Minimizing hypoglycemia while maintaining glycemic control in diabetes

Running title: Minimizing hypoglycemia

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Introduction

In the accompanying Perspective, Cryer identifies a number of different areas where therapeutic interventions have the potential to reduce hypoglycemia without compromising glycemic control. Some approaches provide well defined clinical benefits, a few offer dramatic reductions in hypoglycemia but remain out of reach for most people while others, although promising have yet to be properly evaluated. (Table 1)

In this Perspective, I examine the evidence which underpins these interventions. It is beyond the scope of this article to review the data for each potential intervention in detail but the reader is directed to the appropriate source where appropriate. The Perspective focuses on treatment of Type 1 diabetes as most of the potential specific therapies have been evaluated in this group although I have commented in relation to recent trials of intensive therapy in Type 2 diabetes.

Preventing absolute or relative insulin excess

Education and Skills training in self management

Long before the benefits of tight glucose control had been established,(1) the belief that insulin therapy should be designed to replace insulin "physiologically" had been advocated by a small number of enthusiastic clinicians. The advent of blood glucose monitoring in the late 1970s had a major impact since background and meal related insulin could be given separately and adjusted according to self-monitored blood glucose measurements. Participants were encouraged to eat freely, calculating their insulin dose according to their chosen amount of carbohydrate.

Integrating these components was a complex task, probably beyond that of many physicians, let alone patients. If this was to be undertaken every day then patients needed to acquire the skills of flexible insulin self management and apply it successfully. The therapeutic education approach was pioneered by Assal and colleagues,(2) and Berger and Mühlhauser went on to develop a residential training course (Insulin Treatment and Training programme, ITTP), evaluating the intervention in a series of studies, including randomised controlled trials.(3) Their group highlighted the major differences between rates of severe hypoglycemia in different centres in the DCCT and suggested that these might have reflected a failure to train patients to undertake intensive self-management safely.(4)

Their data which include a large evaluated roll-out suggest that it is possible to improve and sustain glycemic control, comparable to the DCCT using conventional insulin while reducing rates of severe hypoglycemia. (Figure 1) (5; 6) Different definitions of hypoglycemia prevent a detailed comparison between these and other studies but their principle argument that no-one should embark on intensive insulin therapy and aim for tight glucose targets without acquiring appropriate self management skills is compelling. Even in countries where such training is relatively established,(6; 7) relatively few adults with Type 1 diabetes appear to have undertaken validated courses in intensive insulin self-management.

Other programs have been developed to train patients specifically to recognise both high and low glucose values although most interest has centred around their ability to identify impending hypoglycemia. Blood glucose awareness training (BGAT) developed by Cox and colleagues at the University of Virginia(8) seeks to train patients with Type 1

diabetes to improve estimation of their blood glucose based on recognition of external cues and the known pathophyiological changes associated with autonomic and neuroglycopenic responses to hypoglycemia. Participants also receive feedback on their glucose estimations. The approach shares several features with the ITTP training of the Düsseldorf group and has also been extensively evaluated. Trials led by the investigators have demonstrated prevention of a blunted counterregulatory response during intensification of insulin therapy(9) and an improved ability to estimate blood glucose which is maintained over some years with fewer severe hypoglycemic events.(10)

In summary, there is a reasonable body of evidence demonstrating that high quality skills training in insulin self management involving accredited educators leads to improved glycemic control without increasing severe hypoglycemia. Specific programmes appear particularly beneficial to those with hypoglycemic problems.

Improved insulin delivery in routine care

The limitations of subcutaneous insulin delivery have been well recognised ever since its discovery. The intermittent injection of insulin into subcutaneous tissue produces insulin profiles which, while able to control blood glucose sufficiently to relieve symptoms and prevent ketosis are far from physiological. The advent of recombinant DNA technology in the 1980s prompted the pharmaceutical industry to engineer different structures of the insulin molecule to address the limitations of subcutaneous insulin delivery.(11)

