ORIGINAL ARTICLE

Newer Therapies for Diabetes Management

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Introduction

WITH THE INCREASING GLOBAL EPIDEMIC of diabetes, especially type 2 diabetes, all major pharmaceutical companies are focusing on new molecules for the treatment of diabetes and obesity. With the better management of diabetes (improved HbA1c values), the microvascular complications have significantly reduced over the past two decades. This has been achieved without increasing hypoglycemia especially with newer technological advances (discussed at length in chapters 12 and 13 in this yearbook).

We review here the abstracts related to the newer molecules that are being investigated in the management of diabetes. We searched more than 400 articles on newer agents published from July 2012 to June 2013, of which the best 19 abstracts are discussed. Also, we briefly mention newer insulin analogs and alternate insulin delivery methods, as this topic is discussed at length by colleagues in chapter 5 of this yearbook.

SODIUM-GLUCOSE CO-TRANSPORTER (SGLT-1 And 2) INHIBITORS

Canagliflozin: first global approval

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Canagliflozin (Invokana), an oral selective sodium–glucose co-transporter 2 (SGLT2) inhibitor, is under global development with Mitsubishi Tanabe Pharma and Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson, for the treatment of type 2 diabetes mellitus. SGLT2 are mainly located in the proximal tubule of the kidney and are involved in the reabsorption of filtered glucose from the glomeruli into the body. Inhibition of SGLT2 lowers blood glucose in an insulin-independent manner as a consequence of blocking reabsorption of filtered glucose in the glomeruli, thereby increasing urinary excretion of glucose and, in turn, potentially reducing body weight. Canagliflozin is the first SGLT2 inhibitor to be approved in the United States and is under regulatory review

in the European Union. This article summarizes the milestones in the development of canagliflozin, leading to its first approval for use in adults with type 2 diabetes.

Canagliflozin, a new sodium-glucose cotransporter 2 inhibitor, in the treatment of diabetes

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Purpose

The published evidence on the pharmacology, pharmacodynamics, pharmacokinetics, safety, and efficacy of a promising investigational agent for managing type 2 diabetes is evaluated.

Summary

Canagliflozin belongs to a class of agents—the sodium–glucose co-transporter 2 (SGLT2) inhibitors—whose novel mechanism of action offers potential advantages over other antihyperglycemic agents, including a relatively low hypoglycemia risk and weight-loss-promoting effects. Canagliflozin has dose-dependent pharmacokinetics, and research in laboratory animals demonstrated high oral bioavailability (85%) and rapid effects in lowering glycosylated hemoglobin (HbA1c) values. In four early-stage clinical trials involving a total of over 500 patients, the use of canagliflozin for varying periods was associated with significant mean reductions in HbA1c (absolute reductions of 0.45–0.92%) and fasting plasma glucose (decreases ranged from 16.2% to 42.4%) and weight loss ranging from 0.7 to 3.5 kg. More than a dozen phase II or III clinical trials of canagliflozin in adults are ongoing or have been recently completed, but the final results of

most of those studies have not been published. Adverse effects reported in clinical trials of canagliflozin include urinary tract and genital infections, occurring in about 10% of patients. Additional and larger phase III clinical trials to delineate the potential role of canagliflozin and other SGLT2 inhibitors in the management of diabetes (including studies involving the elderly, children, and patients with renal or hepatic dysfunction) are planned or currently under way.

Conclusion

Canagliflozin and other investigational SGLT2 inhibitors have a novel mechanism of action that may offer a future alternative treatment pathway for managing type 2 diabetes.

Ipragliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors in the treatment of type 2 diabetes: preclinical and clinical data

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Pharmacol Ther 2013; 139: 51–59

Sodium–glucose co-transporter-2 (SGLT2) is expressed in the proximal tubules of the kidneys and plays a key role in renal glucose reabsorption. A novel class of antidiabetic medications, SGLT2-selective inhibitors, attempts to improve glycemic control in diabetics by preventing glucose from being reabsorbed through SGLT2 and reentering circulation. Ipragliflozin is an SGLT2 inhibitor in phase 3 clinical development for the treatment of type 2 diabetes mellitus (T2DM). In this review, we summarize recent animal and human studies on ipragliflozin and other SGLT2 inhibitors, including dapagliflozin, canagliflozin, empagliflozin, tofogliflozin, and luseogliflozin. These agents all show potent and selective SGLT2 inhibition *in vitro* and reduce blood glucose levels and HbA1c in both diabetic animal models and patients with T2DM. SGLT2 inhibitors offer several advantages over other classes of hypoglycemic agents. Because of their insulin-independent mode of action, SGLT2 inhibitors provide steady glucose control without major risk for hypoglycemia and may also reverse β -cell dysfunction and insulin resistance. Other favorable effects of SGLT2 inhibitors include a reduction in both body weight and blood pressure. SGLT2 inhibitors are safe and well tolerated and can easily be combined with other classes of antidiabetic medications to achieve tighter glycemic control. The long-term safety and efficacy of these agents are under evaluation.

Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes

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Aims

Sodium–glucose co-transporter 2 (SGLT2) reabsorbs glucose and sodium in the renal proximal tubule. Dapagliflozin, an SGLT2 inhibitor, targets hyperglycemia in type 2 diabetes by increasing renal glucose excretion. To investigate whether the parallel-occurring sodium loss would have diuretic-like physiologic effects, we compared dapagliflozin and hydrochlorothiazide (HCTZ) effects on 24-hour blood pressure (BP), body weight, plasma volume, and glomerular filtration rate (GFR).

Methods

In this randomized, placebo-controlled, double-blind trial, 75 subjects with type 2 diabetes were assigned placebo, dapagliflozin 10 mg/day, or HCTZ 25 mg/day. Changes from baseline BP, body weight, plasma volume, and GFR were assessed after 12 weeks of treatment.

Results

Subjects' mean age was 56 years, type 2 diabetes mellitus (T2DM) duration 6.3 years, and hemoglobin A1c (HbA1c) 7.5%. Treatment with placebo, dapagliflozin, or HCTZ resulted in changes from baseline in 24-hour ambulatory mean systolic blood pressure (SBP) of -0.9 (95% CI $-4.2, +2.4$), -3.3 (95% CI $-6.8, +0.2$), and -6.6 (95% CI $-9.9, -3.2$) mmHg, respectively, at week 12, adjusted for baseline SBP. Body weight decreased with dapagliflozin and HCTZ. In a substudy, plasma volume appeared to decrease with dapagliflozin but did not change with placebo or HCTZ treatment. Dapagliflozin induced a greater reduction in GFR (-10.8% ; 95% CI $-14.6, -6.7$) relative to placebo (-2.9% ; 95% CI $-6.9, +1.2$) or HCTZ (-3.4% ; 95% CI $-7.3, +0.6$).

Conclusions

Dapagliflozin-induced SGLT2 inhibition for 12 weeks is associated with reductions in 24-hour BP, body weight, GFR, and possibly plasma volume. Cumulatively, these effects suggest that dapagliflozin may have a diuretic-like capacity to lower BP in addition to beneficial effects on glycemic control.

Dapagliflozin, an SGLT2 inhibitor for the treatment of type 2 diabetes

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Drugs Today (Barc) 2013; 49: 289–301

Dapagliflozin is a selective, competitive inhibitor of sodium–glucose cotransporter 2 (SGLT2) acting to block reabsorption of filtered glucose in the kidney. Independent of pancreatic β -cell function or the modulation of insulin sensitivity, this novel treatment strategy promotes glucosuria and direct lowering of plasma glucose concentrations. Dapagliflozin has been approved for the treatment of type 2 diabetes in the European Union; however, the U.S. Food and Drug Administration rejected the approval of dapagliflozin based on lack of clinical data to effectively assess the benefit-to-risk profile. This article will highlight the physiology of renal glucose regulation and reabsorption, briefly outline the pharmacology of dapagliflozin, and discuss the results of completed clinical trials as well as the status of the drug.

Safety, pharmacokinetics and pharmacodynamics of remogliflozin etabonate, a novel SGLT2 inhibitor, and metformin when co-administered in subjects with type 2 diabetes mellitus

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Background

The sodium-dependent glucose co-transporter-2 (SGLT2) is expressed in absorptive epithelia of the renal tubules. Remogliflozin etabonate (RE) is the prodrug of remogliflozin, the active entity that inhibits SGLT2. An inhibitor of this pathway would enhance urinary glucose excretion (UGE), and potentially improve plasma glucose concentrations in diabetic patients. RE is intended for use for the treatment of type 2 diabetes mellitus (T2DM) as monotherapy and in combination with existing therapies. Metformin, a dimethylbiguanide, is an effective oral antihyperglycemic agent widely used for the treatment of T2DM.

Methods

This was a randomized, open-label, repeat-dose, two-sequence, crossover study in 13 subjects with T2DM. Subjects were randomized to one of two treatment sequences in which they received either metformin alone, RE alone, or both over three 3-day treatment periods separated by two nontreatment intervals of variable duration. On the evening before each treatment period, subjects were admitted and confined to the clinical site for the duration of the 3-day treatment period. Pharmacokinetic, pharmacodynamic (urine glucose and fasting plasma glucose), and safety (adverse events, vital signs, ECG, clinical laboratory parameters, including lactic acid) assessments were performed at check-in and throughout the treatment periods. Pharmacokinetic sampling occurred on day 3 of each treatment period.

