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Editorial

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Using premixed biphasic insulin analogs humalog® mix 25 and humalog® mix 50 in basal bolus format: evidence from research, clinical practice and case reports

Keywords: humalog®, glulisine; apidra®, aspart, novorapid®, insulin, lantus®, analog, metformin

Abbreviations: RAIs, rapid acting insulin analogs; SMBG, self-monitoring of blood glucose; DSME, diabetes self-management education; HRI, human regular insulin; MNT, medical nutrition therapy

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Editorial

While managing diabetes by insulin injections, physicians must consider physiologic replacement of insulin. Newer Insulin Analogs, such as bolus (lispro/Humalog®, glulisine/Apidra® and aspart/Novorapid® also called rapid acting insulin analogs, RAIs) and basal (glargine/Lantus®, detemir/Levemir® and degludec/Tresiba®) have been proven more safer and efficacious in management of type-1 and type-2 diabetes, as compared to older or traditional insulins (Human Regular and NPH), with better glycemic control (HbA1c reductions) and less or negligible hypoglycemia; these insulin analogs are available as insulin pens and more easy to use. Furthermore, these newer insulin analogs have been proven safer for Ramadan fasting as well. Similarly, premixed or biphasic insulin analog preparations (Humalog® Mix 25, Humalog Mix 50® and Novomix® 30) are proven for their safety, efficacy and easy usage, as compared to premixed human insulin (Human Insulin 30/70). Basal bolus format remains the best way of managing diabetes, especially type-1.[1–6] This technique is somewhat difficult for type-2 older patients, however.

Recently it has been observed that some research trials conducted and demonstrated to prescribe premixed biphasic insulin analogs three times a day. Although such studies have proved better for HbA1c reductions, however this technique is neither standard nor fits to all diabetic patients as this may cause hypoglycemia (30-40%) before bedtime or late night due to insulin stacking (i.e., protamine insulin). This has been observed in our clinical practice where older patients, those with renal impairment, or erratic meal patterns experience hypoglycemia.[7–9]

Recently, it has also been observed that most of the physicians prescribe premixed biphasic insulin analogs three times a day after failure to achieve good glycemic control. Although their patients are experiencing hypoglycemia, but health care professional is unaware of that because lack of patient education and self monitoring of blood glucose (SMBG). In spite of hypoglycemia, their HbA1c remains elevated. Only 20% of patients will achieve the target with difficulty (or with high dose of insulin). Current paper is focusing such problems and has invented a technique where premixed insulin analogs can be prescribed in a basal bolus format, with an example of only one case report summary (out of hundreds of such similar case studies since last 10years of our clinical practice).

A 63year old male patient, who was a known case type-2 diabetes since 13years comes to my diabetology clinic in diabetes center, referred from primary health care center. His weight was 60kg; BMI of 28 kg/m². Other examination was un-remarkable. Renal, hepatic functions and routine laboratory tests were unremarkable, except total cholesterol and LDL-C which were 198 and 122 respectively. After failure of oral agents, his physician had prescribed him Insulin Humalog Mix® 25 (a biphasic lispro insulin with 25% lispro and 75% protaminated lispro) three times a day; pre-breakfast 30units, pre-lunch 28units and pre-dinner 20units (total daily dose 78units/day); he was using metformin (500mg) three times a day. During office interview, he informed that sometimes in evening, after dinner or late night he experiences some hypoglycemia (undocumented), and with frequent eating of sweets. He gave a history of weight gain as well. Point of care HbA1c was 9.5%. Regarding management in my clinic, metformin (500mg three times a day) was continued; statin and aspirin tablets were additionally prescribed. Site of injection and technique was reviewed, which was also unremarkable. Insulin frequency and dose was kept the same. Education was given to him and snacks advised with SMBG until next visit to clinic after 10days. He demonstrated following SMBG in mg/dl:

a. FBS (fasting glucose)=113, 100, 96, 144, 304, 200
b. Post breakfast (2hours)=159, 115, 119, 126, 184
c. Post Lunch (2hours)=378, 282, 216, 228, 190, 248, 163, 270
d. Post dinner (2hours)=241, 110, 137, 138, 126
e. Before sleep=241, 110, 149