The tendency of insulin molecules of conventional animal structure to aggregate in crystalline solution delays its absorption. Transposing or substituting amino acids produces insulins with less tendency to self aggregate. (12) The molecules remain monomeric at high concentration and their more rapid absorption results in a more

physiological insulin profile. Yet the clinical advantages of quick acting insulin analogs over conventional insulin have generally been modest in clinical trials, both in lowering HbA1c and hypoglycemia and some have concluded that they offer little additional benefit.(13) Nevertheless, there is reasonable evidence reporting reduced nocturnal hypoglycemic risk when using rapid acting insulin analogs in those with well controlled Type 1 diabetes,(14; 15) an outcome not included in the recent Cochrane review.(13)

The other main pharmacokinetic limitation of conventional insulin delivery has also been addressed. Human NPH insulin, exhibits considerable inter- and intra-individual variability in part due to the necessity of re-suspension before injection. This, plus a pronounced peak of action around 6-8h after injection contributes to the risk of nocturnal hypoglycemia. Insulin manufacturers have tried to solve these problems in ingenious ways. Insulin glargine (Lantus), a di-arginyl insulin analog is a soluble insulin at an acid pH and then crystallises in the more alkaline subcutaneous environment.(12) Insulin detemir (Levemir) has been constructed by adding a myristoyl fatty acid side chain at the C terminus of the B-chain which causes the insulin to bind to albumin.(12) Both insulins have a more prolonged action than NPH and a reduced peak and provide a more physiological free insulin profile with the potential to lower rates of hypoglycemia. Yet, as with rapid acting insulin analogs the major pharmacokinetic differences compared to NPH insulin are not in general, reflected in the clinical trial data.

Benefits of long acting insulin analogs have been modest in both types of diabetes with little if any difference in glycemic control and only slight reductions in hypoglycemia, mostly at night.(16) The combination of both long and short acting insulin analogs leads

to significant albeit minor reductions in both HbA1c and hypoglycemia in adults with Type 1 diabetes.(17; 18)

A major difficulty in interpreting the mountain of data around insulin treatment is that the limitation of its delivery is just one of many factors determining glycemic control and the risk of hypoglycemia. Thus, regulatory clinical trials may underestimate the potential benefit since they rarely recruit highly motivated individuals who are expert at self-managing their diabetes and can best utilise the pharmacokinetic advantages. Regulatory trials may also favor conventional insulins since clinical experience with the newer insulins is often necessary to establish the most effective combination and timing of injection. However, since asymptomatic nocturnal hypoglycemia may contribute to the generation of hypoglycemia unawareness(19) such insulins should be offered to those skilled in insulin self management who are experiencing hypoglycemic problems.

Continuous subcutaneous insulin infusion

The limitations of long acting insulins have driven the increasing use of continuous subcutaneous insulin infusion (CSII) as a realistic treatment option for many, at least in wealthy countries. The approach is now used by over 20% of individuals with Type 1 diabetes in the USA.(20) CSII is the most effective, generally available method of insulin delivery although subcutaneous administration plus the continued need for frequent adjustments of infusion rates according to intermittent SMBG is hardly physiological. The need to justify reimbursement of the increase in costs has resulted in a substantial number of trials and systematic reviews. The most recent, which include trials involving more modern devices, report falls in HbA1c of around 0.6-0.4% with no

increase in hypoglycemia; advantages confined to adults with Type 1 diabetes.(21; 22) There were insufficient data to establish benefit in children and no advantage of CSII in Type 2 diabetes. Few groups have undertaken a formal meta-analysis of hypoglycemic outcomes due to different definitions and potential bias due to lack of blinding when judging endpoints.

Observational studies report greater reductions in HbA1c and severe hypoglycemia but are inevitably prone to bias since only those who experience benefit are likely to continue using the approach. Furthermore the use of CSII is a complex intervention, involving not only the pump but also instruction in carbohydrate counting and insulin adjustment within a structured training programme. Thus, part of the benefit of pump therapy may relate to the training that accompanies it. Few trials have apparently controlled for the training element and reported falls in rates of severe hypoglycemia are similar to those reported for self-management training using multiple injections.

Nevertheless, it seems clear that for highly motivated individuals with the ability to self-manage their diabetes effectively, modern CSII technology can improve glycemic control without increasing hypoglycemia. If acceptable to the patient, it should also be part of a package for patients experiencing problems with hypoglycemia.