Results

This study demonstrated the lack of effect of RE on steady-state metformin pharmacokinetics. Metformin did not affect the area under the curve of RE, remogliflozin, or its active metabolite, GSK279782, although $C_{\max}$ values were slightly lower for remogliflozin and its metabolite after coadministration with metformin compared with administration of RE alone. Metformin did not alter the pharmacodynamic effects (UGE) of RE. Concomitant administration of metformin and RE was well tolerated with minimal hypoglycemia, with no serious adverse events and no increase in lactic acid.

Conclusions

Coadministration of metformin and RE was well-tolerated in this study. The results support continued development of RE as a treatment for T2DM.

Comment

SGLTs are a family of glucose transporters. There are many SGLTs of which SGLT1 and SGLT2 are well characterized. SGLT2 is localized mainly in proximal convoluted tubules of kidney and involved in glucose reabsorption. Blocking SGLT2 transporter will result in increased urinary glucose excretion, loss of weight, and improvement in glucose control. In addition, SGLT1 inhibition further reduces glucose reabsorption from the distal tubules of the kidney. We chose five abstracts in this category as there is increased activity in this class of molecules by major pharmaceutical companies.

Canagliflozin was the first SGLT2 inhibitor approved by the U.S. Food and Drug Administration (FDA) in the United States, and it is under regulatory review by European Medicines Agency. The first article summarizes the development of canagliflozin and its clinical data. The second article describes the clinical effects of canagliflozin in phase 2 and phases 3 studies in patients with type 2 diabetes. Ipragliflozin is another SGLT2 inhibitor; the third article summarizes the preclinical and clinical data of this agent in the management of type 2 diabetes.

Two more SGLT2 inhibitors are under clinical trials: dapagliflozin and remogliflozin. The last three abstracts present clinical efficacy data of these two SGLT2 inhibitors in patients with type 2 diabetes.

Overall, all four agents showed promise in the management of type 2 diabetes. They do have similar HbA1c reduction by 0.5–0.9% with significant weight and blood pressure reduction compared with the placebo. However, these agents are associated with higher urinary and genital tract infections, especially in women. Earlier studies on dapagliflozin had insignificant imbalance toward bladder and breast cancer. Since the SGLT are ubiquitous, long-term safety is unknown. The combined SGLT1 and 2 inhibitors are currently being investigated in addition to their role in management of type 1 diabetes.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGS

Clinical potential of lixisenatide once daily treatment for type 2 diabetes mellitus

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The glucagon-like peptide (GLP)-1 receptor agonist lixisenatide (Lyxumia) was approved for marketing by the European Medicines Agency in February 2013 and has been evaluated in a clinical study program called GetGoal. Lixisenatide activates the GLP-1 receptor and thereby exercises the range of physiological effects generated by GLP-1, which consist of increased insulin secretion, inhibition of glucagon secretion, and decreased gastrointestinal motility alongside the promotion of satiety. In the GetGoal study program, lixisenatide demonstrated significant reductions in glycated

hemoglobin (HbA1c), and fasting and postprandial plasma glucose compared with placebo. The effect on glycemia was evident, with both monotherapy and in combination with insulin and various oral antidiabetic agents. Furthermore, a general trend toward reduced body weight was reported. In head-to-head trials with the other GLP-1 receptor agonists (exenatide and liraglutide) on the market, lixisenatide demonstrated a superior effect with respect to reduction in postprandial plasma glucose and had a tendency toward fewer adverse events. However, lixisenatide seemed to be less efficient or, at best, equivalent to exenatide and liraglutide in reducing HbA1c, fasting plasma glucose, and body weight. The combination of a substantial effect on postprandial plasma glucose and labeling with once-daily administration separates lixisenatide from the other GLP-1 receptor agonists. The combination of basal insulin, having a lowering effect on fasting plasma glucose, and lixisenatide, curtailing the postprandial glucose excursions, makes sense from a clinical point of view. Not surprisingly, lixisenatide is undergoing clinical development as a combination product with insulin glargine (Lantus). At present the main place in therapy of lixisenatide seems to be in combination with basal insulin. A large multicenter study will determine the future potential of lixisenatide in preventing cardiovascular events and mortality, in patients with type 2 diabetes and recent acute coronary syndrome.

