International Journal of Current Medical and Pharmaceutical Research

IJCMPR

ISSN: 2395-6429

Available Online at http://www.journalcmpr.com

DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20170133

RESEARCH ARTICLE

INSULIN REGIMEN FOR THE TREATMENT OF DIABETES MELITUS

K. N. S. Karthik and Konda Ravi Kumar*

Department of Pharmaceutical Chemistry, Hindu college of Pharmacy
Amaravathi Road, Guntur. A.P, India

ARTICLE INFO

Article History:
Received 8th April, 2017
Received in revised form 13th May, 2017
Accepted 9th June, 2017
Published online 28th July, 2017

Key words:
Diabetes mellitus, Insulin, Combination therapy, Multiple dose regimens.

ABSTRACT

Diabetes mellitus type 1 is a form of diabetes in which not enough insulin is produced. The lack of insulin results in high blood sugar levels. The classical symptoms are frequent urination, increased thirst, increased hunger, and weight loss. Additional symptoms may include blurry vision, feeling tired, and poor healing. The cause of type 1 diabetes is unknown. It however is believed to involve a combination of genetic and environmental factors. Type 2diabetes is characterized by chronic hyperglycaemia caused by the combination of insulin resistance and a progressive decline in insulin secretion. However, both fasting and post-prandial blood glucose (PPBG) levels contribute to the HbA1clevel which reflects the mean glucose control for the preceding 3months. Insulin is the main stay of treatment for patients with type 1 diabetes. Insulin is also important in type 2 diabetes when blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications. Ideally, insulin should be administered in a manner that mimics the natural pattern of insulin secretion by a healthy pancreas Combination therapy is also very useful in the management of early stages of secondary OHA failure. A frequently advised regimen is the use of along or very long acting insulin at bedtime along with the use of small amounts of an OHA at meal times multiple dose regimens are not very commonly required for the routine management of most NIDDMs. Conventional insulin regimens consist of two injections of short and long-acting insulin, split and mixed regimen. Intensive regimens aim to provide glycemic control within, or close to the normal range, using all available resources for this purpose. This is by far the most popular regimen for intensive insulin therapy. In MSII, the basal insulin is provided by multiple subcutaneous insulin injections, (MSII), continuous subcutaneous insulin infusion (CSII), home blood glucose monitoring (HBGM) Hemoglobin..

INTRODUCTION

India leads the world today in the prevalence of diabetes. Genetic factors, changing dietary preferences, sedentary lifestyle and psychological stress are all important contributors to the burden of diabetes in India. [1] Diabetes mellitus type 1 is a form of diabetes mellitus in which not enough insulin is produced. The lack of insulin results in high blood sugar levels. The classical symptoms are frequent urination, increased thirst, increased hunger, and weight loss. Additional symptoms may include blurry vision, feeling tired, and poor healing. Symptoms typically develop over a short period of time. The cause of type 1 diabetes is unknown. It however is believed to involve a combination of genetic and environmental factors. Risk factors include having a family member with the condition. The underlying mechanism involves an auto immune destruction of the insulin-producing beta cells in the pancreas. Diabetes is diagnosed by testing the level of sugar or A1C in the blood. Type 1 diabetes may be distinguished from type 2 by autoantibody testing. There is no way to prevent type 1 diabetes. Treatment with insulin is typically required for survival. Insulin therapy is usually given by injection just under the skin but can also be delivered by an insulin pump. A diabetic diet and exercise are an important part of management. Untreated, diabetes can cause many complications. Complications of relatively rapid onset include diabetic ketoacidosis and non-ketotic hyperosmolar coma. Long-term complications include disease, stroke, kidney failure, foot ulcers and damage to the eyes. Furthermore, complications may arise from low blood sugar caused by excessive insulin treatment. [2] Type 2 diabetes is characterized by Chronic hyper glycaemia caused by the combination of insulin resistance and a progressive decline in insulin secretion. However, both fasting and post- prandial blood glucose (PPBG) levels contribute to the HbA1c level which reflects the mean glucose control for the preceding 3months. It is anticipated that postprandial hyperglycaemia is more closely associated with an increased risk of macro-vascular disease. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) indicates that macro vascular disease has a stronger association with

postprandial hyperglycaemia than with fasting hyperglycaemia. Therefore, it seems reasonable to target postprandial hyperglycaemia, in addition to fasting blood glucose (FBG) levels, to achieve maximum benefits. In this sense, the basal only therapy may be inadequate in glycemic control (especially controlling postprandial hyper-glycaemia) in some patients. Either a basal-bolusor a premixed insulin regimen is suggested at this point.

