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100 years of insulin: Everything old is new again

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INTRODUCTION

2023 is the centenary of the commercial introduction of insulin for the treatment of diabetes. Along with paracetamol and aspirin, it is one of few drugs that remains a mainstay of modern medicine following more than 100 years of use. Insulin is frequently prescribed, or its administration modified, by anaesthetists in everyday practice. Furthermore, based on estimates of population data, 0.44% of people reading this chapter are likely to be type 1 diabetics, 3.1% of those over age 50 are type 2 diabetics requiring insulin, and on retirement, 3.8% may require insulin.[1-3] As a drug, insulin has a history that makes it significant and relevant to all clinicians; its development, introduction into clinical practice, changes in pharmaceutics (and therefore pharmacodynamics), and method of delivery have all evolved to ensure its continued use. In addition to that, it is one of the few drugs that resulted in a remarkable decrease in morbidity and mortality. In this chapter we review the development of the drug and the unusual circumstances surrounding its commercial release. We will also be looking at the changes made to insulin over time, allowing it to serve as an example of the value in continual reassessment of the pharmacology of commonly used drugs to enable optimal usage.

THE DEVELOPMENT OF INSULIN

Although the first recorded clinical description of diabetes occurs in the Ebers Papyrus (c 1550 BCE), it was the development of histology, made possible by improvement in microscope technology in the 1850s, that allowed for the discovery of pancreatic islets by Langerhans in 1869.[4] By 1901 Eugene Opie had demonstrated a connection between islet damage and diabetes, and by 1920 several scientists had managed to develop pancreatic extracts to reduce hyperglycaemia, these developments were however not easily translated into clinical practice.[5]

In Toronto, in the northern hemisphere summer of 1921, the successful extraction and administration of insulin occurred. There are several factors that led to this success, among others the sheer determination of those in the Toronto Laboratory. This well-funded laboratory was equipped with senior staff offering their guidance that led to significant improvements in the measurement of blood glucose.[6] The last mentioned allowed for a more accurate determination of the effects of proposed treatments for hyperglycaemia, a significant advantage over previous researchers. The discovery was a true team effort; in the efforts of orthopaedic surgeon Frederick Banting and Charles Best (laboratory assistant and medical student) to produce animal pancreatic extracts, the advice of Professor of Physiology John McLeod for preservation techniques, and biochemist James Collip in the purification of insulin. Although the chemical structure was yet to be determined, McLeod called the substance insulin, derived from the Latin word for island *insula*, referencing the islets of Langerhans.

Unfortunately, the relationships between the senior researchers Banting and McLeod became strained to the extent of great hostility, which is well documented.[6] This peaked when the Nobel Prize was awarded to them, and Banting originally refused to accept the award as Best was not acknowledged. Fortunately, this animosity did not prevent the discovery of insulin.

THE RAPID CLINICAL RELEASE OF INSULIN – A GIFT TO THE WORLD

Two days after the successful isolation of insulin in January 1921, the University of Toronto's wholly owned Connaught Institute signed an agreement with Banting, Best, Collip and Macleod for the production of insulin. The increasing need for a large-scale production however saw this arrangement unable to provide the amount of insulin required.[6] This necessitated a commercial agreement with a commercial manufacturer, but this agreement was for one year only. With the significant prevalence of diabetes, the discovery of insulin had the potential to reap large financial benefits for its discoverers. It has been documented that two of the physicians involved in its development, Banting and Macleod, were concerned that patenting insulin may reduce the availability of insulin worldwide.[7] However, in the absence of a patent, others would be free to patent and manufacture the discovery, with potential significant financial gains at the expense of widespread availability. Banting famously declared that "insulin does not belong to me, it belongs to the world".[8]

Banting, Best and Collip transferred their patent rights for the purification method to the University of Toronto for one dollar each, after which the university filed the application for the patent, which prevented the discovery's exploitation by a single entity. The University of Toronto then licensed the sale of insulin in North America and granted the patent rights to non-profit organisations in other countries.[7]

The discovery, rapid release and widespread availability of insulin, "gift to the world", stands in stark contrast to the situation surrounding the patent for early HIV (human immunodeficiency virus) infection therapy. In the era of the COVID-19 pandemic, there has been continued discussion of the role of patents in diagnosis and therapy, as well as the need for the widespread availability of medications that includes economically developing nations.[9]

INSULIN PRESCRIPTION – THE CHALLENGE OF DOSING

Unlike many other pharmacological agents used to manipulate physiological parameters, insulin may be challenging to prescribe and administer effectively. Normal physiology dictates that insulin is secreted by pancreatic islet beta cells in response to elevated blood glucose levels. This process is highly regulated by a multitude of complex biological systems including transcription factors, autonomic innervation, and other hormones (such as glucagon-like peptide-1, adrenaline and insulin itself).[10] Insulin is stored and stabilised in the pancreas in the form of hexamers – units of six insulin molecules connected with hydrogen bonds and zinc ions – which readily dissociate into biologically active, rapidly-absorbed monomers for use in cellular glucose uptake upon release.