Lixisenatide: first global approval

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The selective once-daily prandial glucagon-like peptide-1 (GLP-1) receptor agonist lixisenatide (Lyxumia) is under development with Sanofi for the treatment of type 2 diabetes mellitus. Lixisenatide belongs to a class of GLP-1 compounds designed to mimic the endogenous hormone GLP-1. Native GLP-1 stimulates insulin secretion in a glucose-dependent manner, as well as suppressing glucagon production and slowing gastric emptying. A once-daily subcutaneous formulation of lixisenatide has been approved in the European Union, Iceland, Liechtenstein, Norway, and Mexico for the treatment of type 2 diabetes and is under regulatory review in the United States, Switzerland, Brazil, Canada, Ukraine, South Africa, Japan, and Australia. This article summarizes the milestones in the development of lixisenatide, leading to this first approval for use in adults with type 2 diabetes.

Once weekly exenatide: efficacy, tolerability and place in therapy

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Exenatide once weekly is the first glucose-lowering agent available to patients with type 2 diabetes mellitus (T2DM).

This long-acting formulation contains the same active ingredient as exenatide twice daily, except that the exenatide is encapsulated in dissolvable microspheres. After subcutaneous injection, exenatide once weekly microspheres remain in place under the skin and slowly degrade, releasing active exenatide continuously into circulation. In randomized clinical trials, exenatide once weekly was associated with significant glycemic improvement and moderate weight loss in patients with T2DM when administered as monotherapy or in combination with a variety of oral antidiabetic agents. Exenatide once weekly also lowered blood glucose more effectively than titrated basal insulin in patients on metformin or metformin plus sulphonylurea background therapy. Gastrointestinal side effects (nausea, vomiting, and diarrhea) were the most common tolerability issues associated with exenatide once weekly administration, but they occurred at lower rates than in patients on other glucagon-like peptide receptor agonists (i.e., exenatide twice daily or liraglutide). Issues regarding the place of exenatide once weekly in T2DM pharmacotherapy are discussed.

Comment

The first GLP-1 analog, exenatide, was approved by the FDA in 2005 followed by approval of liraglutide in 2010. GLP-1 analogs have shown promise in the management of type 2 diabetes. Lixisenatide, a recently approved GLP-1 analog, demonstrated a modest reduction in postprandial plasma glucose and had a tendency toward fewer adverse events than other GLP-1 analogs. However, overall reduction in HbA1c and weight loss is similar to exenatide and liraglutide. Furthermore, lixisenatide is undergoing clinical development as a combination product with insulin glargine. Similarly, Liraglutide, a once-daily GLP-1 analog, is also being investigated with insulin detemir so that fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) reductions can be achieved with basal insulin and GLP-1 analog, respectively.

Another development is prolonging the duration of exenatide once weekly so that patient compliance can be enhanced. The last article described the efficacy and tolerability of once-weekly exenatide preparation.

Most of the earlier GLP analogs (exenatide) were short-acting and reduce prandial glucose excursion when given before meals. However, newer analogs are longer acting and have a significant effect on FPG. There is preferential efficacy of this class of drug in Asians, probably because of higher carbohydrate intake. Long-term safety of these drugs has been recently questioned, especially in relation to pancreatitis and pancreatic cancer. Many long-term studies are ongoing to investigate their safety as it relates to cardiovascular outcome and cancers. As of July 2013, European Medicines Agency's Committee for Medicinal Products for Human Use concluded that presently available data for incretin-based therapy do not adequately support concerns about pancreatic adverse events.

DIPEPTIDYL PEPTIDASE-IV (DPP IV) INHIBITORS

Effect of sitagliptin on post-prandial glucagon and GLP-1 levels in patients with type 1 diabetes: investigator-initiated, double-blind, randomized, placebo-controlled trial

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Objective

Peripheral insulin resistance in type 1 diabetes may be related to a paradoxical postprandial glucagon increase. This study evaluated the effects of sitagliptin (dipeptidyl peptidase-IV [DPP-IV] inhibitor, approved for patients with type 2 diabetes) in adults with type 1 diabetes to improve glycemic control through decreasing postprandial glucagon.

Methods

This investigator-initiated, double-blind, randomized, parallel, 20-week study enrolled 141 subjects. Subjects received sitagliptin 100 mg/day or placebo for 16 weeks. A subset of 85 patients wore blinded continuous glucose monitors (CGM) for five separate 7-day periods. The primary outcome was postmeal (Boost) reduction in 4-hour glucagon area under the curve (AUC). Secondary endpoints included changes in glycated hemoglobin (A1c), CGM data, insulin dose, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and C-peptide levels.

