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Targeting acute hyperglycaemia in clinical practice

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Abstract

The UKPDS established the benefit of tight glycaemic control in preventing microvascular disease but was unable to demonstrate an effect on cardiovascular disease. This may have been due to the limitation of traditional agents which were unable to maintain particularly tight glycaemic control in the participants. A number of new oral agents and insulins are now available and show promise in achieving better glycaemic control which is maintained for longer. Side effects of weight gain and hypoglycaemia may also be less frequent and some of the new therapies have direct effects on post-prandial glucose. However the precise clinical benefit of new treatments has yet to be established, particularly in terms of relevant clinical outcomes such as death or cardiovascular disease. Many of the existing data are derived from regulatory studies which establish safety and equivalence and do not often define clinical benefit or value for money. However, some trials which do measure relevant endpoints are in progress and are due to report in the next few years. It seems likely that many of the new treatments will supplant existing therapy and the hope is that this will result in better glycaemic control and less micro and macrovascular disease.

Introduction

It is now over 10 years since the publication of the DCCT[1] and around 7 years since the UKPDS[2] which both proved the benefit of tight glycaemic control in reducing the risk of microvascular complications. Data from both studies have also hinted that tight glycaemic control may also reduce cardiovascular risk.[3] Furthermore, we can now use a host of different agents to control blood glucose and are aware that control of BP and

lipids reduces the risk of cardiovascular disease. Yet evidence from the USA indicates that glycaemic control has not improved, indeed it may have actually deteriorated. In this review I consider the claims of new glucose lowering therapies and consider whether there is sufficient evidence to challenge the traditional choice of agents in the management of Type 2 diabetes.

Lessons from the UKPDS and DCCT

These two landmark trials have established the relevance of controlling blood glucose to prevent diabetic tissue complications. Review of their results establishes precisely the extent to which blood glucose control reduces the risk of microvascular disease. In the DCCT,[1] a gap in HbA1c of 2% led to a 30% reduction in the progression of microvascular disease over the course of the study. However, in the UKPDS, a gap in HbA1c of 1% led to around a 15% reduction of microvascular disease during the course of the trial.[2] This indicates that there is a linear relationship between improved glycaemic control as measured by HbA1c and the risk of microvascular disease. Interestingly, an epidemiological analysis of the UKPDS data according to the achieved levels of HbA1c also demonstrated such a linear relationship.[3]

A further crucial observation of the UKPDS trial was that it proved impossible for those involved in the trial to keep those assigned to the intensive treatment group at a tightly controlled level of HbA1c over time; therefore HbA1c drifted up in both intensive and standard groups although the gap between them was maintained. This highlighted two important issues:

- 1) none of the available agents (ie sulphonylureas, insulin or metformin) were able to prevent progressive decline in β cell secretion, the hallmark of the pathology of Type 2 diabetes.
- 2) the investigators involved in the trial were unable to intensify therapy as required in those seeing the intensive group, due to the side-effects of the therapies used during the trial.

The trial also established that in the overweight group who participated in a sub-trial in which patients were randomised to one of three arms to achieve intensive glycaemic control, insulin, sulphonylureas or metformin, those in the metformin showed significant reductions in cardiovascular disease and diabetes related mortality.

Another important clinical message was that tight control of BP had as much effect in reducing microvascular disease as did intensifying glycaemic control.[4] This observation has had a profound effect upon management since tight control of BP is often easier to achieve than maintaining tight control of blood glucose. It also raises the important question as to the amount of added benefit in terms of micro- and macrovascular disease which is produced by intensive blood glucose control in individuals who have already received aggressive lipid and BP lowering.

Side effects of glucose lowering therapy preventing tight glucose targets

The most important side effects which limit the ability of both patients and clinicians to achieve tight glycaemic targets in Type 2 diabetes are hypoglycaemia and weight gain.

Weight gain is common in those taking sulphonylureas or insulin and has both a major effect on quality of life and probably limits the improvement in cardiovascular risk which results from improved glycaemic outcomes.

In the UKPDS weight gain was observed in all intensive treatment arms. In those randomised to sulphonylureas, mean weight gain was around 4kg while subjects allocated to insulin, gained more weight, around 6kg.[2] There was clear evidence that metformin (which was only used in those deemed especially overweight) had a useful effect in limiting weight gain. Those randomised to metformin gained a mean of around 2.5kg over 9 years.

