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NOTE

Troglitazone: Recent Approach to Type-II Diabetes

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Diabetes mellitus is a fairly common metabolic disease, characterised by hyperglycaemia due to lack of insulin secretion from beta cells in the islets of langerhans.

There are two distinct forms of diabetes[1] termed Type-1 diabetes or insulin dependent diabetes mellitus (IDDM) and Type-II diabetes or non-insulin dependent diabetes mellitus (NIDDM). The Type-I diabetes is an autoimmune disease in which there is destruction of beta cells that produce hyperglycaemia and ketosis. Type-II diabetes is a metabolic disease characterised by insulin resistance and hyperglycaemia. In most of the cases, there is some insulin in the body but it cannot serve its purpose because the cells are unreceptive, means insulin resistance develops.

Currently there are three classes of drugs[2] used to treat Type-II diabetes. These are sulphonylurea, biguanides and α-glucosidase inhibitors. For the time being Type-II diabetes that cannot be controlled by diet and exercise is often treated with one or more of these oral medications. The sulphonylureas (*e.g.*, glyburide, diabeta) were the first oral agents and they act by increasing insulin production of the pancreas. Biguanides (*e.g.*, metformin) have no direct effect on insulin production. They prominently lower blood glucose by preventing liver from producing glucose. Lastly, the α-glucosidase (*e.g.*, acarbose) lower blood glucose by delaying the breakdown of dietary sugars and thus slowing the absorption of sugars into the body cells.

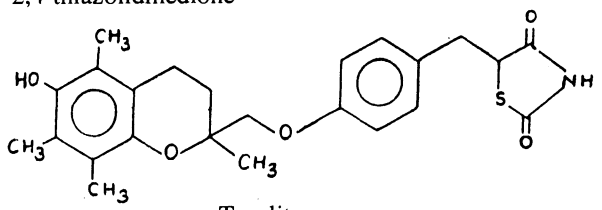
Although many people with Type-II diabetes can manage their condition with diet, exercise and one or more of the sulphonylureas, biguanides or α-glucosidase inhibitors, for others these strategies are insufficient. For these people, insulin injections are required. A new medication for the treatment of Type-II diabetes is on the horizon. The name of the drug is "Troglitazone".

Chemistry: Troglitazone is a member of 3,4-thiazolinedione class of antidiabetic drug[3,4]; chemically, it is 5-[4-(6-hydroxy-2,5,7,8-tetramethyl chroman-2-yl-methoxy)-benzyl] 2,4-thiazolidinedione.

Ciglitazone, proglitazone, etc. are the other members of this class.

Mechanism of action: Troglitazone directly targets insulin resistance, the underlying cause of Type-II diabetes[5]. It is completely different from sulphonylureas, the biguanides and α-glucosidase inhibitors in both its chemical composition and function.

2,4-thiazolidinedione



Troglitazone

It acts by improving the action of insulin in liver, muscle and adipose (fat) tissue. In muscle, it improves glucose utilisation by stimulating the uptake of glucose by muscle tissue. At the liver, the drug works to decrease glucose production. With troglitozone therapy, the cells of the body are made sensitive to the insulin that is already in supply because it allows the body's own insulin to work more effectively. Both glucose levels and insulin levels decrease within weeks of therapy[6].

Food and drug administration in the United States have approved "troglitazone" to treat Type-II diabetes poorly controlled by insulin therapy. It has been suggested as single agent (monotherapy) or in combination with sulphonylurea tablets or insulin injections.

Synergy with sulphonylureas: The addition of troglitazone has a synergistic effect with sulphonylureas, since both agents act to improve glucose tolerance by different but complementary mechanisms. It reduces insulin resistance *via* unique nuclear mechanism, thereby allowing the body to more efficiently use the insulin that it produces or that which is injected.

Dosage form[7]: It is available in the United States as 200 mg and 400 mg tablets, marketed by the Parke-Davis division of Warner-Lambert (developed by Sankyo Pharmaceutical Company) under the trade name "Rezulin". In European countries, it is also marketed by Pfizer Inc. and Glaxo-Wellcome. Its initial dose is 200 mg/day with meals; if no improvement within few weeks, dose can be increased to 400 mg with meals (and later to 600 mg).

Adverse effect: Troglitazone is well tolerated in clinical studies. Adverse effects commonly reported include infection, pain and headache, but these occur at rates comparable to those in the placebo treated patients.

Special precautions: It is used with caution in people with liver disease (may cause reversible jaundice), in women using estrogen for contraception (troglitazone decreases effectiveness of estrogen) and people taking terfenadine (plasma concentration of terfenadine decreased by 50–70%).

Contraindications

1. Pregnancy.
2. Breast feeding women (safety not established).
3. People with congestive heart failure (increase plasma volume).

4. People taking cholestyramine (cholestyramine decreases absorption of troglitazone by about 70%).

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