Lim PC, Chong CP. What's next after metformin? focus on sulphonylurea: add-on or combination therapy. Pharmacy Practice 2015 Jul-Sep;13(3):606. doi: 10.18549/PharmPract.2015.03.606

Review

What's next after metformin? focus on sulphonylurea: add-on or combination therapy

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Received (first version): 14-May-2015 Accepted: 28-Jul-2015

ABSTRACT*

Introduction: The pathophysiology of type 2 diabetes (T2DM) mainly focused on insulin resistance and insulin deficiency over the past decades. Currently, the pathophysiologies expanded to ominous octet and guidelines were updated with newer generation of antidiabetic drug classes. However, many patients had yet to achieve their target glycaemic control. Although all the guidelines suggested metformin as first line, there was no definite consensus on the second line drug agents as variety of drug classes were recommended.

Objectives: The aim of this review was to evaluate the drug class after metformin especially sulphonylurea and issues around add-on or fixed dose combination therapy.

Methods: Extensive literature search for English language articles, clinical practice guidelines and references was performed using electronic databases.

Results: Adding sulphonylurea to metformin targeted both insulin resistance and insulin deficiency. Sulphonylurea was efficacious and cheaper than thiazolidinedione, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide 1 analogue and insulin. The main side effect of sulphonylurea was hypoglycaemia but there was no effect on the body weight when combining with metformin. Fixed dose sulphonylurea/metformin was more efficacious at lower dose and reported to have fewer side effects with better adherence. Furthermore, fixed dose combination was cheaper than add-on therapy.

In conclusion, sulphonylurea was feasible as the second line agent after metformin as the combination targeted on two pathways, efficacious, cost-effective and had long safety history. Fixed dose combination tablet could improve patient's adherence and offered an inexpensive and more efficacious option regardless of original or generic product as compared to add-on therapy.

Keywords: Diabetes Mellitus, Type 2; Drug Therapy, Combination; Drug Combinations; Hypoglycemic Agents; Biguanides; Sulfonylurea Compounds

INTRODUCTION

Diabetes mellitus has affected 382 millions of people worldwide and the prevalence was estimated to increase.[1] With the rising prevalence, it would increase the economic burden especially in developing country which has no national health insurance scheme.[2] The healthcare cost of diabetes was estimated to be USD612 billion globally in year 2014.[3] Besides, it is a chronic illness which led to complications that increased the cost of treatment.[4-6] Therefore, efficacious and inexpensive drugs are essential in diabetes treatment.

The understanding of the pathophysiology of type 2 diabetes (T2DM) is important for effective treatment. Over the decades, main cause of T2DM was focused on two metabolic defects namely beta-cell dysfunction and insulin resistance.[7] Indeed, the pancreatic beta-cell had started to fail way before T2DM was diagnosed.[8,9] The risk factors for T2DM are obesity, sedentary lifestyle and genetic.[10] Genetic had precipitated insulin resistance whereas obese people lived in hyperinsulinemia state to counter the insulin resistance.[11] Over the time, the beta-cell will deteriorate and leads to impaired glucose tolerance (IGT). Further insulin deficiency resulted in elevated fasting plasma glucose level and subsequently overt diabetes.[9,12]

T2DM patients had impaired insulin secretion[13] and this might be further worsened by the beta-cell apoptosis.[14] Subsequently, less insulin was secreted to regulate the hepatic glucose output and glucose uptake after carbohydrate meal that leads to hyperglycemia. The glucagon produced by pancreatic alpha-cell was elevated all the time even after glucose intake causing elevated blood glucose level in T2DM patients.[15,16] Besides, incretin effect that involved intestinal hormones namely glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that regulated insulin and glucagon secretion were impaired in T2DM.[17]

Approximately 180 gram of glucose was filtered and mostly (90%) reabsorbed by the kidney daily at the proximal renal tubule through sodium-coupled glucose co-transporter (SGLT)- 2 whereas the other 10% was reabsorbed by SGLT-1 at the straight segment of the descending proximal tubule.[18] Additionally, accelerated lipolysis in T2DM secondary to resistance towards insulin's antilipotic effect contributed to high free fatty acids (FFA) in the plasma that induced gluconeogenesis, impaired insulin secretion and increased insulin resistance. The failure of brain in suppressing appetite after glucose ingestion especially in obese people can also contributed to hyperglycemia.[9]

