and nerves. Insulin is administered by injection under the skin (subcutaneously). The subcutaneous tissue of the abdomen is preferred because absorption of the insulin is more consistent from this location than subcutaneous tissues in other locations.^{1–3}

Effect of Temperature on Insulin

Insulin being a protein is liable to get denatured. Insulin due to its colloidal nature is highly prone to precipitation induced by changes in the environmental pH and temperatures. Instability in the proteins is attributed to the differential level of changes in the protein structure. This happens when exposed to variable physicochemical changes in the environment. Insulin is very sensitive to sunlight and extreme temperatures resulting in its degradation. Degradation can be broadly of two types: physical and chemical. Physical degradation (e.g., aggregation, adsorption, etc.) occurs when the physical state of the protein undergoes irreversible changes without any change in its covalent structure. In contrast, chemical degradation refers to a change in the covalent structure of the protein. The relative susceptibility of insulin analogues to undergo chemical degradation depends on their

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thermodynamic property and tendency to undergo transient conformational changes. Both physical and chemical degradations could result in loss of bioactivity of insulin. Hence un-opened vials of insulin have to be stored in a controlled environment of 2 to 8°C in a refrigerator protected from light. In a pilot study conducted in JIPMER, Puducherry, by Gitanjali et al, it was found that among 131 diabetic patients, 59% of them had hyperglycemia, indicating poor glycemic control. Out of these hyperglycemic patients, 56% were storing the insulin vials at room temperature.

Recommendation of Storage Conditions

Also, the manufacturer recommendations on the storage and shelf life of opened insulin vial are different among different companies. Eli Lilly (Gurgaon, India) recommends that opened insulin vials can be stored either refrigerated (2–8°C) or at room temperature less than 30°C, without losing biological activity for a period of 31 days. According to Novo Nordisk, (Bangalore, India) and Biocon (Bangalore, India) opened vials can be stored for a period of 6 weeks, when stored at room temperature not more than 25°C and should not be refrigerated. Exposure to higher temperatures other than that recommended during storage as well as while using may degrade insulin by hydrolysis or other mechanisms. Even short periods of exposure of insulin to higher temperatures can cause adverse effects that aggravate the challenges caused by interruption in the cold chain of delivery, distribution, and storage. Exposure to light and high temperatures results in insulin degradation, which leads to formation of transformation products (deaminated insulin, covalent dimers, and higher oligomers) and increased fibril formation, which is a potential cause of loss in biological potency.^{4–6,7} The measure of activity of insulin expressed in terms of the amount required to produce a defined effect (reduction in blood glucose) is called the *potency of insulin*. It is affected by exposure to light, temperature, and vibration. Inappropriate storage of insulin can also decrease insulin's potency, which could contribute to poor response to the insulin. A case report published in *British Medical Journal* (2009) by Pryce described a case of an 11-year-old girl on insulin pump who presented with diabetic ketoacidosis (DKA) because of reduced potency of insulin on exposure to heat and sunlight. A study done by Gitanjali et al⁷ in Puducherry, India, where insulin concentration was measured by HPLC, showed a decrease in the concentration of regular insulin in vials and biphasic formulations by 14 to 18% and 11 to 14%, respectively, in vials stored at 32°C and 37°C when stored for 28 days. There was a considerable reduction in the blood glucose with respect to basal glucose at 15, 30, and 60 minutes after insulin injection in rats, but there was no significant reduction in the blood glucose levels in the animals injected with insulin stored at 32°C and 37°C with respect to that stored at 5°C. Most of the insulin stability studies are from western countries where the room temperature is usually within 25°C. In many places in India during summer season, the temperature rises beyond 35°C and certain times beyond 40°C. The patients from the rural areas who lack the facility to store insulin in the refrigerator are advised by the health professionals to store it in a mud

pot where the inside temperature will be a few degrees lower than the room temperature, to provide a near ideal storage environment for insulin to maintain the stability as far as possible. However, during summers, as the room temperature rises, the pot temperature also may rise above 25°C or even beyond 35°C. Therefore, even the insulin stored in a mud pot is not protected from denaturation due to high temperatures during summer. This could be one of the reasons why some patients require comparatively higher doses of insulin and show clinical symptoms of drug resistance.^{8–18} To attain maximum effect of insulin, one must know the ideal storage condition and how to preserve the insulin. For the people with diabetes who use it, insulin is a vital need. It is important to store insulin as directed, so that it remains usable by those who need it. Follow these tips to ensure effective insulin storage.^{19,20}

Protective Measure to Maintain the Shelf Life of Insulin

1. **Keep it cool:** According to the product labels from all three U.S. insulin manufacturers, it is recommended that insulin be stored in a refrigerator at approximately 36 to 46°F. If you are using ice, avoid freezing the insulin. Do not use insulin that has been frozen.
2. **Know its expiration date:** Unopened insulin refrigerated in the ranges described above maintains potency until the expiration date on the package.