Results

There were no differences at screening between groups; however, after a 4-week run-in phase, A1c was significantly lower in the sitagliptin versus the placebo group. Postmeal GLP-1 levels were higher ($p < 0.001$) and GIP levels lower ($p = 0.03$) with glucagon suppression at 30 minutes (LS means 23.2 ± 1.9 vs. 16.0 ± 1.8 ; $p = 0.006$) in the sitagliptin group at 16 weeks. There were no differences between the groups in change in A1c, insulin dose, weight, or C-peptide after 16 weeks of treatment. However, C-peptide-positive patients randomized to sitagliptin had a nonsignificant trend toward decrease in A1c, mean glucose, and time spent in hyperglycemia.

Conclusion

Sitagliptin use in type 1 diabetes did not change glucagon AUC, A1c, insulin dose, or weight despite postmeal rise in GLP-1 levels. C-peptide-positive subjects treated with si-

tagliptin had a nonsignificant trend in decreasing hyperglycemia, which needs further evaluation.

Comment

The DPP IVs are oral incretins that increase the native GLP-1 levels. Different DPP IV inhibitors approved for use in the United States and Europe are sitagliptin, vildagliptin, saxagliptin, alogliptin, and Linagliptin. These agents have similar mechanisms of actions to GLP-1 analogs (except that reduction in A1c is modest [0.5–0.8%]) and are weight- and lipid-neutral. The effect of this class of drugs in patients with type 1 diabetes is not known. It is known that patients with type 1 diabetes do have postprandial paradoxical rise in glucagon (though small as compared with type 2 diabetes). Few small studies have reported improvement in A1c, loss of weight, and significant reduction in insulin dose in type 1 diabetes. This article described the effect of sitagliptin, a DPP IV inhibitor, on postprandial glucagon and GLP-1 levels in patients with type 1 diabetes. In this randomized study, there was a significant rise in GLP-1 levels as expected in patients with type 1 diabetes receiving sitagliptin but was not associated with improvement in metabolic effects or insulin dosages. This is in contrast to the previous pilot study (Ellis SL, et al. *Diabet. Med* 2011; **28**: 1176–81) by the same investigators, where there was a small reduction in A1c (0.2%). The authors also described possible roles of this class of drugs in C-peptide-positive patients with type 1 diabetes. This area is being investigated further with the use of GLP-1 analogs in which the blood levels of GLP achieved would be much higher.

NEWER INSULINS

Insulin degludec and insulin degludec/insulin aspart: a review of their use in the management of diabetes mellitus

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Insulin degludec (Tresiba) is an ultra-long-acting insulin analog that is also available as a coformulation with rapid-acting insulin aspart (insulin degludec/insulin aspart) [Ryzodeg]. Insulin degludec has a flat, stable glucose-lowering profile with a duration of action of > 42 hours and less within-patient day-to-day variability in glucose-lowering effect than the long-acting insulin analog insulin glargine. In clinical trials, insulin degludec achieved similar glycemic control to that seen with insulin glargine in patients with type 1 or 2 diabetes but with a lower risk of nocturnal hypoglycemia. In addition, trials examining a flexible dosing regimen of insulin degludec in patients with type 1 or 2 diabetes show the potential for adjusting the injection time, without compromising glycemic control or safety. A 200 U/mL formulation of insulin degludec is also available for use in patients who require large volumes of basal insulin. Insulin degludec/insulin aspart was non-inferior to the long-acting insulin analog insulin detemir in patients with type 1 diabetes and has the potential to reduce

the number of daily injections. Trial results also indicate that insulin degludec/insulin aspart may be an appropriate option for initiating insulin therapy in patients with type 2 diabetes inadequately controlled with oral antidiabetic drugs. Subcutaneous insulin degludec was generally well-tolerated in patients with type 1 or 2 diabetes. In conclusion, insulin degludec and insulin degludec/insulin aspart represent a useful advance in the treatment of type 1 or 2 diabetes.

Newer insulin analogs: advances in basal insulin replacement

Zinman B

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Diabetes Obes Metab 2013; 15 Suppl 1: 6–10

Basal insulin analog therapy is the most common method of introducing insulin replacement therapy for the majority of patients with type 2 diabetes mellitus. Long-acting insulin analogs provide relatively peakless and more physiologic insulin replacement therapy than neutral protaminated Hagedorn insulin. Recently, two new basal insulin analogs have been developed with superior pharmacokinetic and pharmacodynamics properties: insulin degludec and a pegylated insulin lispro. These agents are generally well tolerated and have been evaluated in both type 1 and type 2 diabetes. In this article, we review the results of clinical trials assessing the efficacy, safety, and tolerability of these newer longer-acting insulin analogs. In general, rates of hypoglycemia in these trials were low, glucose control was comparable to currently available basal insulin analogs, and rates of nocturnal hypoglycemia were significantly and substantially lower. While further study will be required, advances in basal insulin replacement may offer important advantages over existing options for starting insulin strategies.