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There was a paradigm shift in the T2DM treatment from triumvirate of beta-cell failure and insulin resistance to ominous octet as the pathophysiology expanded to alpha-cell, gastrointestinal hormones, kidney, fat cells and brain.[12] Guidelines on the treatment of T2DM were updated to cater with the change and availability of newer classes of drugs. Nevertheless, all these guidelines had recommended metformin as the first line agent[19-24], as it is inexpensive and has durable efficacy and safety data particularly robust evidence on cardiovascular safety.[25,26] For instance, the American Association of Clinical Endocrinologists (AACE) recommended metformin as first line treatment unless contraindicated in advance kidney disease.[20] If the target HbA1c was not achieved after three to six months, guidelines suggested addition of second line agent. Joint guideline by the American and European associations suggested addition of sulphonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, GLP-1 receptor agonist or insulin.[19] Updated standard care by American Diabetes Association (ADA) added SGLT-2 inhibitor as the second line.[22] AACE offered larger option of add-on therapy that also included colesevelam, bromocriptine mesylate or alpha-glucosidase inhibitor (AGI).[20] Step up to triple therapy was suggested if HbA1c target was not achieved with dual therapy.[20,21,23,24]

There were variations in the HbA1c target recommended by various guidelines which were ranging from <6.5% to <7%.[19-24] However, glycaemic target should be individualized to avoid hypoglycemia. Tighter target of 6.0%-6.5% was recommended for younger and healthier patients whereas looser target of 7.5%-8.0% was recommended for elderly, patients with co-morbidities or hypoglycemia prone patients.[27] However, studies from both developed and developing countries found that many patients' HbA1c were far away from target of control.[28-36]

As guidelines offered flexibility in choosing the next agent after metformin, question arouse as in which drug class was the most suitable second line since most patients were not meeting the target. Therefore, this review aimed to evaluate the second line drug class after metformin particularly sulphonylurea. Besides, the review also evaluated the use of these drugs as an add-on or fixed dose combination therapy.

METHODS

A literature search for appropriate English language articles from year 1984 to 2015 was conducted using electronic databases that consisted of ProQuest, Science Direct, Wiley Online Library and Pubmed. Text word, MeSH terms and keywords for the search included diabetes mellitus, diabetes mellitus type 2, diabetes mellitus type II, glyburide, glibenclamide, glyburide / metformin, glibenclamide / metformin, glimepiride / metformin, glipizide / metformin, metformin and glibenclamide, metformin and glyburide, metformin and gliclazide, metformin and glimepiride, metformin and glipizide and combination tablet. As for the patient's adherence, the search included keywords of diabetes mellitus, adherence, compliance, and combination tablet. Additional search of the references of the articles were also done.

SECOND LINE AGENT AFTER METFORMIN

The UK Prospective Diabetes Study (UKDS) reported that only 25% of patients achieved HbA1c <7% with monotherapy of either metformin, sulphonylurea or insulin after nine years of follow-up.[37] This suggested that majority of patients require more than one medication to achieve their glycemic target. Guidelines provided flexibility to prescribers by recommending choice of several oral anti-diabetic (OAD) drug classes or insulin as the second line if failed to achieve target with metformin.[19-23] However, drug that was efficacious, safe and economical would be more feasible as second line agents considering the increasing prevalence and its impact towards economic burden.