Insulin products contained in vials or cartridges supplied by the manufacturers (opened or unopened) may be left unrefrigerated at a temperature between 59 and 86°F for up to 28 days and continue to work. However, an insulin product that has been altered for the purpose of dilution or by removal from the manufacturer's original vial should be discarded within 2 weeks. Insulin contained in the infusion set of a pump device (e.g., reservoir, tubing, catheters) should be discarded after 48 hours. Insulin contained in the infusion set of a pump device and exposed to temperature exceeding 98.6°F should be discarded.

Effect on Insulin on Temperature Extremities (Hot and Cold)

Insulin loses some effectiveness when exposed to extreme temperatures. The longer the exposure to extreme temperatures, the less effective the insulin becomes. This can result in loss of blood glucose control over time. Keep insulin away from direct heat and out of direct sunlight. Under emergency conditions, you might still need to use insulin that has been stored above 86°F. When properly stored insulin becomes available again, the insulin vials that have been exposed to these extreme conditions should be discarded and replaced as soon as possible. Elevated temperature in countries such as the African continents can severely degrade the insulin. According to findings by Mjota in Kenya 2008, there is a small proportion of patients storing insulin by refrigerators due to poverty. The cultural practices and socioeconomic

and political challenges that unsettle people make most DM patients to live in very pathetic housing conditions, street families in particular. This makes correct home storage practice of insulin to be practically impossible for the low-income earners and the poverty-stricken class that constitutes about 70% of the urban population. The effect of storing insulin in suboptimal conditions is a commonplace for the majority of insulin using DM patients in urban Kenya, which goes a long way in the effectiveness of therapy being suboptimal. Most insulin users from a low economic class use pot with sand in water contraptions from a random survey on storage in sub-Saharan region medical outpatient clinics. Twenty-six to 77% DM patients have refrigerators for storing insulin. Insulin outside the refrigerator should be kept cool within 12 to 30°C; it should not be allowed to freeze. If stored between 2 and 8°C, it will remain stable until the expiry date. According to Garry Gilles 2009 clinical review, insulin used daily should be kept at room temperature and remains potent and stable for 28 days also comfortable for injection. However, it is good to have extra supply of insulin in the refrigerator as a buffer stock for any eventuality of loss of potency, damage, or loss. Most physicians are not aware of the real effectiveness of insulin once it is opened. Also, three pharmaceutical companies that supply insulin reveal different storage indications for every type 9 of insulin they produce, depending on the particular formulation, method of manufacture, its container, and ambient storage conditions. The storage of unopened vials, cartridges, or prefilled insulin delivery systems should be done at recommended temperatures, so that they can be used until the expiration date. Insulin. In-use insulin can be kept nonrefrigerated for up to 28 days away from direct heat and light, at controlled room temperature.^{21–24}

Challenges of Insulin Storage in Cold Climatic Conditions

The diabetes pandemic knows no geographical boundaries. Along with modernization, diabetes has reached the remote areas such as Himalayan areas of Lahaul-Spiti (cold desert) and Kinnaur, in the Indian state of Himachal Pradesh, located in the upper region of the Western Himalayas. Inhabited predominantly by the tribal population, this district is located at an altitude of 8,000 to 16,000 ft above sea level. The unique geographic conditions and far and scarce medical service impose great challenges for the management of diabetes in this part of the world. Dietary patterns, which include drinking of copious amounts of liquor, locally distilled from barley, dependence on local nonvegetarian foods, and scarce availability of fruits and vegetables, go against routine diabetes diet prescriptions.

These tribal areas remain cutoff from rest of the country at least for 3 to 4 months in the winters with interrupted supply of electricity. People with diabetes usually seek specialized diabetic care from the state capital, located 250 to 500 km away (16–24 hours drive through one of the most treacherous roads in the world). The challenges posed by diabetes on the top of the world have been addressed innovatively.