Preventing insulin excess for the few, implantable pumps, pancreas and islet transplantation

There are a number of interventions which have been reported to have major effects in reducing hypoglycemia. The use of implantable pumps with specially designed pumps housed within the subcutaneous tissue of the abdominal wall and insulin delivered into the peritoneum have been pioneered by a group in France. Clinical experience is

relatively limited at around 350 patient-years but the investigators have reported major reductions in severe hypoglycemia, impressive HbA1c concentrations and improved quality of life.(23) Evaluation of such therapy is largely based on observational studies although some randomised trials have been undertaken. Catheter blockage is a continuing problem and after over 15 years experience the approach has not entered mainstream clinical care. It would not appear to be a realistic treatment option for most adults with diabetes in the foreseeable future.

The limitations of current insulin delivery are emphasised by the dramatic effect that pancreas transplantation has in curing the problems of hypoglycemia. Whole pancreas transplantation leads to insulin independence in the short and medium term and the resolution of hypoglycemia unawareness at the expense of considerable perioperative morbidity and occasional mortality. The results of whole pancreas transplantation have improved in recent years with 80% graft survival at 5 years and it is now approved as a treatment for severe hypoglycemic instability.(24)

Islet cell transplantation is less invasive but results in less preservation of insulin secretion; a recent report from specialist North American centres indicates that under 10% of recipients are insulin free at 2 years.(25) Nevertheless, around 70% of individuals had detectable C-peptide, of whom none were experiencing their previous difficulties with hypoglycemia unawareness.

Both treatments are accompanied by the hazards of prolonged immunosuppression with increased risks of infection and malignancy. Add to this the current shortage of donor tissue and it is clear that although this treatment has moved from an experimental to a clinical treatment in some countries and cures even severe hypoglycemia unawareness, it

is not an option for most individuals with Type 1 diabetes, either now or in the medium to longterm. Nevertheless, pancreas or islet transplantation should be considered for patients with profound problems with hypoglycemia in those areas where it is available and when other treatments have failed.

Alerting patients to impending hypoglycemia

Continuous glucose monitoring

Continuous glucose monitoring technology has now been available for over 10 years and each year sees further development and refinement; devices now on the market can provide readings in 'real time' plus the ability to alert patients to a falling glucose. Early studies highlighted the ability of devices to identify unsuspected nocturnal hypoglycemia(26) but reports of 'hypoglycemia' in non diabetic individuals and disparate values registered by two similar devices attached simultaneously to the same person led to a reappraisal of their ability to identify hypoglycemia reliably.(27) The problems are not purely technological.(28) Even if the equipment records glucose concentrations fast and accurately, measurements will inevitably differ from blood glucose due to:

1) the need for calibration with blood glucose. A failure to ensure this is undertaken at steady state will introduce error.
2) the physiological differences between values measured in the sc tissue (interstitial glucose) and blood glucose.

Thus, 'real time' devices may be of more use when providing information about the change in glucose rather than absolute values. Continuous glucose monitoring can identify unsuspected low glucose values, particularly at night which might contribute to

the generation of hypoglycemia unawareness. Yet this cannot overcome the difficulty of adjusting imperfect insulin delivery systems in an attempt to prevent insulin excess.

The real immediate potential lies in their use as a hypoglycemia alarm, yet years after the first introduction of such devices, few individuals with Type 1 diabetes are using them regularly. There will always be a trade-off between sensitivity and specificity but at present, specificity is insufficient,(29) perhaps in part due to differences between interstitial and blood glucose.(28) The need to replace sensors at relatively short intervals, the greater accuracy in the high rather than the low glucose range and the difficulty in arousing patients from sleep during nocturnal hypoglycemic episodes emphasise the hurdles still to be overcome. An independent group recently concluded that none of the current devices performed reliably enough to be recommended as hypoglycemia alarms.(30)

Observational studies have reported reductions in severe hypoglycemia but in the absence of a control group it is unclear whether this fall was entirely due to the provision of the device. Randomised controlled trials have generally shown modest advantages in surrogate endpoints such as the time spent in the normoglycemic range.(28) Whether this translates into a reduced risk of severe hypoglycemia is unclear as most studies are underpowered due to insufficient numbers of patients. A recent systematic review found that the use of continuous monitoring did not reduce HbA1c but there was a suggestion that episodes of nocturnal hypoglycemia were reduced. (31) Unfortunately the heterogeneity of the studies, largely due to different definitions of hypoglycemia made it impossible to increase statistical power by pooling the data. It is important that

investigators agree a common definition of hypoglycemia to allow the future use of metanalyses to analyse future trials.

