Incretin-based Therapy and the Prevention of Hypoglycaemia

a report by

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The prevalence of type 2 diabetes is continuously increasing, and the mean age of affected patients is decreasing. Although several antihyperglycaemic agents are available, there is an urgent need for novel agents with different mechanisms of action. Existing agents are often ineffective (even after initial effectiveness) and/or are associated with considerable side effects. Although antihyperglycaemic agents differ in their side effects, two kinds of adverse events are particularly common, perturbing and potentially harmful: weight gain and hypoglycaemia. One or the other, or both, are typical for all antihyperglycaemic agents, with the exception of metformin and acarbose. These latter agents, however, are typically used in early or less severe forms of type 2 diabetes, have a limited effectiveness and exert frequent gastrointestinal side effects. Therefore, drug development is directed towards effective antihyperglycaemic medications, without the risk of weight gain and hypoglycaemia. Incretin-based therapy is one such new, promising approach and incretin-enhancing agents and incretin mimetics are now available.

Table 1: Comparison of Incretin-based Therapy

Effects	GLP-1	Exenatide	Liraglutide	DPP-4 Inhibitors
Glucose-dependent insulin secretion	+	+	+	+
Suppression of glucagon secretion	+	+	+	+
Slowing of gastric emptying	+	+	+	+
Reduced appetite	+	+	+	-
Weight reduction	+	+	+	-
Application	Intravenous	Subcutaneous	Subcutaneous	Oral
Dosing	Continuous	Twice daily	Once daily	Once/twice daily
Important side effect	Nausea	Nausea	Nausea	None

GLP-1 = glucagon-like peptide 1; DPP-4 = dipeptidyl peptidase-4.

Incretin Effect

The observation that glucose taken orally results in a more pronounced insulin secretion than intravenously given glucose is the so-called incretin effect.[1,2] Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are the most important mediators of this effect.[1] Furthermore, in addition to stimulating insulin secretion in a glucose-dependent manner, GLP-1 exerts other physiological actions, including suppression of glucagon,[3,4] reduction of food intake and bodyweight[5] and delayed gastric emptying.[6,7] Importantly, while it is well known that type 2 diabetes is characterised by a combination of insulin resistance and impaired insulin secretion, elevated fasting plasma glucagon and the failure to normally suppress glucagon following a meal also contribute to dysregulation of endogenous glucose production in patients with type 2 diabetes.[8] Patients with type 2 diabetes usually lack the insulinotropic response to GIP, while GLP-1 levels may be reduced;[9] however, the response is preserved. GLP-1 was therefore developed as a therapeutic target.[10] Indeed, subcutaneously injected GLP-1 induces an increase in insulin secretion, improvement in insulin sensitivity and a reduction of glycated haemoglobin (HbA_{1c}) and bodyweight.[11] Moreover, the glucose dependence of the effect of GLP-1 on both insulin and glucagon secretion may diminish its potential to produce hypoglyacaemia: the insulinotropic properties of GLP-1 are abolished during euglycaemia and hypoglycaemia.[3,12] However, due to its short half-life – a consequence of rapid degradation by depeptidyl peptidase 4 (DPP-4) – its clinical usefulness is limited. Therefore, long-acting GLP-1 mimetics and DPP-4 inhibitors were developed (see *Table 1*). In this short review we evaluate incretin-based therapies with respect to the risk of hypoglycaemia.

How Does Glucagon-like Peptide-1 Result in Insulin Secretion?