Weight gain in people with Type 2 diabetes on sulphonylureas or insulin is multifactorial and probably involves a number of mechanisms. (Table 1) These include: replacement of fat and lean mass after a period of poor glycaemic control and persistent gluconeogenesis, anabolic effects of high-dose insulin,[5, 6] appetite increase[7] and increased freedom to eat without risk of hyperglycemia,[8] and reduction of glycosuria with resultant retention of calories. Those on insulin may increase their food intake, possibly due to a direct effect of insulin on critical brain areas such as the hypothalamus or perhaps because the therapy gives them increased freedom to eat without increasing their blood glucose.

Hypoglycaemia

Hypoglycaemia limits the ability of insulin therapy to achieve near normoglycaemia, particularly in the elderly where episodes can be devastating. However, in practice the risk of hypoglycaemia is generally low among people with Type 2 diabetes when compared to those with Type 1. Epidemiological data indicates that in the early stages of insulin therapy rates of severe and biochemical hypoglycaemia are comparable to those seen in patients taking sulphonylureas.[9] By contrast rates among individuals with Type 1 diabetes are significantly higher in both those recently starting treatment and also in those with longstanding disease. Rates of hypoglycaemia are higher in those with longstanding Type 2 diabetes suggesting that with increased duration people with Type 2 diabetes become progressively more at risk. This may relate both to the progressively more unstable free insulin levels from injected insulin as endogenous insulin secretion declines and an accompanying failure of glucagon release during hypoglycaemia.[10] During the UKPDS rates of severe episodes were relatively rare, being observed in only around 2-3% in the early years of the trial.[2] Interestingly, the proportion of those experiencing severe hypoglycaemia began to increase during the latter part of the trial. Furthermore, these low rates suggest that the teams responsible for care at local centres failed to intensify insulin therapy due to a perception of a high risk which wasn't borne out in reality.

Post prandial glucose

The seminal clinical trials described above have concentrated on the effect on improving overall glycaemic control but there is increasing interest in the relevance of post-

prandial glucose. This has been driven by mounting epidemiological evidence illustrating the independent effect of glucose levels following a glucose challenge on cardiovascular mortality and work in the laboratory which has shown the potent pathological mechanisms provoked by acute rises in glucose. Furthermore, there is evidence that in those with tightly controlled glycaemic control, blood glucose excursions after eating make a disproportionately greater contribution to HbA1c levels. A whole host of large-scale epidemiological studies have demonstrated that glucose levels following a glucose tolerance test, predict cardiovascular mortality to a greater extent than fasting plasma glucose.[11, 12] It is important to note that with some exceptions, these are post-challenge glucose values rather than post-prandial glucose; it is to some extent speculative in generalising these data to post-prandial effects of glucose. Nevertheless, a considerable body of experimental work, beyond the scope of this review, has convincingly demonstrated that post challenge/prandial glucose rises activates a number of pathogenic pathways which can lead to macrovascular disease.[13]

In addition, recent work highlights that post prandial glucose components become particularly relevant to attempt so improve glucose in those with relatively tightly controlled diabetes.[14] This has been based on mathematical modelling of 24h glucose profiles in relation to HbA1c and suggests that once HbA1c levels fall to below 7%, the glucose rise after eating contributes over 70% to HbA1c levels. The implication is that in those who have tightly controlled diabetes, attempts to lower HbA1c still further, need to focus on post-prandial glucose. The clinical consequence is that clinicians should choose agents in those with well controlled diabetes which have specific effects on post-prandial glucose.

The emerging data around post-prandial glucose certainly make a compelling story. The epidemiological evidence is convincing and is backed up by the basic science which explains clearly how raised post-prandial glucose contributes to macrovascular disease. However, the main limitation at present is the lack of evidence that targeting post-prandial glucose has a relevant effect on important clinical outcomes. Designing such studies is not easy, since they require large numbers of patients and need to run for sufficient years to demonstrate differences in relevant clinical endpoints such as cardiovascular mortality and myocardial infarction and stroke. Furthermore, it is difficult to separate the effects of post-prandial and fasting glucose since reducing post-prandial glucose will often have an effect on fasting levels due to a reduction in glucose toxicity. Despite these difficulties a number of large scale trials are ongoing and will begin to report in the next few years. Until then it seems worthwhile using any strategy which lowers HbA1c and to focus on post-prandial glucose in those individuals whose HbA1c remains high despite a well-controlled fasting blood glucose.

