Temperature and blood glucose management

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The weather affects us all, particularly ambient temperature. Heat and cold may have significant effects on people with diabetes, even, rarely, with fatal consequences.

Heat

'I'd heard that having a hot bath can sometimes decrease blood glucose quite rapidly, but had never believed it... until last night. At 10.12 my reading was 6.7, and I knew it was on the way down and probably should have had something to eat, but instead I decided to have a quick bath. Whilst in the tub I started to feel a little bit panicky, and eventually very irritable ... I realized I was having a baaaaad hypo, so got out (carefully) and took a reading: it was 2.2!'[1]

Heat increases cutaneous circulation. At 30ºC room temperature insulin absorption after injection was three to five times greater than at 10ºC, with correspondingly lower blood glucose.[2]

Heat and hypoglycaemia both cause sweating and lethargy leading to delayed recognition of hypoglycaemia. Self-blood-glucose monitoring (SMBG) should increase in hot weather.

Warming the site of continuous subcutaneous insulin infusion (CSII) after a 0.15 unit/kg dose of Humalog or Novorapid significantly reduced glucose excursion after a standard meal.[3]

Hyperglycaemic patients are often polyuric so need extra water to prevent dehydration in the heat. Sugary drinks worsen matters.

Cold

Cold slows insulin absorption. Applying a cold pack to the site of an insulin overdose delays the hypoglycaemic effect. When the site/patient warms up the insulin will be absorbed, risking hypoglycaemia, sometimes hours later.

Hypoglycaemia and hypothermia

Hypoglycaemia and cold are a potentially lethal combination.

A patient with an insulin-producing tumour 'suffered frequent episodes of pronounced hypoglycaemia… During these episodes he felt warm but his skin was sweaty and cold to the touch. Temperatures… were… as low as 34ºC. The association of hypothermia with hypoglycaemia in this patient was confirmed on each occasion by a plasma glucose concentration <2mmol/L... Within an hour of correcting his plasma glucose concentration his body temperature had returned to normal.'[4]

Non-diabetic subjects shivered unclothed in 18–19ºC. Insulin was infused to induce hypoglycaemia. 'Shivering stopped as plasma glucose fell below 2.5mmol/L during insulin infusion and the subjects said they no longer felt cold. During hypoglycaemia in the cold peripheral vasodilatation and sweating occurred, skin temperature fell by up to 0.8ºC and core temperature fell below 35ºC, so subjects had to be rewarmed. Recovery of plasma glucose after hypoglycaemia in the cold was impaired at low body temperatures, but shivering was restored within seconds when glucose was given intravenously.'[5] Glucose is essential for recovery from hypothermia.

Cold causes vasoconstriction causing difficulty in obtaining capillary glucose samples and risking inaccurate results.

The effects of temperature on liquid medications

An 11-year-old girl with type 1 diabetes using CSII was admitted with diabetic ketoacidosis (DKA). 'Two days before admission she had disconnected the pump for swimming… The pump had been left on a table by the side of a pool in direct sunlight on a hot Australian summer's day (35ºC). Later in the day, after the pump had been reconnected, the patient's blood sugar began to rise.'[6]

Store insulins, glucagon-like-peptide (GLP1) agonists, and glucagon in a refrigerator at 2–8ºC before use. Do not freeze them – this risks inactivation.

Insulin vials in use can usually be refrigerated but this does not apply to most insulin cartridges or prefilled pens (cooling may impair pen function). Remove and safely discard needles from pens after use to prevent leakage or air aspiration. Once in use, safe storage times vary (Table 1). In ambient temperatures exceeding manufacturers' guidance, keep injectable medicines in a cooling bag specifically designed for the purpose. Diabetes UK sells these, as do other sources.

Drugs supplied in kits (e.g. glucagon, prolonged release exenatide) should be used immediately after mixing. Once mixed they cannot be stored – discard them safely if unused.

Do not expose the drugs or kits to direct heat or light. After removing the needle, put the cap back on pens. Return pens with visible cartridges to their carton or other dark place.