In the absence of a reliable alarm, as Wolpert has highlighted,(32) the potential of continuous glucose monitoring to reduce hypoglycemia will depend upon the ability of patients to combine the information obtained with adjustments to their insulin and eating habits. This needs an active interest in self-management plus a good working knowledge of the effects of insulin. As with other therapeutic advances assessed in this review, the failure to establish much effect on hypoglycemia, may be because the expert application of these practical skills is limited to relatively few patients.

Closed loop systems

In view of the limitations described above then the development of a closed loop system in which continuous glucose monitoring is combined with the use of a pump controlled by an external computer has major attractions. It would obviate the need for input from the patient apart from filling the insulin reservoir and replacing the sensor and its attachment. The potential for such a device is clearly huge although the expense will limit uptake even within the developed world.

The reader is directed elsewhere for a detailed review of recent approaches.(33) Most of the current work is focussing on devices which incorporate both subcutaneous glucose sensing and insulin delivery. The limitations of sc insulin administration are less important when blood glucose flux is relatively low but are challenged during eating or exercise. Thus, much effort is focussed on overnight glucose control. Some promising early data are emerging and investment in the field is now considerable, but closed loop

devices remain research tools. The development of a practical reliable device, even for those with hypoglycemic problems remains years away.

Restoring symptoms

Programs reversing hypoglycemia unawareness

The observation that repeated episodes of short-duration, mild hypoglycemia impair sympathoadrenal and symptomatic response to subsequent episodes and contribute to HAAF suggested that defects were functional rather than structural. The implication that such impairment might therefore be reversible has been established by different groups in experimental settings.(34-36) What is more relevant is how such approaches work in clinical practice. The essential component reported by the three studies was the avoidance of all hypoglycemic episodes for a few weeks. This required a labour intensive approach with frequent, often daily contact between professional and patient, blood glucose monitoring and insulin adjustment to prevent episodes, particularly at night. In these relatively short-term studies there was no significant deterioration in glycemic control although HbA1c moved higher in all three. It is not clear whether reversal of unawareness can be achieved in all patients or if such benefits are sustained. For those who regain symptomatic awareness there is the challenging task of maintaining reasonable glycemic control while avoiding relapse due to further hypoglycemic episodes.

In a short report from one of the original centres, 4 of the original 6 patients with unawareness were retested 3 years after their reversal program.(37) Relatively tight glycemic control had been maintained, repeated hypoglycemia had generally been avoided and symptomatic responses to experimental hypoglycemia, while lower than

those measured at the end of the original study, were higher than at baseline. However, these are small numbers. It is noteworthy that no centre appears to have published their longterm clinical experience of managing this problem and such reports would be of considerable value. Anecdotally, it is our experience and of others that some individuals find it impossible to alter their glucose targets and continue to be subject to severe hypoglycemic episodes. That severe problems with hypoglycemia and unawareness have emerged as the main clinical indication for whole pancreas and islet transplantation also suggests that hypoglycemia reversal programmes are limited in the degree and duration of benefit.

Specific therapies to prevent or reduce hypoglycemia

Caffeine/theophylline

The adenosine antagonists caffeine and theophylline are probably the most studied of potential therapeutic agents to reverse or prevent hypoglycemia unawareness. The potential of caffeine was suggested by a study which reported increased catecholamines and symptoms during experimental hypoglycemia.(38) Based on this and other studies the authors undertook a 3 month clinical trial in patients with Type 1 diabetes and demonstrated increased number of symptomatic episodes although there was no difference in asymptomatic or severe episodes.(39) A more recent study involving relatively small numbers has reported reduced duration of nocturnal hypoglycemia, (Figure 2) (40) as measured by continuous glucose monitoring.