In healthy individuals, pancreatic β cells respond to elevated glucose by an increase in insulin secretion. Glucose enters β cells through glucose transporters (GLUT-2), resulting in mitochondrial adenosine

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Table 2: Selected Exenatide Studies

Study	Therapy	Additional Therapy	Duration (weeks)	Number	HbA_{1c} Base (%)	HbA_{1c} Change (%)	Rate of Hypoglycaemia (%)
Buse[25]	Exenatide 5µg bid	Sulfonylurea	30	125	8.5	-0.46	14
	Exenatide 10µg bid			129	8.6	-0.86	36
	Placebo			123	8.7	+0.12	3
DeFronzo[26]	Exenatide 5µg bid	Metformin	30	110	8.2	-0.40	5
	Exenatide 10µg bid			113	8.3	-0.78	5
	Placebo			113	8.2	+0.08	5
Kendall[27]	Exenatide 5µg bid	Metformin + sulfonylurea	30	245	8.5	-0.55	19
	Exenatide 10µg bid			241	8.5	-0.77	28
	Placebo			247	8.5	+0.23	13
Heine[28]	Exenatide 10µg bid	Insulin	30	275	8.2	-1.11	0.9 events/patient-year
	Insulin glargine			260	8.3	-1.11	2.4 events/patient-year
Nauck[29]	Exenatide 10µg bid	Insulin	52	253	8.6	-1.04	4.7 events/patient-year
	Insulin glargine			248	8.6	-0.89	5.6 events/patient-year

Table 3: Selected Sitagliptin Studies

Study	Therapy	Additional Therapy	Duration (weeks)	Number	HbA_{1c} Base (%)	HbA_{1c} Change (%)	Rate of Hypoglycaemia (%)
Scott[30]	Sitagliptin 10–100mg	None	12	495	7.9	-0.15 to -0.77	0 to 4.1
	Placebo			125	7.9	+0.23	2
	Glipizide			123	7.9	-0.76	17.1
Raz[31]	Sitagliptin 100mg	None	18	521	8.0	-0.36	1.0
	Sitagliptin 200mg				8.1	-0.48	1.5
	Placebo				8.1	+0.12	0
Aschner[32]	Sitagliptin 100mg	Oral antidiabetic	24	229	8.0	-0.61	1.3
	Sitagliptin 200mg			238	8.1	-0.76	0.8
	Placebo			244	8.0	+0.18	0.8
Rosenstock[33]	Sitagliptin 100mg	Pioglitazon	24	175	8.1	-0.9	1.1
	Placebo			178	8.0	-0.2	0
Charbonnel[34]	Sitagliptin 100mg	Metformin	24	453	8.0	-0.67	1.3
	Placebo			224	8.0	-0.02	2.1
Nauck[35]	Sitagliptin 100mg	Metformin	52	588	7.7	-0.67	4.9
	Glipizide			584	7.6	-0.67	32.0
Hermansen[36]	Sitagliptin 100mg	Glimepiride	24	106	8.4	-0.30	7.5
	Sitagliptin 100mg + metformin			116	8.3	-0.59	16.4
	Placebo			106	8.4	-0.27	2.8
	Placebo + metformin			113	8.3	-0.30	0.9

triphosphate (ATP) production, with subsequent closure of ATP-sensitive K^+ channels. This results in membrane depolarisation, opening calcium (Ca^{2+}) channels, which then leads to exocytosis of the insulin-containing granules. Sulfonylureas directly close K^+ channels and result in insulin secretion independent of the glucose concentration. Therefore, hypoglycaemia is a typical side effect of sulfonylurea therapy.

Insulin secretion stimulates GLP-1 *in vitro* with clear glucose dependency.[13] Several studies in animal models and in human β cells have demonstrated that GLP-1 inhibits K^+ channels in a glucose-dependent manner.[14] Binding of GLP-1 to its receptor on the β cell increases intracellular cyclic adenosine-3' and 5'-monophosphate (cAMP)[15] and thus acts synergistically with glucose to close K^+ channels, which facilitates membrane depolarisation and induces electrical activity. Furthermore, in the presence of GLP-1, Ca^{2+} channels are active at lower action potentials and are more slowly inactivated, resulting in greater Ca^{2+} influx. It is also believed that Ca^{2+} mobilisation from intracellular stores promotes mitochondrial ATP synthesis and produces further membrane depolarisation, and thus enhances insulin secretion. Although the binding of GLP-1 to its receptor affects insulin secretion at several levels, all of these effects are glucose-dependent.[16] As a result of this glucose dependency, it is rather unlikely to induce hypoglycaemia in normal subjects by exogenous GLP-1, regardless of dose. In this context, another observation of interest was that endocrine tumours producing GLP-1 did not show symptoms of hypoglycaemia.[17] On the other hand, an exaggerated GLP-1 response to nutrients was observed in patients with accelerated gastric emptying and reactive hypoglycaemia, indicating that – at least in certain clinical situations – GLP-1 may be associated with hypoglycaemia.[18] It should also be noted that not only the insulin secretion but also the glucagonostatic effects of GLP-1 are glucose-dependent.[8] Thus, GLP-1 results in a much more physiological regulation of β cells and β-cell function, which minimises the risk of hypoglycaemia.