Biphasic insulin as part 30/70 (BIAsp30) (NovoMix30) is an insulin analogue mixture which contains 30% unbound rapid acting insulin as part and 70% intermediate-acting protaminated insulin as part. This premix for mulation aim sattargeting postprandial hyper glycaemia as well as providing a basal insulin supplementation. The 1-2-3 study has demonstrated that initiation of once-daily BIAsp30 in poorly controlled type2 diabetes patients was effective in achieving glycemic goals. With the increase of daily injections from one to two, and from two to three, more patients could safely achieve glycemic goals. The Initiate study indicated that BIAsp30 was more effective than insulin glargine in achieving targeted HbA1c levels in insulin-naïve patients who had poorly controlled blood glucose levels in concomitant treatment with OADs. In this study, the HbA1cwas reduced by 2.9% and 65% patients achieved HbA1c< 7% with twice- daily BIAsp30. In another treat- to -target study in insulin-naïve patients with type2 diabetes poorly controlled with OADs (sulphonyl ureas with or without metformin, or metformin mono-therapy), starting with twice daily BIAsp30 in combination with metformin reduced HbA1ctoagreaterextentthanonce daily insulin glargine and glimepiride.[3]

MATERIALS AND METHODS

Tabl.1 Insulins available in India and their action profile

Insulins	Onset	Peak	Duration
Rapid-acting Lispro Aspart	5-15 min	30-90 min	4 hrs.
Short-acting Regular	30-60 min	2-3 hrs.	6-8 hrs.
Intermediate-acting NPH	1-2 hrs.	4-6 hrs.	10-16 hrs.
Long-acting Glargine Detemir	2-4 hrs.	No peak	20-24 hrs.
Pre-mixed 30%/70% regular/NPH 50%/50% regular/NPH	30-60 min	Dual	10-16 hrs.

Insulin is the main stay of treatment for patients with type 1 diabetes. Insulin is also important in type 2 diabetes when blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications. Ideally, insulin should be administered in a manner that mimics the natural pattern of insulin secretion by a healthy pancreas; however, the complex pattern of insulin secretion by the pancreas is difficult to duplicate. Still, adequate blood glucose control can be achieved with careful attention to diet, regular exercise, home blood glucose monitoring, and multiple insulin injections throughout the day. With the acceleration of scientific research in the latter half of the twentieth century, beef and pork insulin were replaced by human insulin. In 1977, the gene for human insulin was cloned, and through modern Recombinant technology, human insulin is being manufactured in huge amounts and is freely available Human insulin is now widely used. Insulin now comes in a variety of preparations that differ in the amount of time following injection until they begin to work and the duration of the action. Because of these differences, combinations of insulin are often used to allow for a more tailored regimen of blood sugar control. [4]

Tab.2 NPH- Neutral Protamine Hagedorn[5]

Type	Onset (hr.)	Peak (hr.)	Duration	Can be mixed
Rapid acting: Insulin lispro Insulin as part Insulin glulisine	0.2-0.4 0.3-0.5	2-Jan 1-1.5 2-Jan	5-Mar	Regular, NPH
Short acting: Regular(soluble)insulin	0.5-1	4-Feb	8-Jun	All preparations (except glargine)
Intermediate acting: Insulin zinc suspension Lente	2-Jan	10-Aug	20-24	Regular
Neutral protamine Hagedorn (NPH) orisophaneinsulin.	2-Jan	10-Aug	20-24	Regular
Long acting: Protamine zinc insulin(PZI) Insulin glargine	6-Apr 4-Feb	14-20 12-May	24-36 24	Regular None
Premixed insulin: 70/30-70%of protamineaspartand 30%aspart	0.2–0.4 0.2-.4	1-1.5 1-1.5	16-Oct 16-Oct	---- ----
50/50-50%of protaminelisproand 50%oflispro	0.5-1	Dual	16-Oct	----
70/30-70%ofNPHand 30%regularinsulin 50/5050%ofNPHand 50%ofregularinsulin	0.5-1	Dual	16-Oct	----

Primary Care clinicians manage diabetes care including overall plans of care and annual reviews of care.