It can be observed that this patient of more than 60 years of age had one low reading (96mg/dl) in early morning, although did not experience any signs or symptoms of hypoglycemia. There were some elevations up to 300mg/dl. Hence SMBG was somewhat erratic with fasting hyperglycemia.[10–14] This can be explained by Somogyi effect/phenomenon. Furthermore, post lunch readings were very high (although taking 28units at lunch). Some higher readings can be explained by the fact that sometimes (due to insulin stacking; three

times premix insulin) he was experiencing some hypoglycemia or low blood glucose and was eating some sweets which elevated his SMBG reading, HbA1c and weight. This was confirmed by the patient during interview/counseling.

He was on three injections per day, each before meals of 5minutes. Although now he can be shifted ideally to basal bolus (four injections/day), but he was hesitant and not willing because of his working and social conditions. For simplicity, he was prescribed Humalog Mix 25 two times per day (with same dose of 30units AM and 20units PM); and instead of third dose of premix analog insulin, he was given plain insulin lispro only, 12units pre-lunch (total daily dose of 62units per day). Other medications, including metformin, were continued. SMBG and Education was given also until next OPD after 2months. He demonstrated following SMBG (in mg/dl) during his visit to the clinic:

a. FBS (fasting glucose)=123, 111, 105, 144, 130, 126

b. Post breakfast (2hours)=161, 118, 129, 170, 184, 156

c. Post Lunch (2hours)=178, 165, 138, 184, 167, 171

d. Post dinner (2hours)=195, 119, 139, 170, 126

e. Before sleep=128, 113, 149, 128

It can be observed that SMBG is now acceptable. In the clinic point of care HbA1c was 7.2%. Hence previously his insulin dosages were higher, with episodes of hypoglycemia (undocumented) and HbA1c of 9.5. After plain lispro pre-lunch prescription (and less total daily dose), HbA1c came to 7.2 with diabetes self-management education and insulin regimen adjustments.

Learning objective from this short case presentation is using premix biphasic insulin analogs before breakfast and dinner (Humalog® Mix 25) with Humalog® Insulin (plain lispro) pre-lunch in basal bolus format, with three injections per day. Humalog® Mix25 can be replaced with Humalog® Mix 50 if post prandial hyperglycemia is significant. This regimen is initiated when two injections of premix insulin fail to achieve glycemic targets. Additionally, this technique can be applied to other premix biphasic insulin analogs (such as Novomix® 30); premixed human insulin 30/70 can be used in similar format/regimen if morning time or late night hypoglycemia is not an issue.[15] However, newer premix insulin analogs are recommended because of their safety and efficacy. Furthermore, to control pre-lunch hyperglycemia, rapid acting insulin analogs (RAIs; injected just 5minutes before meal) and human regular insulin (HRI, such as Humulin® R and Actrapid®) can be used, where HRI must be injected at least 30minutes before the meal (a difficult option for the patient). However, HRI can be replaced with RAIs if post lunch (or evening) hypoglycemia is experienced because of long duration of HRI. RAIs are preferred and recommended because of their rapid onset of action (within 5-15min) and short duration of action (~4hours) and these usually do not cause post prandial hypoglycemia, and proven for their safety, efficacy and HbA1c reductions.[16]

Diabetes self-management education (DSME) is essential part of diabetes management, which involves medical nutrition therapy (MNT), SMBG, educating the patient about timing of different insulins (action profiles), dose adjustments according to hyperglycemia or hypoglycemia (with prompt treatment with soluble carbohydrates) and regular inspection of injection site by the patient himself and by the physician or diabetic educator.[17]

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Conflict of interest

Author declares that there is no conflict of interest.

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