Using the ‘new’ oral agents to control blood glucose

It is beyond the scope of this review to consider the newer oral agents which have recently become available. However, for each of class of agent it seems appropriate to consider to what extent the available clinical trial data suggest whether there are situations where they should be used in preference to traditional oral agents.

Insulinotropic meglitinide analogues

Two drugs in this class are currently available, nateglinide and repaglinide. Both agents bind to the sulphonylurea receptor and stimulate insulin secretion. Their particular advantage is that insulin release is to some extent dependent upon the prevailing blood glucose.[15] Thus, insulin release is considerably greater when plasma glucose is high and largely inhibited when insulin is in the normal range. This conveys particular advantages in those at risk of hypoglycaemia such as the elderly or in those who eat irregularly. Clearly these agents depend upon intact endogenous insulin secretion and are relatively ineffective in those with significant β -cell loss. Since insulin release is facilitated they might be expected to have advantages over standard sulphonylureas in terms of less hypoglycaemia and weight gain. Clinical trials suggest that the mean fall in HbA1c is generally around 1% in trials lasting between 6-12 months.[15] There are few data indicating their effectiveness beyond this period. Importantly, there are no head to head studies comparing their effects to short acting sulphonylureas such as tolbutamide. However, they do appear to have a role where oral agents are indicated, where eating may be irregular and hypoglycaemia would be a particular problem (such as the elderly).

Thiazolidinediones

There is now an extensive body of data from both clinical trials and clinical experience which is beyond the scope of this article and readers are directed to a recent comprehensive review.[16] The early concern about possible liver toxicity following the problems which followed the cases of fatal hepatic failure which followed the introduction of the first agent, troglitazone have been dispelled. Indeed there is some evidence to suggest that this class of drugs may be useful in treating non alcoholic steatohepatitis (NASH), ie “fatty liver”.[17]

Most clinical trials suggest that HbA1c by around 1% but these mean falls hide the wide inter-individual response in people with Type 2 diabetes. Some individuals reduce and maintain reductions of HbA1c of over 2%. Improvements in glycaemic control are often not observed for over 3 months and worthwhile reduction may take over 6 months to become apparent. Patients are not at risk of hypoglycaemia unless treated concurrently with sulphonylureas. Weight gain is a consistent accompaniment due to a combination of both fluid retention and fat accumulation. Cardiac failure can also be precipitated, particularly in combination with insulin although most cases appear to be fairly mild. There is also some concern that these drugs may increase the risk of fractures.[18] Recent evidence indicates that these agents remain effective in controlling blood glucose over a longer period compared to sulphonylureas.[19] However, although one of the available agents causes a more favourable lipid profile, there is no evidence as yet that they have a any benefit on relevant clinical outcomes such as cardiovascular mortality or morbidity. Clinical trials, whose primary aim is to answer this question are in progress and will report in the next 2-3 years.

Unfortunately there appears to be no reliable clinical characteristic which predicts individual clinical response. Since the TZDs have particular effects on insulin sensitivity it is logical to use these agents in those who are most insulin resistant such as the very

obese but such an approach, although sensible has not been reinforced by any trial evidence. At present, they seem a useful, albeit expensive alternative to sulphonylureas as second-line therapy (after metformin).

Extending the action of Glucagon like Peptide 1 (GLP-1)

The last few years have witnessed an exciting progression of research which surrounds the effect of GLP-1. The potential advantage of using incretin like effects has moved from an exploration of the physiological effects of this gut peptide to a series of potentially effective and exciting therapeutic agents.[20, 21] In many respects the actions of GLP-1 form a list of ideal properties for a drug to treat Type 2 diabetes (Table 2). In combination, agents with these properties seem likely to have a major and perhaps longlasting effect on lowering blood glucose and maintaining metabolic control. The major problem that the pharmaceutical companies have had to overcome is how to prolong the action of native GLP-1 which is broken down within minutes by the action of the enzyme DPPP-IV. The first agent to reach the market is a peptide which is found in the saliva of the Gila monster, exenatide (Byetta).[22] This is given twice daily by injection and can improve glycaemic control and reduce weight. Significant numbers of patients experience nausea and vomiting (although this often diminishes with time) but the weight reduction appears to be independent of the gastro-intestinal side-effects. It is difficult to predict which individual will respond well to such treatment but some patients have experienced remarkable degrees of weight loss and near normal HbA1c which have been sustained over up to 2-3 years.

