New insulin analogues and perioperative care of patients with type 1 diabetes

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Short title: New insulin analogues

Summary

While insulin remains the mainstay of managing type 1 diabetes, much has changed over the last 15 years. These changes should help managing patients with type 1 diabetes during the perioperative period. More flexible insulin therapy has three components: (1) basal, (2) prandial and (3) corrective. Many patients, particularly younger patients, are using genetically modified recombinant human insulin analogues. Two of these analogues, aspart and lispro insulin, are rapid acting with faster onset and offset than subcutaneous regular insulin, allowing both prandial and corrective boluses. Other insulin analogues, particularly glargine, and possibly detemir, have a flat profile of up to 24 hours, providing improved basal insulin delivery. Basal insulin can also be provided by a continuous subcutaneous infusion of rapid acting insulin via a computerized pump that also provides boluses on demand. There is little evidence to help choose the best management of patients with type 1 diabetes during surgery. Some authors still recommend glucose-potassium-insulin infusions for all patients with type 1 diabetes. We challenge this approach given the apparent flexibility of the newer insulin analogues and delivery systems. We suggest that for many procedures, patient's usual regimens can be maintained in the perioperative period, providing less disruption and, possibly, greater safety. Both hyperglycaemia and hypoglycaemia reflect poor management; we suggest a target range of 5 to 10 mmol/L. The importance of frequently measuring blood glucose and appropriate responses cannot be overemphasized.

Introduction

In 2000, Hopkins and Hunter wrote in an editorial that "…Every trained anaesthetist should be able to manage patients competently with any form of diabetes…" but that "…Perioperative management of diabetic patients is often suboptimal: this is inexcusable...."[1]. Managing patients with type 1 diabetes has changed over the last 15 years, particularly during the first years of the new century, with greater understanding of the importance of blood glucose control and advances in insulin pharmacology, delivery systems, and monitoring devices[2,3]. Over the same period there have been marked changes in anaesthesia and surgery often with day of surgery admission. We review changes in managing type 1 diabetes and how these changes may affect the perioperative period.

Type 1 diabetes

Type 1 diabetes is a chronic, life-long disorder caused by autoimmune destruction of pancreatic beta cells, resulting in insulin deficiency[4]. The onset is usually during teenage years, but can occur at any time, including at extremes of age. In Australia and New Zealand, the incidence of type 1 diabetes appears to be higher than many other countries, with at least 130,500 patients affected in Australia and 15,000 in New Zealand[5]. There are 23 new cases per year per 100,000 population in the 0 to 14 years age group, 17 per 100,000 population in the 15 to 19 age group, 13 per 100,000 population in the 20 to 30 years age group, and 9 per 100,000 population in the 30 years plus age group[6].

Treating type 1 diabetes requires therapeutic insulin. Over the last 15 years, the management of type 1 diabetes has become increasingly intensive but more flexible, attempting to provide physiological insulin replacement. Older, less

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intensive, diabetes management utilised twice daily insulin injections and required fixed meal times[7]. Insulin dosing is now matched to carbohydrate intake, exercise and other factors affecting blood glucose levels such as stress, intercurrent illness and growth spurts[2,8]. More recent intensive, but flexible, insulin therapy has three components: (1) 24 hour basal, (2) prandial boluses, and (3) corrective boluses for acute hyperglycaemia[8,9].

The resulting multiple daily injections of insulin are now often with pen devices rather than with traditional syringes[2,3]. As an alternative to multiple injections, continuous subcutaneous insulin infusion (CSII) with electronic pumps may provide similar, or improved, glycaemic control with fewer episodes of hypoglycaemia[10]. An essential feature of intensive diabetes management is frequent monitoring of capillary (finger prick) blood glucose levels[2,11].

New insulin analogues

Insulin has two main actions that authors early last century described as excitatory and inhibitory[4] . The excitatory actions include stimulating glucose uptake by muscle, liver, fat and other cells and lipid synthesis. The inhibitory actions include suppressing gluconeogenesis, lipolysis, glycogenolysis, ketogenesis, and proteolysis[4,12]. Gluconeogenesis is an important cause of hyperglycaemia in type 1 diabetes if insulin therapy is inadequate[4].

