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Abstract

In clinical practice, Oral Hypoglycemic Agents (OHAs) and Oral Antihyperglycemic Agents (OAAs) can be categorized into 3 classes: 1. Insulin Secretagogues (Sulphonylureas = SUS: Glimepiride, Glipizide XL, Glibenclamide, Gliclazide, Gliquidone, etc, and Non-SUS: Meglitinide: Repaglinide, Nateglinide), 2. Insulin Sensitizers and Anti-hyperglycemic Agents (Thiazolidinedions: Pioglitazone, Rosiglitazone, Darglitazone, and Biguanides: Metformin, 3-Guanidinopropionic-Acid), and 3. Intestinal Enzyme Inhibitors: &alpha;-Glucosidase Inhibitors (Acarbose, Voglibose, Miglitol, Castanospermine, etc) and &alpha;-Amylase Inhibitor (Tendamistase). A powerful, endogenous mechanism for protecting the heart, "Ischemic Preconditioning" occurs when cardiac K+ATP Channels open during brief periods of mild myocardial ischemia to protect against a longer ischemic episode. Glimepiride (GLIM), which is thought to be a pancreatic-specific, non-cardiac K+ATP Channel, does not blunt the response to "Ischemic Preconditioning", hence, GLIM may show cardioprotective effect. In contrast, Glibenclamide abolishes such an effect of "Ischemic Preconditioning" by preventing the opening of cardiac K+ATP Channels. GLIM shows insulin-mimetic signaling events through molecular mechanism on the insulin receptor-independent activation of the IRS/P13-Kinase pathway via DIG (Detergent-Insoluble-Glycolipid-enriched rafts) and Caveolin through Non-RTK (Non-Receptor Tyrosine Kinase) pathway in which, normally via IRTK (Insulin Receptor Tyrosine Kinase); hence, GLIM has an Insulin Sparing Effect. Thus, it is suggested that GLIM may contribute to overcome Insulin Resistance. On the basis of clinical experiences and molecular mechanisms, GLIM can be summarized having 3B – 3A – 9D properties which mean: 3–fold higher rate of Binding to receptor (3B), 3-fold lower Affinity to receptor (3A), and 9–fold faster rate of Dissociation (9D). These effects (3B–3A–9D) may result in potential therapeutical benefits, including: rapid onset (due to 3-fold higher rate of Binding = 3B) and less hypoglycemic events due to lower Affinity (3A) and faster Dissociation (9D). By using therapeutic GLIM concentration (in contrast with Glibenclamide), GLIM (via P13-Kinase Pathway) increases insulin &ndash; stimulated Glycogen Synthesis (GS) in human muscle cells (GS Effects). In addition, GLIM inhibits platelet aggregation which may in turn have a preventive effect on the development of diabetic vascular complications (more pronounced effect than Gliclazide). The ideal basal insulin should ideally have the following six characteristics: 1. mimics normal pancreatic basal insulin secretion, 2. long-lasting, 24-hour effect, 3. smooth, peakless profile, 4. reproducible and predictable effects, 5. reduces risk of nocturnal hypoglycemia, and 6. once-daily administration. Insulin Glargine (GLAR) is a novel peakless long-acting insulin analogue that is available for clinical use; it has a smooth profile and long, 24-hour duration of action. GLIM shows insulin-mimetic signaling events through molecular mechanism on the insulin receptor-independent activation of the IRS/P13-Kinase pathway via DIG (Detergent-Insoluble-Glycolipid-enriched rafts) and Caveolin through Non-RTK (Non-Receptor Tyrosine Kinase) pathway in which, normally via IRTK (Insulin Receptor Tyrosine Kinase); hence, GLIM has an Insulin Sparing Effect. Thus, it is suggested that GLIM may contribute to overcome Insulin Resistance. On the basis of clinical experiences and molecular mechanisms, GLIM can be summarized having 3B – 3A – 9D properties which mean: 3–fold higher rate of Binding to receptor (3B), 3-fold lower Affinity to receptor (3A), and 9–fold faster rate of Dissociation (9D). These effects (3B–3A–9D) may result in potential therapeutical benefits, including: rapid onset (due to 3-fold higher rate of Binding = 3B) and less hypoglycemic events due to lower Affinity (3A) and faster Dissociation (9D). By using therapeutic GLIM concentration (in contrast with Glibenclamide), GLIM (via P13-Kinase Pathway) increases insulin &ndash; stimulated Glycogen Synthesis (GS) in human muscle cells (GS Effects). In addition, GLIM inhibits platelet aggregation which may in turn have a preventive effect on the development of diabetic vascular complications (more pronounced effect than Gliclazide). The ideal basal insulin should ideally have the following six characteristics: 1. mimics normal pancreatic basal insulin secretion, 2. long-lasting, 24-hour effect, 3. smooth, peakless profile, 4. reproducible and predictable effects, 5. reduces risk of nocturnal hypoglycemia, and 6. once-daily administration. Insulin Glargine (GLAR) is a novel peakless long-acting insulin analogue that is available for clinical use; it has a smooth profile and long, 24-hour duration of action. GLIM can be combined with insulin therapy (f.e. GLAR) in the treatment of T2DM. Based on the clinical experiences, such a combination can be performed by 3 Methods such as Method-A: both GLIM and GLAR can be given in the morning, Method-B: GLAR is given in the morning and GLIM in the evening, and Method-C: GLIM is given in the morning and GLAR in the evening. Conclusions: Due to its pleiotropic effects (3B-3A-9D Properties, and Cardioprotective, Insulin Sparing, Glycogenic, and Antiplatelet Effects), GLIM may represent the state of the art in modern oral antidiabetic sulphonylurea treatment. Insulin GLAR which mimics normal pancreatic basal insulin secretion and shows smooth-peakless profile, can be safely administered once-daily, and it may reduce risk of nocturnal hypoglycemia. Three Methods (A, B, and C) for combined therapy of GLIM and GLAR can be practically and rationally applied (depends on the life style of diabetic patients)

Keyword : glimepiride, cardioprotective, properties, insulin, Glargine, combined, therapy, of, Glimepiride, and, Glargine, Methods, A.

Daftar Pustaka :