Dual-hormone Automated Insulin Delivery

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Introduction

For the last 100 years, the discovery of insulin has allowed people to live with diabetes. However, the fact that we are using a single hormone to try to replicate the work of the pancreas that uses multiple hormones to maintain glucose homeostasis has meant that for most people, it is impossible to replicate non-diabetic glucose control. Fewer than a quarter of people with type 1 diabetes (T1DM) are able to achieve therapeutic targets,[1] and hypoglycaemia remains a key barrier in our quest to achieve near-normal glucose levels. The role of glucagon in protecting against hypoglycaemia in health is critical, and people with T1DM lose their glucagon responses relatively early in the course of the disease. This is thought to be secondary to the lack of reduction in insulin from the beta cell, as there is a need for reduction in local insulin concentration around alpha cells (together with low glucose) for glucagon secretion to occur.[2] As a result, there is a blunted glucagon response during hypoglycaemia and exercise, increasing the risk of hypoglycaemia. Conceptually, replacing both insulin and glucagon together as part of an "artificial pancreas" makes sense and would allow more aggressive insulin dosing to control glucose rises, since we could rely on glucagon to prevent any resultant hypoglycaemia.

Unlike insulin, glucagon has a rapid onset of action (about five minutes) and time to peak plasma glucagon level of about 15 to 20 minutes.[3] Blauw *et al*. conducted a study to investigate the pharmacokinetics and pharmacodynamics of various glucagon doses at different glucose levels.[4] The authors clamped glucose at 8, 6, 4 and 2.8 mmol and gave different glucagon doses ranging from 0.11 mg to 1 mg. The authors found dose-dependent increases in glucose levels during both normoglycaemia and hypoglycaemia: athe findings from this study support the use of small doses of glucagon during automated insulin delivery.

El Youssef *et al*. conducted a euglycaemic clamp study to investigate the effects of microdoses of subcutaneous glucagon at various insulin doses.[5] They infused at three different insulin infusion rates. At low insulin levels, endogenous glucose production rose proportionately with glucagon dose, whereas at high insulin levels there was no increase in glucose output. This is an important consideration when using low-dose glucagon to treat hypoglycaemia.

Dual-hormone Automated Insulin Delivery (AID)

One of the earlier studies, published in the *New England Journal of Medicine* in 2014, investigated the effects of dual-hormone closed-loop in 20 adults and 32 adolescents who had had TiDM for five years.[6] In this study the control arm used standard insulin pump therapy (only some using continuous glucose monitoring). Rather than having to enter exact carbohydrate content, the meal size was informed (announced) to the algorithm, as "typical", "more than usual", "less than typical" or "a small bite". This system used the tandem T slim insulin pump and iPhone and Dexcom CGM. The authors found significantly better time-in-range with dual hormone closed-loop and reduced time in hypoglycaemia.

In another randomised, three-way, crossover trial, Haider *et al*. compared continuous subcutaneous insulin infusion (CSII) with single- and dual-hormone AID in children aged 9–17 years (n=33) with T1DM during a diabetes camp with unrestricted food intake and physical activity.[7] Each intervention was applied for three consecutive nights. Artificial pancreas interventions started between 2200 h and 2300 h (based on bedtime) until 0700 h. In this study the time spent in hypoglycaemia below 4.0 mmol/L was lowest in dual-hormone AID (0% vs. 3.1% vs. 3.4, dual-hormone vs. single-hormone AID vs. continuous subcutaneous insulin infusion). Additionally, the time spent in target glucose range between 4 and 8 mmol/L was 29% with continuous subcutaneous insulin infusion, 55% with single-hormone AID and 63% with dual-hormone AID.