Endogenous insulin is a protein hormone secreted by pancreatic beta-islet cells as a monomer containing two amino acid chains: the A chain and the B chain[2,12]. The plasma half-life of endogenous insulin is about five minutes, with over 50% cleared

by the liver in a first pass through the portal circulation[12]. In people without diabetes there are two components to insulin secretion: basal insulin secretion and surges associated predominantly with increased blood glucose concentration[2,12]. Replicating the profile of physiological insulin release and activity is the "Holy Grail" of exogenous insulin therapy for people with type 1 diabetes[7] . While still well short of this ideal, new therapeutic insulin analogues are substantially closer to physiological profiles than older types of insulin still widely used in hospitals[3,7].

Until recently, the most commonly used therapeutic insulin has been regular insulin[2,7]. Examples are Actrapid (Novo Nordisk, Baulkham Hills, NSW) and Humulin R (Eli Lilly, West Ryde, NSW). Like endogenous insulin, an intravenous bolus of regular insulin has a plasma half-life of about five minutes but a duration of action of up to an hour due to prolonged binding at receptors[12]. Insulin has a molecular weight of 6500 daltons and is therefore freely filtered at the glomerulus. Like endogenous insulin, therapeutic insulin is metabolised by the liver and the kidney but the usual high first pass metabolism from the portal circulation is bypassed, giving the kidneys a more prominent role[12] . When administered subcutaneously, regular insulin has an onset of action of 30 to 40 minutes, peaking between two and five hours and lasting six to eight hours[2,12]. The relatively delayed onset and prolonged duration of action of regular insulin is due to insulin forming hexamers in subcutaneous tissue creating a "slow release" depot for insulin monomers. Once in the plasma, therapeutic insulin from subcutaneous injection is cleared at the same rate as insulin administered intravenously [2,12].

For many years, therapeutic insulin was extracted and purified from pigs or cattle which have slightly different B chains to human insulin[12]. Therapeutic insulin is measured in units where one unit is the amount of insulin required to decrease the blood sugar in a two kg rabbit to 2.5 mmol/L within five hours [12] . In the 1980's pharmaceutical companies introduced human insulin, produced by recombinant DNA technology from *E Coli* bacteria or yeast[3,7]. The combination of patient demand for insulin products that would allow a more flexible lifestyle[11] and positive results from studies such as the Diabetes Complications and Control Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study [2] led pharmaceutical companies to develop a wider range of insulin analogues[2].

Newer insulin analogues such as insulin aspart (Novorapid, Novo Nordisk, Baulkham Hills, NSW) and lispro (Humalog, Eli Lilly, West Ryde, NSW) have more rapid uptake and shorter duration of action than subcutaneous regular insulin [2,7]. The new analogues have B chain changes, through genetic modification, that prevent insulin hexamers forming in subcutaneous tissues, thus enhancing diffusion of the insulin monomers into plasma. Aspart and lispro insulin have an onset of about 10 to 15 minutes, peak action at about one hour and duration of action of about four hours[2,7]. Each of these times is about half that of subcutaneous regular insulin. Clearance of these insulin analogues is the same as regular and endogenous insulin; therefore, there is no added benefit in administering aspart and lispro intravenously. The pharmacokinetics of subcutaneous aspart and lispro boluses provide a more physiological profile, making aspart and lispro better suited for prandial and corrective boluses than subcutaneous boluses of regular insulin[2,10].

Comment [RT1]: This does not follow, whilst the first statement is true that does not mean that there is no added benefit to IV administration. Holleman and Hoekstra. Insulin lispro. N Engl J Med (1997) vol. 337 (3) pp. 176-83} in Figure 3 show clearly that the peak blood levels after IV administration is about 20-30 minutes..

Also in hypoperfusion states this may be delayed even further.

What would be a better statement would be to say. "As the onset time is short and the clearance is the same as for Intravenous insulin (need ref) then there is minimal additional benefit in administering ….". "Situations where hypoperfusion may be present may delay the onset"