Other agents are in advanced clinical development, liraglutide is a GLP-1 analogue whose action has been prolonged by attaching a fatty acid moiety to a GLP molecule.[23] Subsequent binding to albumin lengthens the effect. This drug is given once daily. A number of companies are working on preparations which have an even longer duration of action and although they will all need to be given by injection, this may be necessary only once a week or even less often.

An alternative approach to prolonging GLP1 is to prevent its breakdown by inhibiting DPPP-IV.[24] At least 3 agents have been developed with one having a license for use in the USA. These agents have a more modest effect on HbA1c than GLP-1 analogues but don't cause nausea and vomiting. They appear to be weight neutral. The differences in efficacy and side-effects between this class of drugs and GLP-1 analogues may merely be a 'dose-response' effect on GLP-1 receptors. Thus DPP-IV inhibitors are unable to boost GLP-1 concentrations sufficiently to produce weight loss (a desirable effect) or effects on the gastro-intestinal tract (an undesirable effect).

Insulin therapy in Type 2 diabetes

In the UKPDS, insulin proved no more effective in maintaining tight glycaemic control. Despite the potential to increase the dose to whatever was necessary to keep blood glucose close to normal, the investigators in the study were unable to maintain this and HbA1c drifted upwards over the years as endogenous insulin secretion declined.[2] It is not entirely clear what factors prevented the achievement of tight glucose targets but the side effects of insulin, weight gain and the perceived risk of hypoglycaemia undoubtedly played a role. The insulin regimens in the UKPDS involved the use of once daily human

ultratard with the addition of soluble insulin pre-meal as necessary. This relatively unusual insulin regime may have contributed to the difficulties in achieving tightly controlled blood glucose.

In recent years, different approaches to insulin therapy in Type 2 diabetes have been explored in an attempt to reduce the side-effects of weight gain and hypoglycaemia. There is reasonable evidence that the use of basal long or medium acting insulin, usually taken at bedtime is a practical, easy to learn approach. Yki-Jarvinen and colleagues have demonstrated in a series of studies that the combination of overnight long acting insulin with continued oral agents can produce less weight gain than conventional twice daily pre-mixed insulin.[8] They have also shown that the combination of NPH and metformin leads to less weight gain than a combination of sulphonylureas and insulin.[25] Such an approach has become extremely popular as an alternative to conventional twice daily injections. Those who are particularly anxious at the prospect of insulin often prefer to start with one injection a day. One additional advantage is the ability to teach the patient to adjust their insulin dose upwards every few days according to the fasting blood glucose.

The advent of rapid acting insulin analogues provides a way of targeting post-prandial glucose since insulin lispro, insulin aspart and insulin glulisine all lower post-prandial glucose by around 2mmol/l compared to their regular insulin counterparts. Clinical trials have not demonstrated that this translates into significant falls in HbA1c when compared to soluble insulin suggesting that blood glucose must rise elsewhere during the day or night.[26] Glucose profiling indicates that glucose runs higher during the night. This translates into a clinical advantage as it accounts for the useful reductions in nocturnal hypoglycaemia that are observed with most trials involving rapid acting insulin analogues.

Reductions in nocturnal hypoglycaemia have also been observed for pre-mix insulins which contain rapid acting insulin analogues.[27] These include Humalog Mix-25 and Novomix 30 which respectively contain insulin lispro and insulin aspart as the fast acting component. Since both insulins also reduce post prandial glucose they provide a useful and simple option for those clinicians who wish to target post-prandial glucose. Of course when given twice daily they will only affect blood glucose rises after breakfast and the evening meal.