Theophylline has also been evaluated as a treatment for hypoglycemia unawareness. Patients were recruited to a study in which theophylline was given as an intravenous infusion during slow fall hypoglycemic clamp.(41) The rise in cerebral blood flow was

prevented and the threshold for the increase in symptoms and epinephrine shifted to a higher level although there was no increase in glucagon concentrations. The same group then studied the effect of oral theophylline over 2 weeks and again demonstrated increases in symptoms (although not epinephrine) during experimental hypoglycemia.(42)

While these results are of interest, the crucial question is whether these agents protect patients from severe episodes during clinical treatment. In no study were sufficient patients treated for long enough to assess the effect on hypoglycemia unawareness or rates of severe hypoglycemia. This is of particular relevance to these agents since they reduce cerebral blood flow. Whilst this might contribute to a more pronounced symptomatic response, an unwanted consequence might actually be increased vulnerability to severe episodes.

Modafanil

The evidence that K ATP channels modulate hypothalamic sensing of hypoglycemia(43) and deficient counterregulation,(44) perhaps through effects on GABA (45) presents other therapeutic targets. Modafanil, an agent used in narcolepsy, reduces GABA activity perhaps through effects on potassium channels.(46) The hypothesis that inhibition of GABAminergic neurones might augment the sympathoadrenal response has been tested in non-diabetic subjects who received a moderate dose of modafanil or placebo immediately prior to a slow fall glucose clamp.(47) There was a modest increase in adrenergic symptoms and protection of cognitive function but no effect on epinephrine levels. The authors concluded that modafanil was worthy of further investigation but

neither they nor apparently anyone else has since studied patients with diabetes or hypoglycemia unawareness.

The same group has also investigated drugs which modify KATP channels, gliburide (a channel closer) and diazoxide (a channel opener).(48) Immediate delivery of either agent to non-diabetic subjects before experimental hypoglycemia had no effect on counterregulatory responses although those treated with gliburide, showed some preservation of cognitive function compared with diazoxide and placebo. A further study where diazoxide was administered immediately prior to experimental hypoglycemia also had no effect on sympathoadrenal responses.(49) These human data contradict the positive effect of potassium channel openers on the hypoglycemic sympathoadrenal response observed in rodents for reasons, as yet unclear. Thus, clinical potential remains uncertain and needs further investigation.

Selective serotonin re-uptake inhibitors (SSRIs)

The use of SSRIs to augment the counterregulatory response has also been explored.(50) Early reports actually associated these drugs with hypoglycemia but the authors reasoned that blocking serotonin uptake might increase sympathetic outflow. They demonstrated increased sympathoadrenal responses and cortisol concentrations during experimental hypoglycemia in non-diabetic subjects although symptoms were unaltered. These observations now need confirming in diabetic subjects and those with unawareness.

Boosting glucose counterregulation

A number of human studies in experimental settings have measured the potential of pharmacological activation of counterregulatory mechanisms to boost blood glucose

levels and so reduce the risk of hypoglycemia, particularly at night. Alanine may restore deficient glucagon responses in individuals with Type 1 diabetes at least in part.(51) Nocturnal hypoglycemia can be prevented by oral terbutaline given at bedtime in contrast to the relative ineffectiveness of bedtime snacks but at the expense of a higher fasting glucose concentration.(52) The authors commented that finding a dose which could reliably prevent nocturnal hypoglycemia without raising fasting glucose concentrations is challenging.(53)

It is noteworthy that as with other potential treatments described above, these small scale studies which provide proof of principle have not been followed by larger trials, adequately powered and of sufficient duration to measure differences in severe hypoglycemia. It is unclear whether this gap in the literature is related to a perception that therapies are ineffective, the difficulty in securing funding or merely the logistics in running multicentre trials.