The most common basal insulin for many years was neutralised protamine Hagedorn (NPH) insulin, where regular insulin is combined with protamine to prolong polymerisation in subcutaneous tissues and delay diffusion into plasma [2,13]. Examples are Protaphane (Novo Nordisk, Baulkham Hills, NSW) and Humulin NPH (Eli Lilly, West Ryde, NSW). NPH insulin has an onset of action of about two hours, a peak between four to ten hours and duration of about 16 hours. Although NPH insulin has been used as a basal insulin, it falls well short of the ideal properties[8,13]. In recent years, new long acting insulin analogues (insulin glargine and detemir) have been developed[3,13 10], to provide an activity profile more similar to basal insulin production in people without diabetes. Glargine insulin (Lantus, Sanofi-Aventis, Macquarie Park, NSW), has been modified, with DNA changes, substituting glycine for asparagine on the A chain and adding two arginine molecules to the B chain, making glargine more acidic and therefore less soluble in the subcutaneous tissues[7,13]. Glargine has onset of action of two hours, with no peak, and lasting 22 to 24 hours[3]. Patients experience improved glycaemic control and fewer hypoglycaemic episodes when using glargine [13]. Detemir (Levimir, Novo Nordisk, Baulkham Hills, NSW) is regular insulin combined with a fatty acid to bind to albumin in the blood stream and delay insulin's access to tissues. It has a one and a half hour onset of action, a slight peak at eight hours and lasts 20 hours [3,13].

Insulin Pumps

Instead of using intermittent injections, some patients with type 1 diabetes prefer to administer their insulin as rapid acting insulin analogues by continuous subcutaneous infusion via a computerised pump[3] . Insulin pumps are pager-sized devices (4 x 6 cm) that are individually programmed for the user[14,15]. They are external devices, not implanted, and have a reservoir with two to three days' supply of

insulin. Insulin is infused via a tiny disposable catheter. The whole infusion set is replaced when the reservoir runs out. The pumps deliver basal insulin at a variable rate to adjust for normal circadian rhythms, while prandial doses are manual boluses based on the carbohydrate content of the meal and the person's estimated insulin needs[14]. The patient can select the dose, or the pump can calculate the dose given the current blood glucose level and the carbohydrate load. The basal rate can be adjusted up or down for periods of low or high activity respectively. The rate can be changed for changes in activity levels and carbohydrate intake[9,15]. Because insulin pumps can deliver small doses accurately, they are suitable for small children, and patients sensitive to insulin: such as those with low body mass index[9]. Recently, pumps with built-in continuous glucose monitors capability have become available, which adds to the attractiveness of these devices for some patients.

Perioperative Management

Surgery often requires patients with type 1 diabetes to fast before the procedure and have changed carbohydrate intake after surgery. The combination of these changes in intake, the effects of anaesthesia and surgery, and associated changes in managing insulin can be complicated by hyperglycaemia, ketosis, or hypoglycaemia[8]. Frequent measuring of blood glucose, and appropriate action with insulin or glucose therapy aims to minimize these complications [16].

Fasting and preoperative management

Preoperative fasting often involves stopping caloric intake for at least 12 hours. In healthy people when hepatic glycogen stores are exhausted, usually after 12 to 24 hours of fasting, the liver uses triglyceride breakdown and ketogenesis to provide an alternative energy supply to the tissues[4]. Even in healthy people, ketones

may be detected after an overnight fast, but more severe ketosis takes days to develop. Acidosis is limited in people without diabetes because endogenous insulin limits ketogenesis[17] and keto-anion levels rarely rise above 1 to 2 mmol/L[17].

In diabetic ketoacidosis, however, hyperglycaemia and increased plasma ketones are related to insulin deficiency[4,17]. The absence of insulin allows increased ketogenesis. Concerns about fasting and withholding insulin leading to ketosis in the perioperative period have led to recommendations for routine use of glucose-insulin infusions (with or without potassium)[18]. However, similar to fasting in healthy people, a fasting patient with diabetes receiving adequate basal insulin therapy is unlikely to experience significant ketosis[4,16,19]. In the past, basal insulin such as NPH insulin has been difficult, because it has a peak in activity often requiring either inadequate dosing or supplemental glucose[4]. If the basal insulin has a little or no peak, as with glargine or detemir or computerized infusion of rapid acting insulin, little, if any, supplemental glucose is needed, because insulin therapy more closely replicates physiological fasting[19].

Day of surgery admission is suitable for patients with stable type 1 diabetes who have a clear management plan[16]. Patients with type 1 diabetes should, however, continue to be scheduled as early as possible on an operating list [16,20] because shorter fasting times make patients with type 1 diabetes less vulnerable, particularly to hypoglycaemia. Patients scheduled for afternoon surgery should have breakfast with an appropriate prandial bolus of short acting insulin. The shorter duration of action of rapid acting insulin analogues may decrease the likelihood of hypoglycaemia before surgery. Basal glargine and levemir insulin (usually given at bedtime) can be taken in

Comment [RT2]: This is in conflict with the stated aim of providing physiological insulin replacement. There is no specific reason why a fasted patient given physiological insulin replacement should be any different to any other patient.