In another study the authors investigated the benefits of dual-hormone AID and single-hormone AID during exercise.[8] This was a randomized four-way crossover trial (two types of exercise and two types of AID). The two exercise types were either continuous exercise (60% $VO_{2\ max}$ for 60 minutes) or interval exercise (two minutes alternating periods of 85% and 50% $VO_{2\ max}$ for 40 minutes plus two 10- minute periods at 45% $VO_{2\ max}$ at start and end). The study was conducted in 17 adult participants with no carbohydrate ingestion. Two types of AID (single- vs. dual-hormone AID) were applied from 15:30 hours until 19:30 hours. Exercise started at

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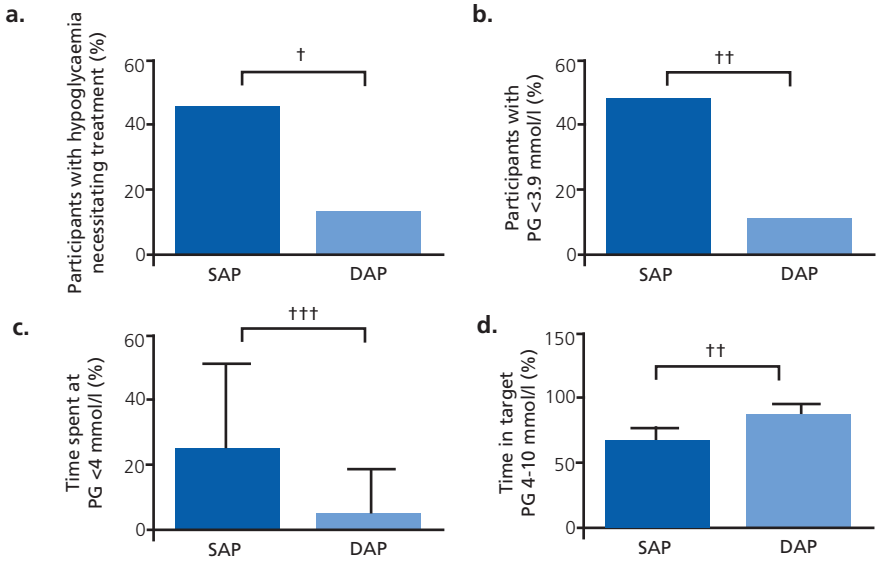
Figure 1. Hypoglycaemia during exercise: single- vs. dual-hormone AID



a. Percentage of participants with hypoglycaemia necessitating treatment
b. Percentage of participants with PG <3.9mmol/l
c. Percentage of time spent at PG <4 mmol/l
d. Percentage of time spent in target (PG 4-10 mmol/l)

For c and d, data are presented as means ± SD

†p=0.02, ††p=0.003, †††p=0.0001

0.11mg (110µg) glucagon per hour exercise. More during continuous than interval exercise

Reproduced from Taleb N *et al*.[8]

18:00 hours with the algorithm informed about exercise (exercise announcement) 20 minutes prior to exercise. The percentage of participants experiencing hypoglycaemia was lower with dual-hormone AID compared to single-hormone AID (Figure 1). In a recent meta-analysis of nine studies comparing dual- vs. single-hormone AID, the time in range was not different but time in hypoglycaemia was shorter with dual-hormone AID (mean difference -1.2% (-1.85, -0.56) in favour of dual-hormone (17 minutes).[9]

Novel glucagon preparations

Dasiglucagon is an analogue of glucagon with seven amino acid substitutions.[10,11] It is physically and chemically stable in aqueous solution and ready-to-use formulation. Biochaperones are polymers, oligomers and organic compounds that can form a complex with glucagon and improve its stability in aqueous solution. Another ready- to-use glucagon is non-aqueous soluble glucagon, G-Pump™ or G-Pen Mini™. Nasal dry powder (Baqsimi) 1mg glucagon per 10mg dry-powder inhaler is also available in the USA.[11]