Both hyper- and hypoglycaemia are associated with a variety of medical complications, the use of insulin as a treatment for diabetes mellitus thus aims to target near-normal blood glucose levels – approximately 4-10 mmol/L. Monitoring blood glucose as an indicator for effective treatment is, however, a challenge in itself. Traditional finger-prick testing can only be undertaken a few times a day in a practical manner, each requiring a separate blood lancet and sample. These discrete readings may pose a challenge to the clinician to accurately predict glucose trends and thus difficulties in safely prescribing insulin doses. Likewise, many variables affect how a patient processes exogenous insulin at any particular time: dietary intake, physical activity, concurrent illnesses, body temperature, blood flow to the injection site, lipodystrophy and the development of insulin resistance, to name a few.[11]

Prior to the development of accurate home and hospital glucose monitoring systems, a large margin of error existed when it came to insulin prescriptions. This was detrimental given the hazardous consequences of hypo- and hyperglycaemia. Insulin dosing had to err on the side of safety (avoiding hypoglycaemic episodes), which naturally gravitated towards sub-optimal management of diabetes. This necessitated the improvement in glucose monitoring systems, insulin formulations and delivery systems to refine the ability to mimic physiological endogenous insulin secretion.

INITIAL CHANGES IN INSULIN PREPARATIONS

Initial insulin preparations were crude by today's standards, being prepared from bovine and porcine pancreases. Although there are amino acid differences between the above mentioned animal and human insulin, the pharmacodynamic and pharmacokinetic effects are remarkably similar. However, animal insulins are exogenous, and long-term insulin administration was associated with the development of anti-insulin antibodies, insulin resistance and lipoatrophy in a significant proportion of patients.[12]

In the 1970s and 1980s, improvements in processing and chemical techniques allowed for the development of modified animal insulins. The modifications resulted in insulins which were free of proinsulin and other immunogenic polypeptides, also more closely resembling the amino acid sequencing of human insulin.[13] By 1982 the discovery of the gene for human insulin and the development of recombinant DNA technology

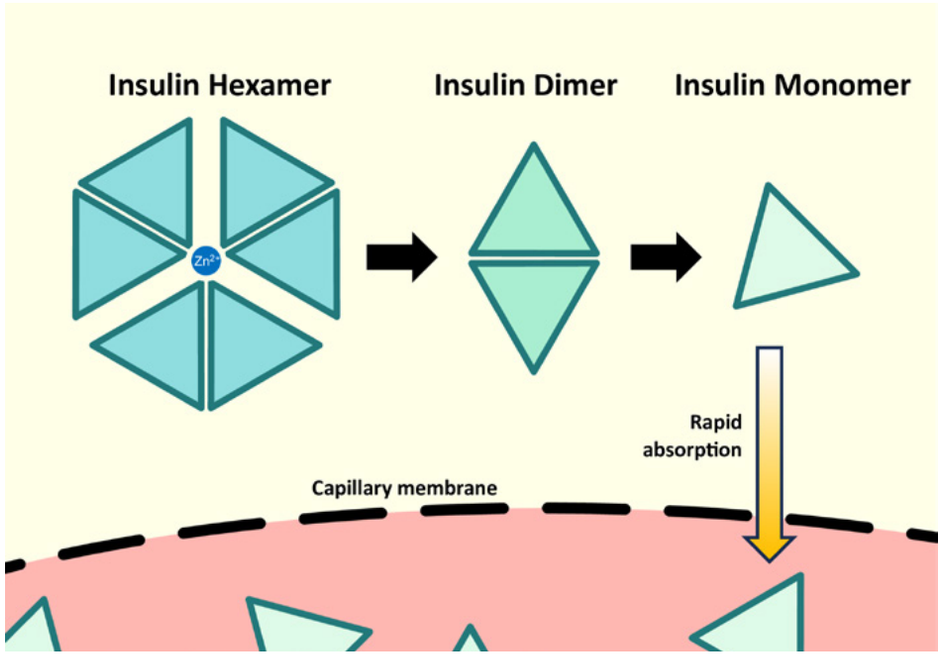
allowed for the production of biosynthetic insulin, which has superseded animal insulin. Interestingly, human insulin is also associated with development of anti-insulin antibodies, but these are generally in low titres and are clinically insignificant.[5,13]

