Type 2 Diabetes:
Pharmacological Management

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Type 2 diabetes conceptually is a combination of genetic predisposition of relative insulin deficiency and insulin resistance. The most prevalent cause of acquired insulin resistance is obesity. Because of the obesity epidemic, diabetes is increasingly becoming more prevalent.[1]

Treatment of Type 2 diabetes consists of lifestyle intervention (diet and exercise) and, if needed, pharmacological therapy. Canadian Diabetes Association guidelines aim for preprandial blood sugars on average < 7 mmol/L and a hemoglobin A1C < 7%.[2]

Smith's case

Smith is a 55-year-old overweight Type 2 diabetic who, despite 3 months of dietary intervention and 30 hours of vigorous exercise 4 times a week, has suboptimal glycemic control. His home glucose readings before meals and bedtime average 9.0 mmol/L. His most recent hemoglobin A1C is 9.5%.

What are his options? Turn to page 76 for the answers...

Pharmacological classes of diabetes medication

Biguanides (metformin)

Advantages:

- Only diabetic medication that is associated with weight loss
- Does not cause hypoglycemia

Disadvantages

- GI side-effects
- Theoretical risk of lactic acidosis[3]

Sulfonylureas (glyburide, glimepiride, gliclazide)

Advantages:

- Generally well tolerated

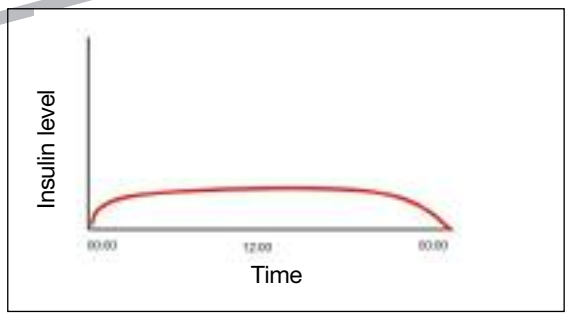

Figure 1. Profile of once daily glargine/levemir.

Disadvantages:

- Contraindication: allergy to sulfonamides
- Can cause hypoglycemia
- Newer agents cause less hypoglycemia (*e.g.*, glimeprimide, gliclazide)
- Glyburide cannot be used in impaired renal function

Thiazolidindiones (TZDs)—rosiglitazone, pioglitazone

Advantages:

- First class of medication that specifically targets insulin resistance
- Does not cause hypoglycemia

Disadvantages:

- Weight gain, edema from fluid retention
- Rosiglitazone has been associated with MI but this is highly controversial[4-6]

Meglitinides (nateglinide, repaglinide)

Advantages:

- Specifically target postprandial hyperglycemia
- Have less hypoglycemia than traditional sulphonylureas

Disadvantages:

- Hypoglycemia

Disaccharidase inhibitors (acarbose)

Advantages:

- No systemic side-effects

Disadvantages:

- GI side-effects (*i.e.*, flatulence)
- Little change in hemoglobin A1C

Insulin

Available insulins are divided into basal insulins and fast-acting (prandial) insulins. Neutral Protamine Hagedorn (NPH) is the prototypical basal insulin. Newer longer acting analog basal insulins include determir and glargine. NPH is generally used once daily for partial day basal insulin coverage, or twice daily for full day basal insulin coverage. Insulin determir and glargine are generally used once daily for full day basal insulin coverage.

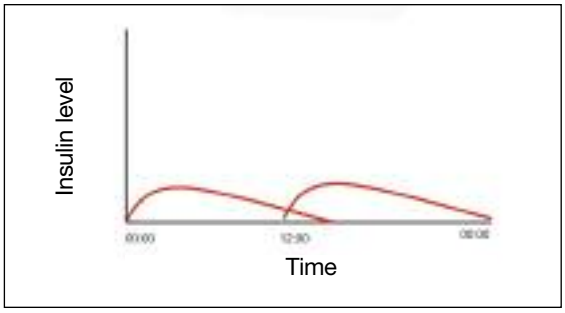

Figure 2. Profile of twice daily NPH.