A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, versus insulin glargine in basal insulin-treated patients with type 2 diabetes

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Diabetes Care 2012; 35: 2140–47

Objective

To evaluate whether LY2605541 results in lower fasting blood glucose (FBG) versus insulin glargine (GL).

Research Design and Methods

This 12-week, randomized, open-label, phase 2 study enrolled patients with type 2 diabetes (hemoglobin A(1c) [A1C] $\leq 10.5\%$), taking metformin and/or sulfonylurea with GL or neutral protamine hagedorn (NPH) insulin once daily. Pa-

tients converted to morning insulin administration during lead-in were randomized 2:1 from GL ($n = 248$) or NPH insulin ($n = 39$) to LY2605541 ($n = 195$) or GL ($n = 95$) once daily in the morning.

Results

At 12 weeks, FBG (mean $\pm$ SE) was similar with LY2605541 and GL (118.2 ± 2.0 mg/dL [6.6 ± 0.1 mmol/L] vs. 116.9 ± 2.7 mg/dL [6.5 ± 0.2 mmol/L], $p = 0.433$) as was A1C ($7.0 \pm 0.1\%$ vs. $7.2 \pm 0.1\%$, $p = 0.279$). Intraday blood glucose variability was reduced with LY2605541 (34.4 vs. 39.1 mg/dL [1.9 vs. 2.2 mmol/L], $p = 0.031$). LY2605541 patients had weight loss (-0.6 ± 0.2 kg, $p = 0.007$), whereas GL patients gained weight (0.3 ± 0.2 kg, $p = 0.662$; treatment difference: -0.8 kg, $p = 0.001$). The incidence and rate of both total hypoglycemia and nocturnal hypoglycemia were comparable between LY2605541 and GL; however, LY2605541 had a 48% reduction in nocturnal hypoglycemia after adjusting for baseline hypoglycemia ($p = 0.021$). Adverse events were similar across treatments. Alanine aminotransferase and aspartate aminotransferase remained within normal range but were significantly higher with LY2605541 ($p \leq 0.001$).

Conclusions

In patients with type 2 diabetes, LY2605541 and GL had comparable glucose control and total hypoglycemia rates, but LY2605541 showed reduced intraday variability, lower nocturnal hypoglycemia, and weight loss relative to GL.

Coverage of prandial insulin requirements by means of an ultra-rapid-acting inhaled insulin

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Barriers to the use of prandial insulin regimens include inadequate synchronization of insulin action to postprandial plasma glucose excursions as well as a significant risk of hypoglycemia and weight gain. Technosphere insulin (TI) is inhaled as ultra-rapid-acting human insulin that is quickly absorbed in the alveoli. With a time to maximum plasma drug concentration of approximately 14 min and a time to maximum effect of 35–40 min, TI more closely matches the postprandial insulin concentrations seen in nondiabetic individuals. Studies have shown that long-term administration of prandial TI in combination with long-acting basal insulin results in reductions in hemoglobin A1c comparable to conventional subcutaneously injected prandial insulins but with improved control of early postprandial BG. Furthermore, TI has been associated with less weight gain and a lower incidence of hypoglycemia, which may enhance patient satisfaction and acceptability of insulin therapy. This review discusses the clinical properties of TI and proposes strategies for optimal use.

Novel lyophilized hydrogel patches for convenient and effective administration of microneedle-mediated insulin delivery

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A lyophilized hydrogel patch system was developed for microneedle-mediated insulin delivery. The matrix of cross-linked poly(acrylamide-co-acrylic acid) was synthesized by precipitation polymerization. Recombinant human insulin was loaded into the lyophilized polymer matrix, which can be rehydrated by water. After the hydrated patch was applied to the abdominal skin of diabetic rats after microneedle pretreatment, pharmacodynamics and pharmacokinetics evaluation was performed. The blood samples were collected to monitor blood glucose and serum insulin levels for 12 hours. Blood glucose was lowered in proportion to the concentration of insulin loaded in lyophilized hydrogel patches ($R(2)=0.99$), with a longer duration of action compared to subcutaneous injection. Stability study confirmed that more than 90% of insulin activity was retained in lyophilized hydrogel after 6 months of storage at 4°C. In conclusion, hydrogel patches were demonstrated to be an appropriate drug reservoir for sustained release of insulin with microneedle-mediated transdermal delivery.