After all several paragraphs before you say; However, similar to fasting in healthy people, a fasting patient with diabetes receiving adequate basal insulin therapy is unlikely to experience significant ketosis"

This is a bit of a cop out to "tradition" which you are trying to overcome.

Perhaps you should say something like " the usual rule of operating on patients with Type 1 Diabetes first on a morning list may no longer be necessary if physiological insulin replacement is given and frequent blood glucose measurements are done"

In fact one could argue the relatively uncontrolled administration of food makes the BGL harder to manage compared with the relatively stable fasting state!

the usual dose, unless a patient has a tendency to low early morning blood glucose, in which case the basal insulin could decreased by 20%[9]. No short acting insulin is required in the morning if there is no meal. The blood glucose should be checked hourly from when the patient wakes. If the blood glucose is falling significantly, it should be checked more frequently.

Patients who are still using the older insulin preparations such as NPH, alone or in combination with regular insulin, need more traditional management, with a portion (usually half) of the morning dose being given[9,21]. Anaesthetists should remember the peak and long duration of NPH insulin[13] may lead to delayed hypoglycaemia. Another option, with Endocrinology advice, is to change the patient to a basal/prandial/ corrective regimen using the newer insulin analogues for the patient's inpatient stay or as a permanent change[9].

Intraoperative and postoperative management

Endocrinologists and Diabetes Educators will often play a role in the care of patients with type 1 diabetes having surgery, particularly patients having longer inpatient stay[16,20]. Many patients, however, will have a stable insulin regimen and will be scheduled to have a short hospital stay[16]. For these patients, anaesthetists will play an important role in managing the patient's diabetes during their hospital stay. Further, in rural and regional hospitals, there may be limited access to specialist endocrine services[22]. However, General Physicians with expertise in contemporary diabetes care may provide suitable support.

While the insulin plan and managing any co morbidities during the perioperative period is important, the single most important aspect of perioperative care for patients with type 1 diabetes is to measure the blood glucose frequently and respond appropriately. All anaesthetists should find the newer glucometers easy to use at the point-of-care. A digital reading is provided within 30 seconds or less after applying a drop of blood to a disposable electrode that tends to draw in the blood. Further, some commercial glucometers also measure blood ketones.

The American Diabetes Association[23] and American College of Endocrinology [24] both conclude that inpatient hyperglycaemia is common and detrimental and improved control can decrease short- and long-term mortality, illness complications, hospital lengths of stay and healthcare costs[25]. There is, however, ongoing controversy regarding very tight glycaemic control during the perioperative period. This is because possible benefits of blood glucose maintained within the physiological reference range may be offset by increased complications from hypoglycaemia or insulin therapy[26-28], particularly stroke[29]. The recent NICE-SUGAR randomised trial[30] of 6100 Intensive Care patients, most from Australia and New Zealand demonstrated that tight blood glucose control (blood glucose: 4.5 to 6.0 mmol/L) was associated with greater mortality than "conventional" control (blood glucose: <10 mmol/L). The highest odds ratio for death (1.31) was in the surgical subgroup. Further, severe hypoglycaemia (blood glucose <2.2 mmol/L) occurred in 6.5% of the tight group but only 0.5% of the conventional group. We suggest, based on current evidence, that to avoid the risks of excessive hyperglycaemia and hypoglycaemia, the target range for blood sugar during surgery should be 5 to 10 mmol/L[16,21,27,30].

Comment [RT3]: Missing reference

Some suggest using glucose-insulin-potassium infusions for most surgical patients with type 1 diabetes[18,31]. One reason for this suggestion is that these infusions appeared superior to subcutaneous insulin[16]. These studies, however, were conducted before the new insulin analogues were introduced[16]. We argue that new insulin analogues combined with basal/prandial/corrective insulin dosing during the perioperative period will provide adequate glucose control for many patients with type 1 diabetes and have several advantages[16,32]. First, for many patients, the approach is identical, or similar to, their outpatient management, reducing problems with transition to and from different regimens while in hospital. Patients who are well stabilised on insulin therapy, particularly teenagers[15], are unlikely to welcome changes in their usual management. Second, some of the problems associated with continuous glucose and insulin therapy, including hyponatraemia and complications of infusion malfunction can be avoided. Third, fluid management can be the same as patients without diabetes; there will often be no need for glucose infusions. A patient who remains nil-orally for a short time after abdominal surgery can continue on basal insulin with corrective boluses, but without prandial doses[8,16], mimicking the management of patients without diabetes[4]. Importantly, the basal insulin makes this approach a significant improvement on traditional sliding scales[28,33]. For patients having extensive surgery or who are critically ill, however, perioperative management will centre on infusions of regular insulin and matched dextrose delivery[21].

