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An Evaluation of Fixed-Dose Combinations (FDC's) for Treatment of type 2 Diabetes Mellitus

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Abstract

Today, when we look at diabetes care management as a comprehensive approach to improve quality of life health outcomes and reduce the economic burden of medical care. Evidence-based clinical guidelines for Type 2 DM recommends fixed dose combination (FDC) based Pharmacotherapy involving early utilization of multiple drug agents as a single FDC's. This study examines the rationality of diverse FDCs used for Diabetes Mellitus and to find out the irrational FDCs currently available in Indian drug market. Material and Methods: - Analytical Study Design. Data aboutvarious FDC's used for Diabetes Mellitus, which are authorized in Indian marketplace was gathered from Present Index of Medical Specialties (CIMS) and Monthly Index of Medical Specialties (MIMS) and their rationality was analysed using a pretested device instrument primarily based on FDCs listed in WHO essential listing of drugs and National List of Essential Medicines (NLEM), others based totally on their pharmacodynamic properties, Pharmacokinetic parameters and significant drug interactions taking place due to API (Active pharmaceutical substances) contained within the product. Result: A general of 18 mixtures were analysed, amongst those eleven combos were irrational. Conclusion: Predominantly some irrational FDCs are being circulated within the Indian market therefore utmost importance has to be given before prescribing FDC's to the patients inorderto avoid unnecessary Adverse Drug Reactions (ADR). A wider reform is needed in the government regulatory architecture to inspectof advertised FDCs available in the market. The ignorance and negligence among medical practitioners and pharmacists with regard to the irrational FDC's has to be addressed immediately.

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Introduction

Diabetes is a chronicmultifactorial metabolic disease requiring constantmonitoring and medical care for stringent glycemic control. Significant evidence exists that supports a range of interventionsreducing the risk of long-term complications and to improve diabetes outcomes [1].The Indiandrug medicine market has become the global hub of FDCs. The first US-FDA authorizedFDC for salein the USA was Glucovance (glibenclamide + metformin) in the 20th century [2]. According to the Clinical Practice Guidelines, diabetes mellitus condition requires intake of multiple oral hypoglycemic agents and prolonged treatment protocols to be followed, which leads to non- compliance and failed treatment outcomes. The FDC is a combination of two or more pharmaceutical active ingredients prepared at acertain permissiblefixed dose into and made into a single dosage form which addresses all the above said issues. TheFDC need is intended only if the combination has verified gain over single compound administered one at a time in terms of safety, efficacy or tolerability[3].The Government of India's on 2018 had passed the decision to ban a wide number of "irrational" Fixed-Dose Combination drugs (FDCs) based on the Kokate Committee report and prioritizing patient safety [4]. With the market worth of 16 billion rupees a year,the ban on these FDC's drugs had already led to significant repercussions in terms of the revenue loss [5].

Diabetes mellitus (DM) is a chronic metabolic illnesswith high blood sugar levelsassociated with impaired insulin secretion and insulin resistance. Internationally, an anticipated 422 million adults are existing with diabetes mellitus, conferring to the modern 2016 records from the World Health Organization (WHO) [6]. Type 2 diabetes mellitus (T2DM) display as a multifacetedpathogenesis namely obesity, unhealthy diet and genetic mediated factors leading to impaired glucose homeostasis. T2DM Individuals with hyperglycaemiaare at high possibilities of both macrovascular and microvascular complications leading to the insulin resistance syndrome. Insulin resistance and sparse insulin secretion due to beta cell dysregulation are major pathophysiology in T2DM. The multi-faceted long-term pathogenetic disturbances in T2DM warrants the use of multiple antidiabetic oral agents as FDC combinations in order to maintain normoglycaemia.[7].

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The FDC ofChlorformin (phenformin 25 mg + chlorpropamide 50 mg) was introduced in the market by Cadila (Zydus) in the late mid Seventies were the prominent FDC's used for DM in world market. The first FDC approved by US-FDA in the USA was Glucovance (glibenclamide + metformin) which became popular to the fact that it was able to accomplish theglycaemic targets at much lower doses of metformin or glibenclamide compared with the stand-alonemonotherapies with promising tolerability and efficacy.Indian pharmaceutical industry was able to come up withthe Glucored (glibenclamide + metformin) and Glynase MF (glipizide + metformin) which had helped in treating large population of diabetes patients in a cost-efficient manner [8].