Comment

Currently available basal and prandial insulins do not mimic the physiological release of insulin from a β -cell of the pancreas. Insulin degludec is an ultra-long-acting insulin analog. It is also available as a coformulation with rapid-acting insulin aspart (degludec plus). Insulin degludec has a longer duration of action of >42 hours with a longer $t_{1/2}$, and less within-patient day-to-day variability in glucose-lowering effect than insulin glargine. Advantages of insulin degludec are at lower risk of nocturnal hypoglycemia and more flexibility in injection time. However, it is not approved by the FDA because of cardiovascular concerns. The peripheral subcutaneous administration of currently available insulin analogs does not mimic the twofold higher portal-versus-systemic circulating insulin levels seen with endogenously secreted insulin. The newer insulin Ly2605541 is developed to mimic physiology, that is, more hepatic insulin delivery. In a 12-week phase 2 trial in subjects with type 2 diabetes randomized to LY2605541 or glargine once a day. At 12 weeks, reduction in FPG and HbA1c was similar in both groups; however, the blood glucose variability was less and there was a 48% reduction in nocturnal hypoglycemia with LY2605541 group compared with glargine with modest weight loss because of liver-specific effects (hepatic glucose studies are pending).

The currently available rapid-acting insulin analogs are not that rapid, and these need to be given 15–30 minutes before meals, which are not optimal in real life. The only inhaled insulin being investigated in phase 3 clinical trials is Technosphere insulin (TI), which is ultra-rapid-acting human insulin that is quickly absorbed from the lung alveoli.

Another approach to rapid onset of insulin is to deliver insulin in the intradermal space. The last article in this section by Qiu *et al.* describes the lyophilized hydrogel patch system, which is developed for microneedle-mediated insulin delivery. It was demonstrated to be an appropriate drug reservoir for sustained release of insulin with microneedle-mediated transdermal delivery.

Many of these currently available insulin analogs (glargine and lispro) are going off patent in the next 1–2 years, and thus many biosimilars are expected to be available.

GLUCOKINASE ACTIVATORS

Discovery of a novel phenylethyl benzamide glucokinase activator for the treatment of type 2 diabetes mellitus

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Novel benzamide derivatives were synthesized and tested at *in vitro* assay by measuring fold increase of glucokinase activity at 5.0 mM glucose concentration. Among the prepared compounds, a benzamide glucokinase activator (YH-GKA) was found to be an active glucokinase activator with EC₅₀ of 70 nM. YH-GKA showed similar glucose AUC reduction of 29.6% (50 mg/kg) in an oral glucose tolerance test (OGTT) study with C57BL/J6 mice compared to 29.9% for metformin (300 mg/kg). Acute treatment of the compound in C57BL/J6 and ob/ob mice elicited basal-glucose-lowering activity. In subchronic study with ob/ob mice, YH-GKA showed significant decrease in blood glucose levels and no adverse effects on serum lipids or body weight. In addition, YH-GKA exhibited high bioavailability and moderate elimination in preclinical species.

Small molecular glucokinase activators: has another new anti-diabetic therapeutic lost favour?

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Glucokinase activators (GKAs) represent one of the leading hopes for the next generation of type 2 diabetes (T2D) therapeutics, showing efficacy in reducing blood glucose and HbA1c levels in animal models of T2D and short-term human trials. While the hypoglycemic risks of glucokinase activation in pancreatic beta cells have long been appreciated, the hepatic effects of GKAs have generally been perceived to be without significant side effect. In this

issue of the *British Journal of Pharmacology*, (Br. J Pharmacol 2013; 168: 339–53), De Ceuninck *et al.* report that acute and chronic GKA treatment of normoglycemic and hyperglycemic rodent models results in significant accumulation of triglycerides in the liver. This suggests that GKA-mediated activation of hepatic glucose uptake and suppression of endogenous glucose production may come at a significant cost; namely, the development of hepatic steatosis. This raises important questions regarding the safety of GKAs, and emphasizes that both plasma and hepatic lipid profiles should be carefully monitored in ongoing and future studies of these molecules.

Comment

The enzyme glucokinase (GK) is a rate-limiting enzyme for hepatic glucose clearance and glycogen synthesis, both processes that are impaired in type 2 diabetes. Therefore, it was identified as a possible target for diabetes management. The first article describes the discovery of a molecule “phenylethyl benzamide,” which is a glucokinase activator, while the second article discusses the clinical effects and potential concerns with the use of these molecules. These molecules are in early phase of development, and we are not sure if they will make it to the market in the near future because of safety concerns.

OTHER NEWER AGENTS FOR THE MANAGEMENT OF DIABETES

Effects of JNJ-38431055, a novel GPR119 receptor agonist, in randomized, double-blind, placebo-controlled studies in subjects with type 2 diabetes

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Aim

G-protein-coupled receptor agonists are currently under investigation for their potential utility in patients with type 2 diabetes mellitus (T2DM). The objective was to determine the pharmacokinetics, pharmacodynamics, safety, and tolerability of GPR119 agonist, JNJ-38431055, in T2DM subjects.