Mini-dose glucagon for exercise and non-severe hypoglycaemia

In a four-session RCT, the role of mini-dose glucagon was investigated by Rickels *et al* in 15 adults with T1DM on CSII.[12] The trial details are as follows: exercise intensity was 55% $VO_{2\ max}$ for 45 minutes with no intervention, 50% basal reduction, 40g oral glucose tablets and 150mcg subcutaneous glucagon. Outcomes were assessed during 45 minutes of exercise and 30 minutes of early recovery. Basal insulin reduction at the start of the exercise period was no different to control. No participant in the mini-dose glucagon or glucose tablets had an episode of hypoglycaemia. Less hyperglycaemia occurred with mini-dose glucagon. In another randomised crossover trial (two 3-week periods), mini-dose glucagon for treatment of non-severe hypoglycaemia (n=20) was evaluated by Haymond *et al*.[13] This study showed comparable glucose outcomes with mini-dose glucagon and glucose tablets.

Other hormones and approaches

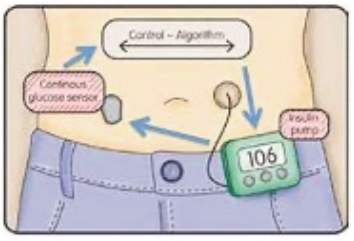
Adding glucagon to insulin is not the only form of dual-hormone automated insulin delivery. Another form of dual-hormone automated insulin delivery (AID) is the combination of standard AID systems with adjunctive agents such as GLP-1 receptor agonists or hormones such as amylin or pramlintide. Most of the work with these adjunctive hormones has focused on reducing the burden of carbohydrate counting for people with T1DM.

Addition of subcutaneous GLP-1 receptor agonists or addition of pramlintide to an ultra-fast insulin (Fiasp) have been shown to improve time in range and to reduce the post-meal glucose excursions following unannounced meals in people on a hybrid single-hormone AID.[14,15]

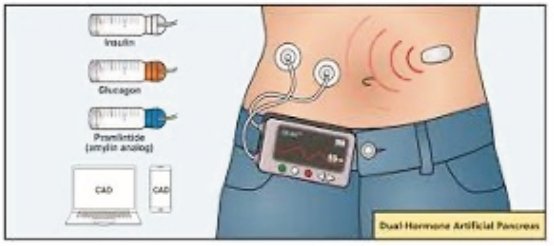
While there are clear theoretical and clinical advantages of dual-hormone closed loops, the possible drawbacks must also be considered. For a long time, there was no such thing as stable soluble glucagon, although the recent launch of pre-mixed liquid stable glucagon products such as Dasiglucagon or Gvoke may make a difference.[10,16] However, since dual-hormone pumps will be more complex and may be bigger, they are likely to cost more. If two cannulas are required, that will also double the consumable costs for tubing and reservoirs. The benefits of these systems must be weighed up in the context of these extra costs (Figure 2). The pros and cons will be different in each individual: for some the pros will clearly outweigh the cons, and for others the opposite will be true.

In summary, stable glucagon preparations are here, and dual-hormone systems that use it have shown improved time in range, although most studies are short-term with small numbers. The long-term safety, effectiveness, acceptability and cost-effec-

Figure 2. Advantages and limitations of single- and dual-hormone AID



- Simplicity
- Adequacy - up to 80% TIR already
- Can be improved with adjuvant therapy if needed
- Safety
- Size/bulk
- Reduced alarms/interventions



- Complexity → increased size / cost and weight of pump
- 2 x reservoirs and canulas that need changing
- Double the risk of site issues / canula occlusion
- Increased risk of alarms / intrusion
- Safety - if insulin or glucagon occlusions are not detected
- Stability of glucagon

Key messages

- Novel more stable glucagon preparations are on the way
- Mini-dose glucagon may become a treatment option for non-severe hypoglycaemia
- Dual-hormone automated insulin delivery (AID) (closed-loop) may be more effective in further reducing hypoglycaemia than single-hormone AID. However further studies are needed at assess longer term safety, effectiveness, acceptability and cost-effectiveness. Increased system complexity and cost may limit its use to certain sub-populations

tiveness of multi-hormone systems, including those with other adjunctive hormones, need to be assessed in larger and longer studies.

Conflict of interest None.

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