Three patients from tribal areas living at an “altitude” of 9,500; 12,000; and 14,500 ft at a distance of 250 and 450 km

from the state capital were prescribed insulin for uncontrolled blood glucose. The unique geographic condition of these areas, and peculiar social habits and dietary patterns of the inhabitants, imposes unique challenges for the use of insulin in this part of the world. Besides having the danger of hypoglycemia, however, the biggest challenge remains how to store insulin in the winter when outside temperature dips to –30°C mostly during midnight and inside temperature of the living room goes up to 40 to 70°F due to constant burning of “Bukhari” made up of iron. Difficulty in access and storage of insulin creates a need for crafting a locally relevant, improvised solution for the same. In winters, people of these areas wear warm clothes made up of sheep and yolk wool to protect from severe cold. One such unique cloth people wear in the winter is an abdominal binder, which measures 2 to 3 ft in width and 5 to 15 ft in length. Seeing a woman wearing the traditional attire in a hospital, an innovative idea of insulin storage that was “locally” relevant and easily acceptable struck in mind: “It was thought to store insulin in multiple layers of abdominal binder, which prevents it from freezing in winter” and was discussed with patients on their follow-up visit. They were advised to wrap the insulin vials and/or pens in “multiple layers” in the abdominal binder (where the temperature recorded was between 5 and 10°C).

The success of this practice was evident from the normal HbA_{1c} values and the smiles on their faces, when they visit state capital for routine medical consultation. Normally, we think of people living with diabetes at normal altitude, not of those living in the extreme conditions of the world; one like those living “in the Himalayas” and this improvised method of insulin storage may be of great value for those diabetic patients living at the top of the world(► Fig. 1).

As the recent cold waves in North America and Europe show, no part of the world is immune to extremes of temperature. Best practice sharing is required between people living with, and caring for, diabetes, in other, similarly inhospitable regions of the world, to help improve the quality of care.^{25–28}

Changes in the Atmospheric Pressure

Changes in atmospheric pressure that occur during airplane travel may lead to insulin pumps unintentionally delivering insulin while flying, as per recent data. After becoming aware of 50 cases in which patients with type 1 diabetes using insulin pumps developed recurrent hypoglycemia during commercial air travel, researchers in Australia sought to investigate the effect that atmospheric pressure has on insulin pumps. They included five Animas 2020 pumps (IR1200/2020) and five Medtronic Paradigm pumps (1.8 mL cartridge) with 60-cm infusion systems in their analysis.

Effect of Pressure Changes

To gauge the effect that changes in pressure may have in the pumps, the researchers conducted a hypobaric chamber study in which they mimicked normal flight in a commercial airliner, as well as abnormal flight with catastrophic decompression. Results revealed that during ascent, from 760 to



Fig. 1 Abdominal binder used for the protection of Insulin.

560 mm Hg, the Animas pumps delivered 0.776 excess units of insulin ($p < 0.000001$), whereas the Medtronic pumps delivered 0.709 excess units of insulin ($p < 0.000001$). During descent, from 560 to 760 mm Hg, the pumps delivered 0.663 units less than expected and the Medtronic pumps delivered 0.533 units less than expected, as per the researchers. Catastrophic depressurization, a decrease in pressure from 760 to 260 mm Hg during 1 minute, however, led to the delivery of more than eight excess units due to plunger movement. In a second pressure study, the researchers examined the pumps' insulin delivery during actual flight of a Boeing 767-338. Findings from this analysis showed that Animas pumps delivered 1.37 units of excess insulin (0.685% of cartridge volume; $p < 0.001$) and Medtronic pumps delivered 1.01 units of excess insulin (0.561% of cartridge volume; $p < 0.001$) during ascent. In contrast, during descent, insulin appeared to be sucked back into pumps, leading to deficits of 0.87 and 0.58 units of insulin for Animas and Medtronic pumps, respectively. The researchers also performed a bubble study in which they found gas bubbles in all syringes after 50-mm Hg decreases in pressure. Bubbles disappeared after an atmospheric pressure of 760 mm Hg was restored. Changes in bubble size were consistent with Boyle's law, they said. Plunger movement was also examined. According to the researchers, the Animas cartridge plunger moved after a 273.48-mm Hg decrease in pressure. Because of their findings, the researchers said the insulin pump cartridge should contain only 1.5 mL of insulin, and patients should disconnect the pump before takeoff. When at cruising altitude, remove the cartridge from the pump and ensure that there are no air bubbles before reconnecting. After landing, disconnect the pump, prime the line with two units, and then reconnect. If cabin decompression occurs, disconnect the pump.

Conclusion

It could be thus concluded that insulin is a lifesaving therapy in management of DM type 1. Insulin has to be stored with caution as extremes of temperature or change in altitude can lead to its decomposition and reducing its efficacy.

Conflict of Interest

None declared.

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