Methods

This was a randomized, double-blind, placebo- and positive-controlled, single-dose, crossover study and a randomized, double-blind, placebo-controlled, multiple-dose, parallel design study. The study was conducted at four U.S. research centers. Two different experiments involving 25 and 32 different subjects were performed in male and female subjects, aged 25–60 years, mean body-mass index between 22 and 39.9 kg/m², who had T2DM diagnosed 6 months to 10 years before screening. JNJ-

38431055 (100 and 500 mg) or sitagliptin (100 mg) as a single dose or JNJ-38431055 (500 mg) once daily for 14 consecutive days was tested. Effects on stimulated plasma glucose, insulin, C-peptide, and incretin concentrations were prespecified outcomes.

Results

JNJ-38431055 was well tolerated and not associated with hypoglycemia. Plasma systemic exposure of JNJ-38431055 increased as the dose increased, was approximately twofold greater after multiple-dose administration, and attained steady state after approximately 8 days. Compared with the placebo, single-dose administration of oral JNJ-38431055 decreased glucose excursion during an oral glucose tolerance test, but multiple-dose administration did not alter 24-hour weighted mean glucose. Multiple dosing of JNJ-38431055 increased postmeal total glucagon-like peptide 1 and gastric insulinotropic peptide concentrations compared to baseline.

Conclusions

These studies provide evidence of limited glucose lowering and incretin activity for JNJ-38431055 in subjects with T2DM.

Comment

JNJ-38431055 is a novel GPR119 receptor agonist. This molecule has been tried in patients with type 2 diabetes in this dose-finding study. It was found that JNJ-38431055 was well tolerated and not associated with hypoglycemia. However, phase 2 and phase 3 clinical trials are needed before any conclusions can be made.

Targeting VEGF-B as a novel treatment for insulin resistance and type 2 diabetes

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The prevalence of type 2 diabetes is rapidly increasing, with severe socioeconomic impacts. Excess lipid deposition in peripheral tissues impairs insulin sensitivity and glucose

uptake, and has been proposed to contribute to the pathology of type 2 diabetes. However, few treatment options exist that directly target ectopic lipid accumulation. Recently, it was found that vascular endothelial growth factor B (VEGF-B) controls endothelial uptake and transport of fatty acids in heart and skeletal muscle. Here we show that decreased VEGF-B signaling in rodent models of type 2 diabetes restores insulin sensitivity and improves glucose tolerance. Genetic deletion of *Vegfb* in diabetic db/db mice prevented ectopic lipid deposition, increased muscle glucose uptake, and maintained normoglycemia. Pharmacological inhibition of VEGF-B signaling by antibody administration to db/db mice enhanced glucose tolerance, preserved pancreatic islet architecture, improved β -cell function, and ameliorated dyslipidemia, key elements of type 2 diabetes and the metabolic syndrome. The potential use of VEGF-B neutralization in type 2 diabetes was further elucidated in rats fed a high-fat diet, in which it normalized insulin sensitivity and increased glucose uptake in skeletal muscle and heart. Our results demonstrate that the vascular endothelium can function as an efficient barrier to excess muscle lipid uptake even under conditions of severe obesity and type 2 diabetes, and that this barrier can be maintained by inhibition of VEGF-B signaling. We propose VEGF-B antagonism as a novel pharmacological approach for type 2 diabetes, targeting the lipid transport properties of the endothelium to improve muscle insulin sensitivity and glucose disposal.

Comment

Type 2 diabetes is a combined defect of inadequate insulin secretion from beta cells of the pancreas for the degree of hyperglycemia and insulin resistance, which is the principal defect. This article describes the role of VEGF-B in controlling the endothelial uptake and transport of fatty acids in heart and skeletal muscle. Therefore, targeting this receptor, we can expect reduction of insulin resistance by these tissues. However, there is no clinical trial involving human subjects, but the animal data are promising.

Conclusions

Many newer pharmaceutical agents may become available in the near future to allow providers to individualize treatment for patients with diabetes. Long-term safety of these agents, especially related to cardiovascular outcomes and cancers, will need to be evaluated over time. These agents will allow us to better manage diabetes, reduce hypoglycemia, and be weight neutral, thus reducing long-term complications of diabetes. At the same time, several insulin analogs are going to be off-patent in 2014 and 2015. Biosimilars will be available with a hope to reduce the overall cost to the healthcare system.

Author Disclosure Statement

No competing financial interests exist.