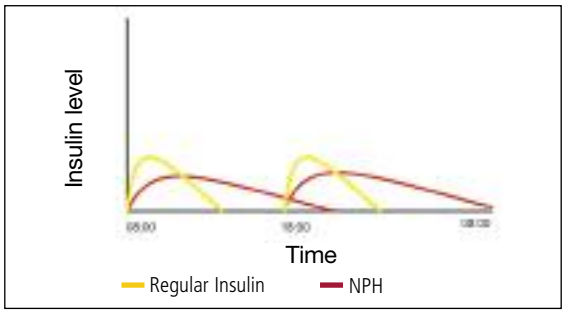

Figure 3. Profile of twice daily NPH and regular insulin.

Type 2 diabetes conceptually is a combination of genetic predisposition of relative insulin deficiency and insulin resistance.

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Fast-acting (prandial) insulins are used to prevent postprandial hyperglycemia. The prototypical fast-acting insulin is regular insulin. Aspart insulin and lispro insulin are the two faster acting analog insulins.

Principles of pharmacological therapy for Type 2 diabetes

Metformin, glyburide and insulin have clearly shown to reduce the incidence of microvascular complications.[7] Other agents reduce blood glucose and hemoglobin A1C, but have not been studied in respect to microvascular prevention.

Patients who fail to reach goal on lifestyle intervention should use a stepwise-approach:

1. Add metformin
2. If still suboptimal glycemic control, add a sulphonylurea
3. If still suboptimal glycemic control, add a TZD or a single dose of long-acting insulin
4. If hemoglobin A1C is ≥ 9% add two simultaneous oral agents
5. If still suboptimal glycemic control despite multiple oral agents and a single dose of long-acting insulin, discontinue oral agents and add multidose fast-acting insulin

Pearls and caveats of oral agent/insulin combination

1. Add a single dose 0.1 u/kg at bedtime to oral agents and titrate to achieve am fasting glucose readings of 7.0 mmol/L
2. Metformin is commonly combined with insulin to limit insulin associated weight gain[8]

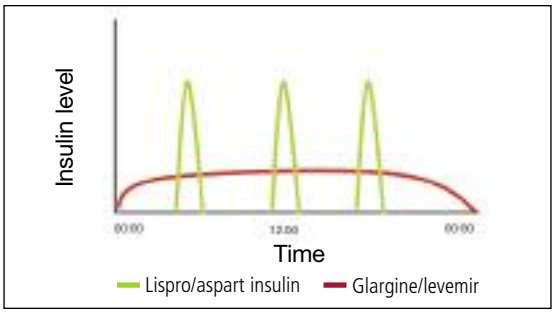

Figure 4. Profile of once daily glargine/levemir and three times daily lispro/aspart insulin.

Smith's case cont'd...

Despite metformin 1 g b.i.d. and glyburide 10 mg b.i.d., Smith's blood sugars before breakfast average 8.5. NPH 8 u q.h.s. is started. Smith increases his NPH by 1 u increments every week until his fasting blood sugars average < 7%. Eventually, Smith titrates his insulin to 14 u q.h.s. which achieves fasting blood sugars < 7%. His follow-up hemoglobin A1c is now 6.8%

3. Insulin use with a TZD is an off-label combination in Canada and may lead to accelerated weight gain and potentiate TZD-associated fluid retention
4. Eat a bedtime snack (*e.g.*, low-fat cheese and a slice of whole grain bread) to prevent hypoglycemia from bedtime NPH which peaks four to six hours after administration

New therapies

Glucagon-like peptide-1 based agents

Glucagon-like peptide-1 (GLP-1) in response to food ingestion is secreted from L-cells of the small intestine. GLP-1 enhances postprandial insulin release, inhibits glucagon and slows gastric emptying.[9] GLP-1s half-life is minutes as it is metabolized by dipeptidylpeptidase IV

Take-home message

- Patients not achieving glycemic goals with lifestyle intervention need pharmacological therapy
- Use a stepwise approach with pharmacotherapy
- Patients who fail to reach glycemic goals should be candidates for adjunctive basal insulin or multidose insulin

(DPP-IV). The DPP-IV inhibitor sitagliptin has been approved in the treatment of Type 2 diabetes. It has been available for use since early 2008. Officially, it has been approved for use alone or in combination with metformin. Exenatide is a long GLP-1 agonist as it is resistant to DPP-IV. Exenatide twice daily injections have been FDA approved in the treatment of Type 2 diabetes in combination with oral agents. Dx

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