Long acting insulin analogues have become increasingly popular as a treatment option for people with Type 2 diabetes. In a recent trial, Riddle and colleagues used the term 'treat to target' to describe an insulin adjustment algorithm in which investigators and their teams were asked to adopt an aggressive policy of up-titrating insulin to achieve very tight fasting glucose targets.[28] The two comparators in this study were insulin glargine and NPH insulin. In this trial, the proportion of patients who achieved a target fasting glucose value (< 7 mmol/l) were the same in both arms as was mean HbA1c. The only difference between the groups was in the proportion of participants experiencing symptomatic nocturnal hypoglycaemia. In those taking NPH the proportion was around 60% compared to around 40% in those on insulin glargine. There were very few severe

episodes in either arm. Thus aggressive use of overnight longacting insulin can produce remarkable tight glycaemic control in most patients with acceptable rates of symptomatic hypoglycaemia, even in those taking NPH.

Possibility of ‘smart’ therapy, tackling different pathological areas of Type 2 diabetes at the same time

The traditional approach to therapy in people with Type 2 diabetes is to use a ‘sequential’ approach in which the initial first step is diet and lifestyle encouraging exercise and weight loss.[29] For those who don’t respond the next option is metformin and individuals then move onto either glitazones or sulphonylureas before ending up on insulin as their β cell function declines. It seems clear that the available agents are not able to slow the progressive decline in β cell mass to any great extent. However, more agents are now available which act in different ways and in theory it might be more logical to attack different aspects of the pathology at the same time. This might even halt progressive β -cell failure. There have been relatively few trials which have tested such a hypothesis but a rather small scale trial explored this area recently. Poulsen and colleagues randomised 16 subjects either to twice daily NPH/pre-mixed insulin or a triple combination of pre-meal insulin aspart, metformin and rosiglitazone.[30] After 6 months, HbA1c had remained static in the insulin treated group while in the triple therapy arm, it had fallen to under 7%. Rates of hypoglycaemia were no different between the groups although those with the better glycaemic control had gained more weight. Of course a study of such limited duration could not measure the rate of decline of β -cell function and any important benefit needs to be determined by longer term and larger scale trials.

Does tight glycaemic control reduce cardiovascular risk?

Many diabetes organisations around the world are now recommending much tighter glucose targets with HbA1c recommended to be held below 7%. This is largely based on the belief and hinted by the epidemiological treatment of the UKPDS data that this kind of glucose control is necessary to help to reduce the risk of cardiovascular disease. Two largescale studies are now underway. The ADVANCE trial, involving 10,000 people with Type 2 diabetes in many different countries across the world is due to report in 2008,[31] while the results of the ACCORD trial, taking place in the USA[32] will be available 3-4 years later. Hopefully these studies will establish the precise extra benefit of tight blood glucose control in an era of much more effective management of BP and lipids.

Conclusions

Since the publication of the UKPDS in 1998, a number of new oral agents and insulins have become available to control blood glucose. It is often difficult to establish their precise benefit since many are undertaken as part of regulatory studies by the pharmaceutical industry. The point of such trials is generally to establish equivalence and safety, essential hurdles for companies before they launch new products. There have been relatively few ‘independent’ trials which also explore the precise benefit of new products and approaches. It appears that new agents may offer more benefit than

traditional therapy but at present the degree of advantage is not clear, particularly in relation to the increased cost. We need to await the results of ongoing trials and commission some additional work before we can recommend a major shift in the therapeutic approach to Type 2 diabetes. It is important to note recent population surveys from the USA which suggest that glycaemic control might be worsening rather than improving despite the greater number of new agents which can control blood glucose. This suggests that patient education and training of primary care based professionals (who largely look after individuals with Type 2 diabetes) may be just as important as investment in new medication.

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Table 1 Possible causes of weight gain as a consequence of insulin therapy in diabetes

Anabolic effect increasing skeletal muscle and fat mass following period of poor glycaemic control
 Reduction of glycosuria
 Increased appetite
 Increased freedom to eat freely
 Defensive eating to prevent or treat hypoglycaemia

Table 2 Physiological effects of glucagon like peptide 1 which have potential therapeutic use in management of Type 2 diabetes

Increase insulin secretion (at high glucose levels only)
 Inhibit glucagon secretion (but not at hypoglycaemic levels)
 Delay gastric emptying
 Anorectic and causes weight loss
 In animals increase number of β cells