Two human insulin formulations (regular and biphasic) from each of three different manufacturers were stored at five different temperatures. After 28 days' storage at 32ºC and 37ºC, insulin potency *in vitro* fell by 14–18% for all insulins with no significant fall in test rabbits' glucose compared with those injected with insulin stored at 5ºC.[7] 'The stability of three commercial "fast-acting" insulin analogs, insulin lispro, insulin aspart, and insulin glulisine, was studied at various concentrations of phenolic preservatives (phenol and/or metacresol) during 9 days of incubation at 37ºC… Insulin glulisine was much more stable than the other analogs.'[8]

Insulin pumps and sets are worn on/near skin, and pens may be in a warm pocket. In one study, CSII site skin temperatures were 32.3–36.7ºC. Skin temperature did not affect infusion set occlusion rates.[9] A review of *in vitro* studies of stability and performance of rapid-acting insulin analogues as used in CSII (including 'patch

Drug name	Temperature	Discard after**	Comment
Abasoglar	<30°C	28 days	
Actrapid	<25°C	6 weeks	Do not refrigerate vial in use/carried as spare
Apidra	<25°C	4 weeks	
Humalog insulins including mixtures	<30°C	28 days	
Humulin insulins including mixtures	<30°C	28 days	
Hypurin Bovine and Porcine including mixture	<25°C	28 days	
Insulatard vial	<25°C	6 weeks	Do not refrigerate
Insulatard pen	<30°C	6 weeks	
Insuman including mixtures	<25°C	4 weeks	
Insuman Infusat		2 weeks	During use in pump
Lantus	<25°C (5ml vial) <30°C (10ml vial, pen)	4 weeks	
Levemir	<30°C	6 weeks	
Novomix 30	<30°C	4 weeks	
Novorapid	<30°C	4 weeks	Do not refrigerate vial in use/carried as spare
Novorapid PumpCart	<37°C in use in pump <30°C carried as spare	2 weeks carried as spare	After carriage as spare may be used in Accu-chek Insight pump for up to 7 days at <37°C
Tresiba	<30°C	8 weeks	Flextouch pen in use can be stored in refrigerator at 2–8°C
Xultophy (Tresiba + liraglutide)	<30°C	21 days	
Exenatide prolonged release	<30°C kit only	4 weeks	Once mixed use immediately
Exenatide	<25°C	30 days	
Liraglutide	<30°C / 2–8°C fridge	1 month	
Lixisenatide	<30°C	14 days	
Glucagon	<25°C kit only	18 months	Once mixed use immediately

Check up-to-date summary of product characteristics (SPCs) or patient information leaflet for details for individual insulins. www.medicines.org.uk/emc/ [accessed 22 July 2015]

*Do not refrigerate pens/cartridges in use or carried as a spare unless otherwise stated. Vials in use can be refrigerated unless otherwise stated.
**Discard insulin in insulin pump infusion sets (reservoir, tubing, catheter) after 48 hours unless manufacturers state otherwise.

Table 1. Storage temperatures of injectable diabetes drugs in use or carried as spare*

pumps') suggests that these insulins are 'relatively resistant to degradation at high temperatures [studied at 37ºC for 2–14 days]'. Other factors such as movement/agitation may cause variable insulin precipitation and set occlusion *in vivo*.[10]

The US Food and Drug Administration (FDA) states: '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 98.6ºF [37ºC] should be discarded.'[11]

Liquids subjected to rising temperatures form bubbles. This occurred reproducibly in tubing and cartridge as Novorapid at 4ºC was put in two different manufacturers' pumps at room temperature which were then warmed to 37ºC. Wait until refrigerated insulin is at room temperature before use to reduce bubbles in pumps and pain on injection.[12]

Blood glucose measurement

In venous blood in a fluoride tube left uncentrifuged at room temperature, plasma glucose concentration at 48 hours was 96% of baseline vs 101% when centrifuged and placed on ice within 2 hours. While this may not seem a significant difference, it could be if relying on a single result for diagnosis of diabetes (7.1mmol/L becomes 6.8).[13]

Ambient temperature may affect capillary blood glucose meters. This was a problem in the past but nowadays many meters cover a wide temperature range. Storage at high temperatures or humidity may adversely affect readings in different ways for different test strips. Do not freeze strips. For example, temperature ranges for Abbott Freestyle meters vary from 4–10 to 40–50ºC in use and -20 to 60ºC for storage; glucose test strips in use 15–40ºC and 4–30ºC in storage.[14]

Continuous glucose monitoring sensors are affected by temperature. For example, the storage range for Medtronic's Enlite sensor is quoted as 2–30ºC.[15]

Summary

Heat increases insulin absorption, risking hypoglycaemia. Sweating may be attributed to heat, delaying glucose rescue. Controlled warming of CSII sites may improve post-prandial glucose levels. Sugary people need to maintain good hydration. Cold slows insulin absorption. Hypothermia impairs recovery from hypoglycaemia. Hypoglycaemia prevents recovery from hypothermia. Give glucose fast.

Freezing or over-heating insulin impairs potency, even causing DKA. More clinical studies are needed to clarify effects of temperature on insulin in use within pump systems.

Temperature extremes may impair the accuracy of SMBG.

Warn patients about the possible effects of temperature upon their glucose control. Remind them to read the instructions with medicines or equipment – and don't forget to do so yourself!

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Declaration of interests

There are no conflicts of interest declared.

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