

Triple fixed drug combinations in type 2 diabetes

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Type 2 diabetes is characterized by progressive beta-cell failure that results in sequential adding of different oral and injectable medications to achieve optimal glycemic control.^[1,2] This necessitates administration of multiple tablets or pills to achieve good glycemic control as the disease progresses.^[2] In addition, subjects with type 2 diabetes may have other co-morbidities such as dyslipidemia, hypertension and cardiovascular disease, which further increase the burden of medications. Polypharmacy with increased pill burden and dosing frequency is identified as one of the factors responsible for poor adherence to oral hypoglycemic therapy.^[3] Even in countries with high access to healthcare, only 39% of patients reported good medication adherence.^[4] In a study of 2741 patients on oral antidiabetic drug (OAD), there was an inverse relationship between OAD adherence and HbA_{1c}; controlling for baseline HbA_{1c} and therapy regimen, each 10% increase in oral diabetes medication adherence was associated with a 0.1% HbA_{1c} decrease ($P = 0.0004$), suggesting that adherent patients are more likely to achieve glycemic control than the nonadherent ones.^[5]

FIXED DRUG COMBINATIONS

One method to improve drug adherence is to use fixed drug combinations (FDC).^[6] United States Food and Drugs Administration (USFDA) defines FDC as “two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount,

frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such con-current therapy as defined in the labeling for the drug.”^[7] The rationality of FDCs should be based on certain aspects such as:

- The drugs in the combination should act by different mechanisms
- The pharmacokinetics must not be widely different and
- The combination should not have supra-additive toxicity of the ingredients.^[8]

Among chronic disease therapies, FDC is quite popular among antiretroviral, anti-tuberculosis, bronchial asthma, anti-cancer and anti-hypertensive preparations. In a meta-analysis of studies in patients with anti-retroviral, tuberculosis, hypertension and diabetes, FDC resulted in a 26% decrease in the risk of noncompliance compared with free-drug component regimen.^[6]

Various FDC involving two drugs have been approved by USFDA: Glucovance (glibenclamide + metformin), actoplusmet (pioglitazone + metformin), janumet (sitagliptin + metformin), kombiglyze XR (saxagliptin + metformin), jentadueto (linagliptin + metformin), oseni (alogliptin + pioglitazone), invokamet (canaglifozin + metformin) and xigduo XR (dapaglifozin + metformin). Combination of nateglinide and voglibose (Basen, Japan) is approved in Japan.^[9] USFDA approved triple drug oral hypoglycemic combinations are not currently available.

TRIPLE FIXED DRUG COMBINATIONS

For most patients with type 2 diabetes in developing countries, the sequential addition of OAD is metformin and sulfonylurea (SU), followed by thiazolidinediones or α -glucosidase inhibitors.^[10] The most prevalent multiple drug therapy is a combination of metformin, SU and pioglitazone.^[10] Whenever the combination of OAD was used, FDC was preferred in 58% of patients in a study

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done in India.^[11] In this context, it is natural to consider a FDC of three drugs.

India is well known for innovations in FDC in diabetes.^[12] Following the widespread acceptance of two drugs FDC for OAD, Indian pharmaceutical companies have introduced triple FDC of SU, metformin and pioglitazone; as well as SU, metformin and voglibose, in varying doses. SU acts by insulin release from the beta cell of pancreas, metformin by improving insulin sensitivity at the muscle and liver and pioglitazone by improving adipose tissue insulin sensitivity by PPAR- γ agonism. Voglibose is an α -glucosidase inhibitor that acts by reducing the postprandial blood glucose by regulating glucose absorption. Studies have shown the effectiveness of both these combinations of triple OAD.^[13,14]

TIMING OF ADMINISTRATION

There is a concern regarding the timing of triple OAD FDC in relation to food. We accessed the label information of individual innovator molecules from the FDA website for to analyze the validity of this concern. The label of glimepiride Amaryl (sanofi aventis) recommends that the drug be given with the first main meal or the breakfast. There was no difference in glycemic response when the glimepiride was given once or twice daily.^[15] The label of metformin Glucophage (Merck Serono) recommends that the tablet be taken with meals.^[16] The pioglitazone Actos (Takeda) package insert does not mention dosing in relation to food.^[17] The prescribing information of voglibose Basen (Takeda) recommends that it be administered before the meal.^[18] Considering these recommendations of innovator molecules, the FDC of SU with metformin and voglibose/pioglitazone can be consumed just before the first major meal of the day or with breakfast. Dose titrations can be done by adding a similar tablet before dinner. Glimepiride can be given twice daily without causing any increased risk of hypoglycemia or worsening of glycemic control.^[19]

ADVANTAGES

Fixed drug combinations has been associated with improved compliance and improved glycemic control. In a study with 16,490 diabetes subjects, switching to a FDC of SU and rosiglitazone improved compliance and HbA1c levels compared with switching to dual therapy.^[20] Similar data exists with FDC of glibenclamide and metformin.^[21] This is particularly relevant since the overall compliance of medication in subjects with diabetes is already suboptimal.^[4] In addition to a reduction of the pill burden, FDC has

been shown to reduce the dosing frequency and thereby improve adherence.^[22] The components of FDC acts by different mechanisms thereby targeting multiple pathophysiological targets. Theoretically, the FDC may also neutralize the potential side-effects. The potential of weight gain with pioglitazone and SU may be neutralized by the weight loss properties of metformin and voglibose. Since metformin and voglibose increase glucagon-like peptide-1 levels, additive action may be present while using the combination.^[23,24] FDC is also associated with a reduction in cost compared with its components. Some manufacturers produce scored tablets, which can be halved, without loss of dosage precision, to achieve fine titration if dose.

CAUTION

However, FDC use should be propagated with due of caution. The trade names of FDC may not give an indication of the exact components and their dosage in the FDC, and may confuse the prescriber. The same holds true for other health care professionals, including, pharmacists, nurse and diabetes educations, as well for persons with diabetes themselves. The prescriber should be aware of the drug interactions and contraindications of individual components of the FDC, e.g. in a patient with stable cardiac failure class 3, pioglitazone may be contraindicated, but metformin and glimepiride may be acceptable options for treatment. In the event of suspected adverse event, the entire medication may have to be replaced. It is likely that the gastrointestinal adverse effects of metformin may be worsened by voglibose. The ceiling dose or tolerable dose of one component of the FDC may be different from that of other. The potential for dose titration may be limited with FDC, which may eventually lead to the addition of other OAD and hence increase the pill burden at a later date.

CONCLUSION

Used wisely, with adequate medication counseling, triple FDCs provide effective glycemic control in a safe, well-tolerated, and economic manner. Physicians should take the effort to educate themselves and their paramedical colleagues, about proper content and dose of FDC to avoid potential prescribing errors.

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