The newer agent was SGLT-2 inhibitor that inhibited the reabsorption of glucose in the kidney independent of insulin.[18,38] The first SGLT-2 inhibitor, dapagliflozin was approved by the European Medicines Agency (EMA) at the end of 2012. However, the US Food and Drug Administration (FDA) granted marketing to canagliflozin first and later dapagliflozin owing to safety concerned on the increased risk of bladder and breast cancer.[39,40] The evidence on the safety of this drug class was still ongoing.[41] Indeed, EMA and US FDA were following the post-marketing surveillance on its cardiovascular, renal safety and cancer risk.[39] Although AACE and ADA recommended addition of SGLT-2 inhibitor as second line, yet IDF did not recommend SGLT-2 inhibitor.[20,22,24]

Guidelines suggested GLP-1 analogues as one of the option of second line as it was first approved by the US FDA in 2005.[19-24,42] The use of GLP-1 analogues such as exenatide and liraglutide was lower as it was in injection formula as compared to DPP-4 inhibitor that was administered orally.[43] Both of these drug classes worked in glucose dependent manner.[44] However, the use of liraglutide was higher in Denmark compared to exenatide.[45] GLP-1 analogues reduced the body weight significantly by about 1.7 kg but long term data of its safety was lacking. There was association of GLP-1 analogues with pancreatitis, hyperplasia of the pancreas and thyroid cancer but it was inconclusive.[46-48] Zhang *et al*. demonstrated that GLP-1 analogue was the most expensive drug compared to sulphonylurea, insulin and DPP-4 inhibitor.[49]

Rosiglitazone, an insulin sensitizer like metformin[9] had restricted use following the suspension of rosiglitazone-containing drug in Europe[50] after the meta-analysis demonstrated increased risk of myocardial infarction and cardiovascular death.[51] However, the US FDA has removed the restriction following recent outcome of no increased in cardiovascular event of rosiglitazone-containing drug in several landmark studies.[52] As metformin

was an insulin sensitizer, it would be better if the second line agent could target other pathway.

The drug of choice after metformin would usually be sulphonylurea as it was inexpensive and had long term efficacy and safety history.[25] Besides, the combination of metformin with sulphonylurea targeted both insulin resistance and insulin deficiency.[8] Sulphonylurea that triggered insulin release was equally effective among the agents in the group.[53] It reduced HbA1c further by 0.8% with more patients achieving glycemic target when adding to metformin.[47,54] Studies reported that combination of sulphonylurea and metformin was the most cost-effective option compared to DPP-4 inhibitor, GLP-1 analogue, insulin and thiazolidinedione.[49,55] Besides, sulphonylurea was associated with the longest insulin independence time and hence it might be the choice for those who reluctant to receive insulin therapy at the early stage.[49] Conversely, glibenclamide monotherapy required insulin earlier and had low glycemic durability as compared to metformin and rosiglitazone.[56] Sulphonylurea was associated with increased hypoglycemia risk and weight gain.[47] Nevertheless, there was no difference in severe hypoglycemia event when comparing combination of sulphonylurea or GLP-1 analogue with metformin to metformin monotherapy.[47] Other evidences on the safety of sulphonylurea such as cardiovascular events and mortality as well as cancer were inconclusive due to diverse study outcomes.[57,58]

Consensus by the ADA and EASD did not recommend alpha-glucosidase inhibitor as second line agent unlike the Australia, IDF and AACE guideline.[19-24] It reduced HbA1c for about 0.8% compared to placebo but was less effective compared to sulphonylurea and metformin. Besides, it did not affect HbA1c in dose-dependent manner and higher dose contributed to more side effects.[59] Although systematic review demonstrated that addition of alpha-glucosidase inhibitor to metformin did not increase hypoglycemia rate and weight, there was no study on its long term side effect.[47]

Similar to alpha-glucosidase inhibitor, DPP-4 inhibitors reduced HbA1c by about 0.7%, which was slightly less effective compared to sulphonylurea.[60] It was weight neutral and had no difference in hypoglycemia risk when adding to metformin.[47] The cardiovascular events due to DPP-4 inhibitors treatment were less compared to sulphonylurea.[61] However, recent cardiovascular outcome study of saxagliptin reported increased hospitalization due to heart failure.[62] Besides, there were multiple studies that provided contraindicated data on DPP-4 inhibitors effect on pancreatitis. Case controlled study reported that exenatide and sitagliptin doubled the risk of hospitalization due to pancreatitis[48] whereas retrospective cohort study found that there was no association of exenatide or sitagliptin to risk of acute pancreatitis when compared to metformin or glibenclamide.[63] Besides, addition of DPP-4 inhibitor to metformin was more expensive, less benefits in quality adjusted life years (QALY) and required insulin therapy earlier as compared to sulphonylurea.[49] Therefore, DPP-4 inhibitor might be drug of choice as second line in patients that were obese or prone to hypoglycemia.