Risk-reduction goals [6]

Cardiac risk reduction is the most important management issue for patients with diabetes.

Tab.3 Selected cardiac risk factors and goals for risk reduction

Risk factor	Goal
Blood pressure	
Age 79 or younger	Lower than 140/90 mm Hg
Age 80 or older	Lower than 150/90 mm Hg
With microalbuminuria (at any age)	Lower than 130/80 mm Hg
LDL cholesterol	Lower than 100 mg/dL
Hemoglobin A1c (HbA1c)	Lower than 7%
Fasting blood glucose	80–120 mg/dL

While a target HbA1c of lower than 7% is ideal, it may not be achievable for all patients. Any progress should be encouraged. For frail elderly patients, a target HbA1c of 7–9% is reasonable.

Glucose control goals [7]

Tab.4 Ideal glucose targets

Timing	Target
Before meals	70–120 mg/dL
2 hrs. post-meals	160 mg/dL
Bedtime	70–120 mg/dL
3 a.m.	70–120 mg/dL

Initiating Insulin Therapy

There are no precise formulae by which the initial dose can be calculated, start with a small dose of an intermediate acting insulin (IAI), 8-12units s c. before breakfast; the therapy can

be initiated with a mixture of a short acting insulin(SA)and IAI in small doses.

Commonly Used Multiple Dose Regimens (MDRs)

Multiple dose regimens are not very commonly required for the routine management of most NIDDMs, but maybe important in special cases. Most NIDDMs who require insulin for optimal management do well with judicious use of combination therapy (insulin with OHA). Twice-daily mixture of short, acting and intermediate acting insulins; one given before breakfast and the other before dinner. Once the daily dose at a single injection reaches around 30 units, it would be preferable to divide the insulin requirements in to twice-daily injections. This is the most commonly used MDR regimen in NIDDMs. The same as above, but with the addition of a short acting insulin injection given before lunch.

Combination Therapy [8]

Combination therapy is also very useful in the management of early stages of secondary OHA failure. A frequently advised regimen is the use of along or very long acting insulin at bedtime along with the use of small amounts of an OHA at meal times. The ration ale for this is that the insulin will lower the fasting blood glucose levels, which is essential for glycemic control and will maintain a basal insulin level. The OHAs will cause a bolus increase in the endogenous insulin to cover the mealtime rise in the blood glucose levels. A regimen that has also been found to be practical and effective is the use of combination of small doses of SAI and IAI in the morning along with an OHA at meal times, especially with dinner. [9].Any form of insulin replacement which provides separately for basal insulin requirements and meal-related increments of insulin, and which allows for adjustment of insulin dosages in relation to ambient blood glucose, meals, exercise etc. is known as physiological replacement.

Non-physiologic regimens

Regimens that do not mimic the normal insulin secretion pattern are known as non-physiological. The use of intermediate (basal) insulin or short acting insulin alone are examples of such regimens. Fixed combinations of short acting and NPH insulin in ratios of 30:70 and 50:50 are the most popular forms of insulin sold worldwide (and in India). These combinations may be useful in patients with type 2 diabetes. While such combinations provide ease of use, they have no role in the management of type 1 diabetes, in view of the large variability of insulin requirements and frequent changes in daily insulin requirements. Such combinations result in poor glycemic control or lead to frequent hypoglycemia if strict control is attempted.

Physiologic Insulin Regimens [10]

Such regimens mimic insulin secretion by the beta-cell and provide separate basal insulin and meal-related increments.