INSULIN ANALOGUES

Insulin analogues are insulin molecules in which, by means of recombinant DNA and genetic engineering technology, changes are made to the amino acid structure to result in pharmacokinetic and pharmacodynamic properties that differ from the original molecule. The biological properties and stability of the insulin molecule is however preserved.[14] The development of different analogues had made it possible for the development of intermittent insulin dosing allowing for a closer imitation of the normal physiological variability in insulin secretion.

As mentioned before, insulin is stored as hexamers which dissolve into active molecules in the blood stream upon release (see Figure 1). The time effects of rapid acting insulins are facilitated either by altering the molecule by one or two amino acids to reduce the strength of the interactions that hold insulin molecules together, or by formulating the molecule in a monomeric/dimeric state, removing the time delay associated with hexamer dissolution.[14] Varying the insulin formulation and thus the molecule to affect hexamer formation is the key to speeding or slowing the absorption of injected insulin into the circulation. Examples of currently prescribed insulin analogues include intermediate acting insulin glargine (an example being Optisulin®), and rapid acting insulin lispro (Humalog®), and insulin aspart (Novorapid®).

Figure 1. Dissociation of insulin hexamers into rapidly-absorbed monomers



INNOVATIVE DELIVERY SYSTEMS

Traditionally, exogenous insulin has been administered via subcutaneous injection – a reliable technique that is still used commonly today. Subcutaneous insulin can be considered the gold-standard route of insulin delivery. Plunger syringes were associated with inaccurate dosing (due to syringe dead space) and a negative psychological impact, thus modern insulin pens were developed with smaller needles to provide a more convenient, precise and flexible way to administer specific doses.[15,16] Subcutaneous administration however is associated with adverse effects including lipodystrophy, scar formation, oedema and allergy symptoms, leading to investigations for improved methods of delivery.

Oral insulin has shown to be an ineffective alternative due to issues with poor absorption and enzymatic proteolysis leading to low bioavailability.[17] Although pulmonary delivery of insulin was first unsuccessfully trialled in 1924, modern development of inhaled insulin was made possible by improvements in aerosolised delivery systems and particle pharmacology.[18] Inhaled insulin is associated with faster absorption, peak concentration,

and more rapid metabolism. It is licensed in the US and has been used in the UK in select patient subgroups (but not in Australia or New Zealand), albeit with a shaky start. The first approved product (Exubera®) was withdrawn from the market in 2007 due to risks of hypoglycaemia, and the only remaining product (Afrezza®) faces limitations in acceptance when compared to the more established subcutaneous insulin.[19] Despite the theoretical benefits of this route of administration, inhaled insulin has not penetrated the commercial insulin market to a significant extent. The reasons are multifactorial; the perceived risks of altered respiratory function, the lack of insurance coverage in the US, and the concurrent development of continuous delivery systems that allow for insulin administration to more closely match that of normal physiology. Despite the low uptake, there is continued research into this mode of delivery, including the potential for vibrating mesh technology (nebulisers), especially for type 2 diabetics.[20]

Insulin pumps are portable devices that provide an uninterrupted infusion of insulin, reducing the need for repeated injections. This is termed "Continuous Subcutaneous Insulin Infusion" (CSII), and the initially introduced systems supplied insulin at a steady basal rate with additional user-initiated bolus doses. Introduced in the 1960s, they broadly are comprised of an insulin reservoir and infusion set.[16] Pumps often take on the form of a wearable electronic device (which stores the insulin and controls the rate of infusion) connected to a subcutaneous cannula within the infusion set. However, patch pumps (such as the Omnipod DASH® or Accu-Chek® Solo available in Australian and New Zealand markets) combine the two components into a single unit that eliminates the need for connective tubing, attaching to the skin with an adhesive and improving freedom of movement for patients.[21]