Insulin was estimated to further reduced HbA1c by 0.8% when added to metformin and it was as effective as sulphonylurea.[37,47] Likewise to sulphonylurea, insulin increased risk of hypoglycemia and weight. However, insulin was more expensive and had no added benefit in QALY comparing to sulphonylurea.[49] As insulin was available as an injection, barriers like inconvenient treatment regimen and risk factors of hypoglycemia should be considered before initiating insulin. Besides, studies found that patients were unwilling to initiate insulin due to fear of needles and lack of knowledge on the importance of insulin injection.[64,65]

Above all, sulphonylurea would be the better second line agent after inadequate diabetic control with metformin. Combination of these two classes targeted both insulin resistance and insulin deficiency. Moreover, sulphonylurea was effective, cost-effective and its oral administration could surpass the fear of insulin injection among the patients. Currently, combination sulphonylurea and metformin tablets are available as fixed dose glibenclamide/metformin, glimepiride/metformin and glipizide/metformin tablets. Nevertheless, there are issues around the use of fixed dose combination versus co-administered tablets in terms of their efficacy, safety, patient adherence and cost.

FIXED DOSE COMBINATION VERSUS CO-ADMINISTERED TABLETS

Efficacy

Previous studies revealed that lower dose of fixed dose glibenclamide/metformin tablet significantly reduced HbA1c greater than metformin co-administered sulphonylurea of either glibenclamide, glipizide or gliclazide.[66-68] Besides, the fixed dose tablet had showed better glycemic control compared to co-administered metformin plus rosiglitazone.[71] When the baseline HbA1c was higher, more reduction in HbA1c ranging from about 1.3% to 2.4% was observed with fixed dose glibenclamide/metformin therapy.[66-68] The fixed dose combination provided additional benefits as lower dose of glibenclamide/metformin tablet showed better efficacy and might reduce the risk of hypoglycemia caused by glibenclamide.[66] Moreover, this enable further upward dose titration in future management, thus delays the introduction of triple therapy.

Fixed dose glimepiride/metformin was available in normal and sustained release tablet. A multicenter randomized study reported similar efficacy, hypoglycemic events and compliance between these two formulations. Mean HbA1c reduced by 0.59% and 0.61% in sustained release group and normal group respectively.[70] Besides, fixed dose glimepiride/metformin was as effective as glibenclamide/metformin in reducing HbA1c but more patients achieved HbA1c<7% at 12-month of treatment with glimiperide/metformin (44.6% versus 26.8%).[71]

Safety

The main concern for sulphonylurea was hypoglycemia. A multicenter retrospective study involved 72 patients demonstrated that three patients had hypoglycemia with glibenclamide or glipizide co-administered metformin while eight patients had hypoglycemia after switched to glibenclamide/metformin combination tablet.[68] However, three out of these eight patients had concurrent use of insulin and hence the dose of insulin was reduced.[68] Study comparing fixed dose glimepiride/metformin and glibenclamide/metformin demonstrated similar adverse events between the two groups but more patients (28.9%) in glibenclamide/metformin group had mild and moderate hypoglycemic events compared to glimipiride/metformin group (17.1%).[71]

As the T2DM patients were mostly obese, weight gain was another concern in the treatment. Hence, therapy that was weight neutral or weight reduction was preferable. Weight gain was one of the side effects of sulphonylurea. However, metformin might counter the weight gain effect of glibenclamide when used in combination. Hermann et al. proved that there was no difference in patients' body weight in the combination therapy when comparing with metformin monotherapy.[72] Indeed, the patients' weight was maintained after switching from glibenclamide or glipizide co-administered metformin to glibenclamide/metformin combination.[68]