Conventional

Conventional insulin regimens consist of two injections of short and long-acting insulin, split and mixed regimen. The timing and dose of short and intermediate acting insulin can be altered depending on the blood glucose, meals or other factors. The intermediate acting insulin given before breakfast acts as both basal insulin during daytime, as well as prandial insulin for lunch. In general, with this regime the timings and amounts of meals and snacks and exercise have to be fixed and remain relatively constant. Glycemic control achieved is reasonably good, but attempts to normalize blood glucose may result in unacceptably high risk of hypoglycemia in between meals and at night. Hence, it is important to prescribe snacks in between meals. By taking the intermediate acting insulin later i.e. at bedtime rather than pre-dinner, both nocturnal hypoglycemia as well as fasting hyperglycemia can be reduced. Conventional insulin regimens are relatively easy to explain and require lesser resources from the diabetes management team. It also places a smaller financial burden on patients and their families. Such regimes are presently most suitable for vast majority of patients in our country, since the resources required for more intensive regimens are not affordable nor are diabetes education teams available to provide the necessary support.

Intensive

These regimens aim to provide glycemic control within, or close to the normal range, using all available resources for this purpose. They provide for completely separate basal insulin and insulin boluses for meals. To be successful, the regimes require frequent adjustment of insulin dosage taking into account the ambient blood glucose, food (especially carbohydrate) intake and exercise schedule. Thus, frequent monitoring of blood glucose 3-5 times per day is an important prerequisite of such regimens. Adjustment of basal insulin and meal-related bolus of insulin is done separately according to previously defined algorithms. The basal-bolus regime can provide excellent glycemic control, though risk of severe hypoglycemia is high as hemoglobin A1c reaches normal range. The regimen provides greater flexibility in meal timings and amounts, but it requires greater motivation and financial resources from the patient and family members. In addition, the availability of an experienced team (doctor, nurse educator and dietician) who can assist the patient is essential. Indications for intensive insulin management include adults and selected adolescents and children with type 1 diabetes, pregnant women with diabetes, labile diabetes and those with renal transplantation. Intensive insulin replacement can be provided by regimens of multiple subcutaneous insulin injections (MSII) or by continuous subcutaneous insulin infusion (CSII). This is by far the most popular regimen for intensive insulin therapy. In MSII, the basal insulin is provided by multiple subcutaneous insulin injections, (MSII), continuous subcutaneous insulin infusion (CSII), home blood glucose monitoring (HBGM) Hemoglobin A1c: normal range 4-6%; goals of therapy will vary depending upon age, motivation and economic status and need to be individualized 2 injections of NPH insulin taken 12 hours apart or by a single injection of insulin glargine or determine every 24 hours. In addition, injections of short acting (regular) or rapid- acting (insulin as part or lispro) are used before each meal. Approximately half the insulin is provided as basal replacement and half as meal-related boluses. Home blood glucose monitoring (HMBG) is required between 3-5 times per day, especially before each meal. Changes of pre-meal insulin doses are made depending on the ambient blood glucose and amount of carbohydrates consumed in the meal. Insulin pens are a convenient means of taking multiple injections. Also known as, insulin pump therapy, insulin is delivered continuously into the subcutaneous tissue at selected rates through a portable electromechanical pump. Either regular or rapid-acting insulin is used for this purpose. The insulin is delivered at pre-selected rates of continuous basal output throughout 24 hours. The ability to have multiple

programmable infusion rates allows rates of infusion to be increased in the early morning to take care of the phenomenon of rise of blood glucose before breakfast. Patient-activated boluses of regular or rapid-acting insulin are delivered before meals. CSII is becoming increasingly popular as a means for providing intensified insulin therapy, with the greatest experience in USA. It allows for excellent glycemic control and good quality of life in selected patients. With careful attention to details, the frequency of hypoglycemia is not higher than with conventional therapy. However, the patients who opt for this form of therapy need to carefully chosen. Technical support for the pump and a diabetes care team trained in pump usage is also essential. Indications of CSII include patients unable to achieve glycemic targets despite being on MSII, recurrent hypoglycemia on MSII and motivated patients who indicate a preference for CSII over MSII. Patients who have brittle diabetes, with frequent episodes of ketoacidosis and hypoglycemia, may not be good candidates for CSII, since they often have psychological reasons for their poor control. Currently, insulin infusion pumps are available in India through Medtronic Mini Med.