Table 4: Selected Vildagliptin Studies

Study	Concomitant therapy	Additional therapy	Duration (weeks)	Number	HbA_{1c} Base (%)	HbA_{1c} Change (%)	Rate of Hypoglycaemia (%)
Pi-Sunyer[37]	Vildagliptin 50mg	None	24	88	8.4	-0.5	0
	Vildagliptin 50mg bid			83	8.4	-0.7	0
	Vildagliptin 100mg			91	8.3	-0.8	0
	Placebo			92	8.5	0	0
Bosi[38]	Vildagliptin 50mg	Metformin	24	177	8.4	-0.5	0.6
	Vildagliptin 100mg			185	8.4	-0.9	0.5
	Placebo			182	8.3	-0.2	0.6
Rosenstock[39]	Vildagliptin 100mg	None	24	459	8.7	-1.1	0.2
	Rosiglitazone 8mg			238	8.7	-1.3	0.4
Garber[40]	Vildagliptin 50mg + pioglitazone 45mg	None	24	147	8.6	-0.8	0
	Vildagliptin 100mg + pioglitazone 45mg			158	8.7	-1.0	0.6
	Pioglitazone 45mg + placebo			158	8.7	-0.3	1.9
Rosenstock[41]	Pioglitazone 30mg	None	24	161	8.7	-1.4	0
	Vildagliptin 50mg + pioglitazone 15mg			144	8.8	-1.7	0
	Vildagliptin 100mg + pioglitazone 30mg			148	8.8	-1.9	0.7
	Vildagliptin 100mg			154	8.6	-1.1	0
Fonseca[42]	Vildagliptin 100mg	Insulin	24	144	8.4	-0.5	1.95 events/patient-year
	Placebo			152	8.4	-0.2	2.96 events/patient-year

Rates of Hypoglycaemia in Clinical Studies Using Incretins to Lower Glucose Concentration

Native Glucagon-like Peptide 1

Since native GLP-1 is degraded rapidly by DPP-4, it must be given as a continuous infusion. A six-week continuous infusion of GLP-1 in type 2 diabetes subjects decreased HbA_{1c} by 1.3%.[11] No hypoglycaemias were reported. Similarly, in another study in which a continuous infusion of GLP-1 for 12 weeks was compared with standard treatment, no difference in diabetic control was noted, but a markedly reduced number of hypoglycaemic events was reported (0.5 events/patient-year during GLP-1 versus 43.5 events/patient-year during standard treatment).[19]

Glucagon-like Peptide-1 Mimetics and Analogues

Exanatide (Byetta®), the synthetic form of exendin-4, was developed as a GLP-1 mimetic. It has a 53% amino acid overlap with human GLP-1 and resembles a super-agonist at the GLP-1 β-cell receptor.[20] In contrast to GLP-1, it has a much longer half-life, because it is resistant to degradation by DPP-4.[21]

Exenatide was used in several placebo-controlled studies as monotherapy in combination with metformin, with sulfonylurea or with both. *Table 2* shows that this therapy resulted in a significant change of HbA_{1c} associated with a wide range in the rate of hypoglycaemia. However, in studies where exenatide is used in combination with oral antihyperglycaemic medications that do not induce hypoglycaemia, such as metformin, the rates of hypoglycaemia are not increased.[25] On the other hand, if exenatide is used together with potentially hypoglycaemia-inducing agents, hypoglycaemia is observed in up to 36%.[24] This indicates that exenatide itself has no, or only very little, potential for inducing hypoglycaemia. Rather, if glucose metabolism is improved by exenatide, other potentially hypoglycaemia-inducing agents can cause hypoglycaemia. It should also be noted that the rates of hypoglycaemia vary considerably between studies; this is mostly related to varying definitions of hypoglycaemia and different patient populations.