For patients receiving rapidly acting insulin via computerised subcutaneous, infusion the best approach is unclear[9]. If there are team members who feel confident with the technology, the infusion pump could be continued with appropriate

Comment [RT4]: If you are going to stick to your guns you should state "there will be no need for glucose infusions except for when hypoglycaemia occurs.

Comment [RT5]: This is another cop out. This article is worthwhile because it challenges existing dogma, that if you give insulin you MUST give glucose.

You have cogently argued your case, there are NO studies that I am aware of that suggest that giving dextrose is "safer" than not giving it. If you give more glucose you need more insulin than you would need if you did not give insulin. This means that if the dextrose delivery fails you are MORE likely to get hypoglycaemia.

The added complexity of a second infusion makes errors more likely. Having a second variable makes the management more complex as well.

Normal patients do not get dextrose perioperatively.

Schnipper et al. Effects of a subcutaneous insulin protocol, clinical education, and computerized order set on the quality of inpatient management of hyperglycemia: results of a clinical trial. Journal of hospital medicine (Online) (2009) vol. 4 (1) pp. 16-27 have shown that one can effectively manage hypoglycaemia without administering dextrose except when hypoglycaemia occurs.

Your article should challenge this almost religious dogma of Endocrinologists.

monitoring and vigilance [16]. The basal rate functions in a similar way to the basal insulin in a patient using multiple daily injections, but can be easily adjusted both up and down in the face of rising or falling blood glucose levels respectively. Alternatively, the infusion can be interrupted, but intermittent subcutaneous or intravenous infusion insulin will be required. As there is no background long acting insulin, stopping the pump (or pump malfunction) can lead to hyperglycaemia and possibly ketosis within hours[4]. For a short procedure, an intravenous infusion of regular insulin at the patient's usual basal rate is one alternative. Otherwise, basal insulin will need to be given as glargine or detemir; this will require switching the night before. The safety of continuous subcutaneous insulin infusions for in-hospital use has not been established[9]. Further, manufacturers recommend removing insulin pumps during radiological procedures to avoid artefacts in images and electromagnetic interference during magnetic resonance imaging (MRI) [15]. In hospitals without expert diabetes physicians, Diabetes Educators can be an excellent resource for information about insulin pumps[15].

Following surgery, there must be regular frequent monitoring of the blood glucose[21]. The frequency will depend, in part, on pre and intra operative results. We suggest that testing be at least hourly[27] until the patient is sufficiently alert to detect symptoms of hypoglycaemia and react appropriately. The frequency will also depend on any hypoglycaemia or hyperglycaemia and subsequent management[21]. Once the patient is tolerating oral intake, prandial bolus insulin can be resumed. Vomiting and associated loss of ingested carbohydrate or nausea and decreased intake of carbohydrate require caution when administering prandial and corrective doses of short acting insulin[21]. For day surgery, the patient should be feeling well and have

been fed before hospital discharge[16,21]. They must have instructions to return to the hospital if they become unwell. We suggest that anaesthetists ensure patients get optimal antiemetic prophylaxis and treatment. Importantly, dexamethasone may increase the blood glucose [34].

Summary

Patients with type 1 diabetes are increasingly using intensive and flexible insulin regimens[11] based around newer insulin analogues and frequent blood glucose testing[3,16]. The flexibility of these regimens invites their ongoing use in the perioperative period. Continuous computerised subcutaneous infusions present new challenges[9,15]. Older approaches, such as glucose-insulin-potassium infusions[18,31] should be reserved for more complex surgery and sicker patients. The evidence, however, is limited, and there is need for more research into perioperative management of diabetes.

Comment [RT6]: I think you should be more provocative than this. GIK infusions are rarely used in Australia and the logic behind them limited.

It would be better if you said "Older approaches with Insulin and Dextrose infusions may offer no advantages over physiological insulin replacement and are more complex and expensive to administer. More research is needed to determine whether or not they offer any advantages over simpler methods."

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