Patient adherence

Fixed dose combination tablet contained at least two drugs in a tablet.[73] This would provide convenience to the patients and enhance patients' adherence as the pill burden reduced.[74,75] Studies showed that adherence to fixed dosed glibenclamide/metformin and glipizide/metformin tablets were better compared to dual therapy.[66,74,76] A previous study showed improvement in patients' adherence by 16% when converting from metformin co-administered glyburide to fixed dose combination tablet.[77] Additionally, the less adverse effect and lower cost with fixed dose glibenclamide/metformin tablet might further improve the adherence.[74]

Cost

The treatment cost of combination tablet might be cheaper than add-on therapy as lower dose of combination tablet was as efficacious as higher dose of co-administered tablet. Cheong *et al*. reported significant lower reimbursement for combination tablets compared to dual therapy regardless of branded or generic.[74] Another study found that the drug cost was reduced by 44% when switching to fixed dose glibenclamide/metformin tablet from co-administered gliclazide plus metformin.[67] Surprisingly, a study conducted in France revealed that combination tablet was more cost-effective than monotherapy of either metformin or glibenclamide.[78] QALY improved and direct medical cost reduced with fixed dose glibenclamide/metformin 5/500mg as compared to metformin and glibenclamide. This might be attributed to better glycemic control with combination tablet and subsequently reduced the relative risks of complications and improved patients' quality of life.[78]

CONCLUSION

When metformin failed to achieve the target glycaemic goal, sulphonylurea would be the best second line agent in view of its favorable efficacy, safety and cost profile. Fixed dose combination tablet could improve patient's adherence and offered an inexpensive and more efficacious option regardless of original or generic product as compared to add-on therapy.

CONFLICT OF INTEREST

No conflict of interest.

No sponsorship or funding.

QUÉ VIENE DESPUÉS DE LA METFORMINA? FOCO EN SULFONILUREAS: ADICIONAR O TRATAMIENTO EN COMBINACIÓN?

RESUMEN

Introducción: La fisiopatología de la diabetes tipo 2 (T2DM) se centró en las pasadas décadas principalmente en la resistencia a la insulina y al déficit de insulina. Actualmente, la fisiopatología se ha expandido hacia el octeto ominoso y se actualizaron las guías con las nuevas generaciones de clases terapéuticas de antidiabéticos. Sin embargo, muchos pacientes aún tienen que alcanzar sus objetivos terapéuticos de control de glucemia. Aunque todas las guías sugieren a la metformina como primera línea, no hay un consenso establecido sobre los agentes de segunda línea, ya que se recomiendan una gran variedad de clases terapéuticas.

Objetivos: El objetivo de esta revisión fue evaluar las clases terapéuticas después de la metformina, especialmente la sulfonilureas, y los problemas asociados a la adición o a los tratamientos con combinaciones en dosis fija.

Método: Serealizó una búsqueda extensiva de artículos en inglés, guías de práctica clínica y referencias utilizando bases de datos electrónicas.

Resultados: Añadir sulfonilurea a la metformina tiene como objetivo tanto la resistencia a la insulina como el déficit de insulina. La sulfonilurea fue eficaz y más barata que la tiazolidindiona, inhibidores de la dipeptidil peptidasa-4, análogos del péptido de tipo glucagón e insulina. El principal efecto adverso de las sulfonilureas fue la hipoglucemia, pero no hubo efectos en el peso corporal cuando se combinaba con metformina. La combinación de sulfonilurea/metformina era más eficaz a baja dosis y reportó menos efectos adversos con mejor adherencia. Además, la combinación a dosis fija era más barata que el tratamiento en asociación.

En conclusión, la sulfonilurea es factible como tratamiento de segunda línea después de la metformina como tratamiento de combinación en las dos líneas de tratamiento, eficaz, coste-efectivo, y tienen una historia de seguridad mayor. Los comprimidos con combinaciones a dosis fija podría mejorar la adherencia del paciente y ofrecer una opción barata y más eficaz, independientemente de que fuese genérico u original, en comparación con el tratamiento en asociación.

Palabras clave: Diabetes Mellitus Tipo 2; Farmacoterapia Combinada; Medicamentos en combinacion; Hipoglucemiantes; Biguanidas; Compuestos de Sulfonilurea

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