By themselves, pumps rely entirely on user input to determine the rate and timing of insulin doses, especially mealtime boluses. The development of continuous glucose monitoring (CGM) systems has opened up the possibility of allowing pumps to auto-regulate insulin dosing by providing ongoing blood glucose level feedback, helping to alleviate the issues associated with individual finger-prick testing. Dexcom, Medtronic and Abbott are among some of the medical technology companies that offer CGM devices that attach externally for 1-2 weeks and transmit data wirelessly to smartphones through Bluetooth scanning (or other similar digital connection).[22] While not approved in Australia or New Zealand as yet, long-term implantable devices in the upper arm or abdominal fascia that stay in situ for over six months provide a glimpse into the future of CGM, and have been introduced into clinical practice in other countries.[23]

Automated insulin delivery systems have been a breakthrough in the management of type 1 diabetes, aiming to function as an "artificial pancreas" that responds intelligently to blood glucose levels. They incorporate three components: an insulin pump, a CGM, and an algorithm that communicates information between the two. The first commercial device emerged in the late 1970s in the form of the Biostator – a bulky ventilator-sized machine that was for inpatient use that relied on intravenous glucose sensing and insulin infusion.[24] Since then, many refinements have been made over the years, both to the equipment as well as the algorithms, improving their ability to extrapolate glucose patterns and predict hypoglycaemia. A true closed-loop system that requires no external input is still in only trial-stage technology, but several hybrid closed-loop (HCL) devices exist that are partially automated, they still require user input for factors such as insulin-carbohydrate ratio and insulin action time. Examples of portable HCL devices currently commercially available in Australia and New Zealand are the Medtronic MiniMed™ 780G and the Tandem t:slim X2™ pump. Trials have demonstrated effective glycaemic control with these systems, and they remain popular options for type 1 diabetics to this day.[25,26]

Automated insulin delivery (AID) systems are recommended for all type 1 diabetics. They are associated with significant improvements in quality of life, a reduced diabetes management burden to patients and their families and are safe and effective in helping patients achieve their long-term glycaemic goals while reducing hypoglycaemia risk.[27] Despite the improved technology and advantages, patients still require basic diabetic management skills to ensure optimal results, and it may not be suitable for all patients.

CHANGES IN PERIOPERATIVE GLYCAEMIC MANAGEMENT

In an intraoperative setting, anaesthetists aim to regulate blood glucose levels between 5-10 mmol/L^{-1} (depending on various protocols) to avoid the increased morbidity and mortality associated with hypoglycaemia, and the risk of nosocomial infection associated with higher blood glucose levels.[28] While more liberal intraoperative glucose control ranging up to 12 mmol/L^{-1} allows anaesthetists to err on the side of safety and lowers the medication burden on the patient, it is associated with higher short-term mortality and postoperative complications in both diabetic and non-diabetic patients.[29] Tighter control is therefore desirable, this however requires more attentive glucose monitoring to avoid hypoglycaemia.

The relatively recent introduction of AID systems into society has significant potential to change our approach to perioperative glycaemic management. As detailed above, they can autonomously monitor blood glucose and self-initiate insulin administration, theoretically making it easier to maintain tight glycaemic control

intraoperatively. While research is still somewhat limited, initial trials on the perioperative use of AID systems have been promising by demonstrating their ability to maintain patients in a safe glucose range.[30,31]

Current approaches to CSII (which also apply to AID systems) suggest re-siting the infusion set the day before surgery in an area away from the operative field but still accessible to the anaesthetist, such as the abdomen or thigh (depending on the operation). There are still limitations to insulin pumps intraoperatively though. They are not appropriate for every procedure: emergency and protracted surgeries provide logistical barriers in managing glucose with the pump's supply of insulin, and radiological intervention may alter the device's ability to function. In these cases, disconnection is recommended with reversion to the 'intraoperative gold standard' of intravenous insulin infusion.[32] However, the possibility of continuing the use of AID systems for shorter and/or elective procedures provides an exciting area for further investigation in the future.

CONCLUSION

Compared with other medical specialties, anaesthesia makes use of a relatively narrow spectrum of medications, many of which have had a long history of use in the specialty. As one of the few medical specialties in which extensive postgraduate education in clinical pharmacology occurs, anaesthetists have the unique opportunity to consider new and alternate methods of delivery of the drugs that we administer. That a drug such as insulin has retained its place in clinical practice through these changes is a reminder that there is always room for improvement and that change is necessary in our pursuit to improve the quality of life of patients. In the absence of a functioning crystal ball, it is difficult to make predictions about the long-term future of drugs, but in the absence of a cure for diabetes, it is likely that in another one hundred years insulin will continue to be in use, albeit in different molecular forms and with delivery systems that will continue to have evolved.

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