Type 2 diabetes

It is beyond the scope of this review to evaluate specific treatments for Type 2 diabetes. Montori et al have recently commented (54) that there are few independently funded trials which have addressed the effects of glucose lowering therapy using endpoints that are relevant to patients. However some relevant observations can be drawn from the recent publication of the ACCORD (55) and ADVANCE (56) trials although more detailed information around hypoglycemia will emerge shortly. The ACCORD trial utilised an aggressive glucose control strategy with multiple oral agents and the early use of insulin combining both overnight and pre-prandial insulin and aiming for an HbA1c of 6% or below. This produced considerable severe hypoglycemia which may have

contributed to the adverse outcomes. In contrast, a less aggressive approach targeting fasting glucose by the stepwise addition of oral agents and eventually overnight basal insulin produced much less severe hypoglycemia and weight gain with an HbA1c level of 6%. (Figure 3) (56)

Conclusions

The virtual elimination of severe hypoglycemia in the few patients receiving either islet or whole pancreas transplants demonstrates vividly, the failure of current treatment to reproduce the physiology of the β-cell. As we approach 100 years of insulin therapy, many who strive for tight glycemic control are prevented from achieving these targets by the frequently troublesome and occasionally devastating side effect of hypoglycemia. Data from clinical trials indicate that insulin analogs, pumps and continuous glucose monitoring have generally modest effects in reducing hypoglycemic risk: those who appear to gain most benefit are those actively and skilfully engaged in their own diabetes self management. Reversal of hypoglycemia unawareness, at least in part, can be achieved within relatively short time-periods and without major deterioration in glycemic control although the longterm experience of individuals remains unclear.

Some of the pathological pathways emerging from animal studies have identified potential therapeutic targets but early clinical trials have been unimpressive. It remains to be seen how useful animal models of hypoglycemia will be in identifying specific therapies to prevent or reverse hypoglycemia. Promising pilot work in human studies should be followed by adequately powered studies measuring severe hypoglycemia. It is also important that trials, including those sponsored by the pharmaceutical industry use similar definitions of hypoglycemia.

The closed loop device trials signal a potentially exciting advance as would the availability of reliable hypoglycemia alarms but the technology is currently inadequate to the task.

In the short-term, it appears that high quality educational/behavioural interventions offer the most cost-effective way of enabling less hypoglycemia without worsening glycemic control, particularly as successful graduates of such programs appear best placed to take advantage of technological advances.

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Table 1 Approaches to reducing hypoglycemia in clinical practice

Preventing relative or absolute insulin excess

Training in insulin self management

Blood glucose awareness training (BGAT)

Insulin analogs

Continuous subcutaneous insulin infusion

Pancreas transplantation

Islet Cell Transplantation

Alerting patients to impending hypoglycemia

Hypoglycemia alarms utilising continuous glucose monitoring technology

Restoring symptoms of awareness of hypoglycemia

Hypoglycemia unawareness reversal programs

Augmenting glucose counterregulation

Indirect

K ATP channel openers

Modafanil

Diazoxide

Selective serotonin re-uptake inhibitors (SSRIs)

Direct

Alaninine

Terbutaline

Table 2 Features of hypoglycemia reversal programmes

- Preventing all hypoglycaemic episodes for 3-6 week while keeping glycaemic control unaltered
- Frequent blood glucose monitoring (especially at night)
- Insulin adjustment of dose and type
- Labour intensive for patient and clinician
- Often takes months

Figure Legends

Fig. 1. HbA1c and incidence of severe hypoglycaemia (per patient/ preceding year) at baseline and at the follow-up examinations in patients with a diabetes duration > 1 year at entry, following delivery of an intensified treatment and teaching programme)ITTP) (n = 538). Severe hypoglycaemia was defined as a self-reported episode of hypoglycaemia necessitating treatment with intravenous glucose or glucagon injection. Figure reproduced from (5) with permission

Fig 2 Total number of hypoglycemic events in 34 individuals with Type 1 diabetes over 3 months. Biochemical □, P=ns, Symptomatic ■ ($P < 0.03$ caffeine vs. placebo), figure reproduced from (39) with permission

Fig 3 Absolute rates of severe hypoglycemia (% of subjects affected during the trial) in the 2 glucose arms of the ACCORD and ADVANCE trials.