Mode of Administration

Unlike many medicines, insulin cannot be taken orally at the present time. Like nearly all other proteins introduced in to the gastro intestinal tract, it is reduced to fragments (even single amino acid components), where upon all 'insulin activity' is lost. There has been some research in the way to protect insulin from the digestive tract, so that it can be administered in a pill. So far this is entirely experimental.

Subcutaneous

Insulin is usually taken as subcutaneous injections by single-use syringes with needles, an insulin pump, or by repeated-use insulin pens with needles. Patients who wish to reduce repeated skin puncture of insulin injections often use an injection port in conjunction with syringes.

Insulin Pump

Insulin pumps are a reasonable solution for some. Advantages to the patient are better control over background or basal insulin dosage, bolus doses calculated to fractions of a unit, and calculators in the pump that may help with determining' bolus' infusion dosages. The limitations are cost, the potential for hypoglycemic and hyperglycemic episodes, catheter problems, and no closed loop means of controlling insulin delivery based on current blood glucose levels.

Inhalation

Inhaled insulin claimed to have similar efficacy to injected insulin, both in terms of controlling glucose levels and blood half-life. Currently, inhaled insulin is short acting and is typically taken before meals; an injection of long-acting insulin at night is often still required. When patients were switched from injected to in haled insulin.

Transdermal

There are several methods for transdermal delivery of insulin. Pulsatile insulin uses micro jet stopules insulin into the patient, mimicking the physiological secretions of insulin by the pancreas. Researchers have produced a watch-like device that tests for blood glucose levels through the skin and administers corrective doses of insulin through pores in the skin by insulin jet injector.

Oral Insulin

The basic appeal of oral hypoglycemic agents is that most people would prefer a pill to an injection. However, insulin is a protein, which is digested in the stomach and gut and in order to be effective at controlling blood sugar, cannot be taken orally in its current form. The potential market for an oral form of insulin is assumed enormous, thus many laboratories have attempted to devise ways of moving enough intact insulin from the gut to the portal vein to have a measurable effect on blood sugar.

Pancreatic Transplantation

Another improvement would be a transplantation of the pancreas or beta cell to avoid periodic insulin administration. This would result in a self-regulating insulin source. Transplantation of an entire pancreas (as an individual organ) is difficult and relatively uncommon. It is often performed in conjunction with liver or kidney transplant, although it can be done by itself. It is also possible to do a transplantation of only the pancreatic beta cells. Beta cell transplant may be come practical in the near future. Additionally, some researchers have explored the possibility of transplanting genetically engineered non- beta cells to secrete insulin.

CONCLUSION

Insulin is the main stay of treatment for patients with type 1 diabetes. Insulin is also important in type 2 diabetes when blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications. Ideally, insulin should be administered in a manner that mimics the natural pattern of insulin secretion by a healthy pancreas. Combination therapy is also very useful in the management of early stages of secondary OHA failure. Multiple dose regimens are not very commonly required for the routine management of most NIDDMs, but maybe important in special cases. Most NIDDMs who require insulin for optimal management do well with judicious use of combination therapy (insulin with OHA).

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047-53.
2. Warren ML, Conway MJ, Klaff LJ, Rosenstock J, Allen E. Postprandial versus preprandial dosing of biphasic insulin aspart in elderly type 2 diabetes patients. *Diabetes Res Clin Pract* 2004; 66:23-9.
3. Boehm BO, Vaz JA, Brøndsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. *Eur J Intern Med* 2004; 15:496-502.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2007; 30(Suppl. 1):S42-S47.
5. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005; 28:260-5.
6. V.Mohan, sandeep. Epidemiology of type-2 diabetes: Indian scenario. *Indian J MED Res,* 2007 march: 217-230.
7. American Diabetes Association, (2010). Standards of Medical Care in Diabetes--2010. *Diabetes Care* 33:

S11-S61

8. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329:977-86.
9. Ahmed J, Ward TP, Bursell SE, Aiello LM, Cavallerano JD, Vigersky RA. The sensitivity and specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. *Diabetes Care*. 2006; 29(10):2205-2209.
10. Anderson J H; Brunelle R L; Koivisto V A; Pfutzner A; Trautmann M E; Vignati L; DiMarchi R Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. *Diabetes* Feb 1997: 46 (2) p.265-70.

****