Other Glucagon-like Peptide-1 Analogues

Several other GLP-1 analogues are currently under development. Liraglutide has a long half-life (13 hours) and shows similar antidiabetic effects to exenatide. In monotherapy, no hypoglycemias were observed despite significant HbA_{1c} reduction.[9]

Dipeptidyl Peptidase-4 Inhibitors

Another approach to using the effect of GLP-1 as an antidiabetic therapy is by inhibiting DPP-4, the enzyme responsible for the short half-life of GLP-1.[24] DPP-4 can be found ubiquitously and can deactivate many hormones, neuropeptides, cytokines and chemokines. Despite this broad function in metabolism, it has very few side effects.

Although DPP-4 inhibitors also result in an elevated concentration of GLP-1, there are some clinically relevant differences compared with GLP-1 analogues. DPP-4 inhibitors can be applied orally. Furthermore, during DPP-4 therapy GLP-1 concentration is not continuously elevated, but only following meals (when endogenous GLP-1 is secreted). On the other hand, the effect on glucose concentration and gastric motility seems to be less pronounced, since GLP-1 concentrations are much lower during DPP-4 inhibitor therapy compared with GLP analogues.

A number of DPP-4 inhibitors are on the market or in development.[23,24] For sitagliptin (Januvia®) and vildagliptin (Galvus®) there are a number of clinical studies in which the rate of hypoglycaemia was also examined (see *Tables 3* and *4*).

Table 3 indicates that sitagliptin results in an average reduction of HbA_{1c} of approximately 0.7% (with a baseline HbA_{1c} of approximately 8%). The rates of hypoglycaemia vary between 0 and 16.4%, depending on the clinical setting and the concomitant therapy. It should also be noted that in the study with the lowest baseline HbA_{1c}[35] the rate of hypoglycaemia was highest. However, when glipicide was used to achieve an identical HbA_{1c} reduction, the rate of hypoglycaemia was almost seven times higher (32 versus 4.9%). Furthermore, there seems to be no dose-dependency in the rate of hypoglycaemia. These data again indicate that sitagliptin itself at 100mg/day or 200mg/day does not induce hypoglycaemia. However, similar to GLP-1 analogues, this form of therapy can decrease glucose concentration to a point at which concomitant therapy (such as sulfonylureas or insulin) may induce hypoglycaemia.

Very similar data are available for vildagliptin (see *Table 4*). Data from these studies suggest that vildagliptin possesses comparable glucose-lowering efficacy to established antidiabetic medications, including metformin, rosiglitazone and pioglitazone, while exhibiting advantages with respect to tolerability, lipid profile and weight regulation. With respect to the effect on HbA_{1c} and the rates of hypoglycaemia, no clinically relevant difference compared with sitagliptin can be observed, although, notably, vildagliptin was generally investigated in patients with higher HbA_{1c} baseline values. The rates of hypoglycaemia for the vildagliptin studies vary between 0 and 0.7%, depending on the clinical setting and the concomitant therapy.

Summary

Clinical data indicate that incretin-based therapy results in a very low rate of hypoglycaemia. Hypoglycaemia observed in studies using native GLP-1, GLP-1 analogues or DPP-4 inhibitors is usually related to concomitant therapy such as sulfonylureas or insulin. This makes this form of therapy a very valuable tool for diabetes management. This is particularly true because incretin-based therapy is also not associated with the other major complications of many glucose-lowering therapies (weight gain), since DPP-4 inhibitors are weight-neutral and GLP-1 analogues even result in weight reduction. ■

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