Prescribing Fixed Dose Combinations (FDCs) in Diabetes mellitus treatment is often a routine practice. Although FDCs are related to advantages like synergistic action, advanced patient'scompliance.However certain disadvantages like incompatible pharmacokinetics, mismatched dose ratio and extended toxicity are some of the limiting factors of an FDC [9].

Early Life style modification and monotherapy with oral hypoglycemic agents are the 1st line of treatment as per the standard of care recommended by the American Diabetic Association (ADA). Sulfonylurea with biguanide or the biguanide with thiazolidinedione are the most formulated FDC's combinations [10].

Materials and Methods

This study was done in a multispecialty tertiary care treating hospital. Study Design was an analytical observationalstudy. The data analyzed were inclusive of the FDC's used for the treatment of DM which are currently available inside the Indian drug market.

Methods: This consequential observational analysis wascarried out between December 2019 to March 2020, by the Department ofPharmacology, Saveetha Medical College and Hospital.The Rationality of the FDC's were analysed the usage of a pretested device which validates them using the Pharmacokinetic, Pharmacodynamic & ADR profiles. Our study data was compared with the FDCs listed in WHO essential listing used for theDrug treatments,Pharmacodynamic, Pharmacokinetic parameters &notable drug-drug interactions taking place due to API (Active pharmaceutical ingredients) contained inside the product. The statistical analysis included all the

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quantitative variables and the averageunconventionality and qualitative variables were also articulated as chances and proportions in SPSS software data entry.

Results and Discussions

In this study theFDC's were analyzed as per the known repositories of the available drugs in the market. It was observed that 7 of the FDCs in Oral Hypoglycemic Agents (OHA) meet the criteria for rationality but there are 11FDC combinations found to be irrational. The following are those

1. Glibenclamide+ Metformin
2. Gliclazide + Metformin+ Voglibose
3. Metformin + Voglibose+ Chromium picolinate.
4. Glipizide + Metformin
5. Glipizide + Metformin + Pioglitazone+ Chromium picolinate
6. Glibenclamide+ Metformin + Voglibose
7. Glimepride+ Metformin + Pioglitazone
8. Glimepride+ Metformin + Ramipril + Atrovastatin
9. Glimipride+ Metformin + Atrovastatin
10. Metformin + Fenofibrinate
11. Metformin+ Bromocriptine

As per the evidence-based medicine the Sulphonylureas(SU)can be considered for use in Fixed Dose Combination's with all classes of oral antidiabetic drugs except glinides [11,14]. Furthermore, low-dose FDC combination therapies when compared to high-dose monotherapy showed lesser ADR's and helped in achieving better glycemic control [12,13]. The recent FDCs pioneered the shortcomings faced in the conventional FDC's likedosage reduction, frequency,flexibility of dosage, Drug scheduling complexity, thereby improving the patient adherence [14]. In few meta-analysis studies done on the FDC combination of Sulphonylureaswith antihyperglycemic agents were associated with lower A1C when compared to dual therapies in patients with T2DM [15]. The FDC's have increased combined efficacy in comparison to the same drug given as monotherapy on the equal dose. Improved adherence,

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compliance and simplified drug scheduling therapy. The right combination of FDCs helps to lessen the hyperglycemia effectively [16].

Conclusion

The FDCs do have to undergo many clinical trial testing phases as per the Central Drug Standard Control Organisation (CDSCO) and applicable international regulatory guidelines. Inflated drug prices manifest direct liability on consumers due to the expenses incurred in the research and development of the FDC.s which makes the diabetes care management a costly affair. Treating physicians shouldbe more rational and judicial enough in prescribing FDCsto avoidunwarranted FDC prescribing habit without proper evidence-based understanding of the disease conditions.

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