

Rationale for Prescribing Fixed Drug Combinations in Dental Practice – A Wide-Ranging Review

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Abstract:- Routine use of drugs has become the integral part in the maintenance of health care of an individual. Blending of various number of drugs in a fixed ratio to the single drug form – FDC. FDC have been turned out to be beneficial when compared to single drug, in-terms of safety and effectiveness, yet some irrational combination persists. FDC's are admissible only when the dosage of each ingredient in the mixture meets the requirements of the proposed population group and also when the combination has a proven advantage over single drug in terms of therapeutic effect & patient compliance [1]. FDCs are gaining popularity in the Indian Pharmaceutical Market and have been prospering from last decade[2]. This manuscript intends to appraise the common FDC's prescribed in the various dental treatments and discuss the merits and demerits of FDC, irrational combinations, Indian scenario of FDC and its approvals, its controversies in general and creating awareness among dental practitioners regarding this aspect [2].

Keywords:- Fixed Drug Combinations, Irrational Combinations, Compliance, Banned Drugs, Regulatory Bodies, Rational Combinations, Ingredients.

I. INTRODUCTION

WHO DEFINES THE RATIONALITY AS “THE USE OF RIGHT DRUG IN A RIGHT MANNER, IN THE RIGHT PATIENT AT THE RIGHT TIME AT THE LOWEST COST TO THEM AND THEIR COMMUNITY [9]. The term FDC refers to a product that contains two or more active ingredient in a fixed ratio [1,3]. Prescribing FDC's have certain advantages like synergistic action of one drug is enhanced by other additive, reduced cost of the drug, lowered adverse side effects, better

patient's acquiescence. The FDCs are available in the form of a tablet, capsule, syrup, powder, injection, suspensions etc [4]. Prescribing the irrational combinations not only create a problem like adverse side effect, drug-drug interactions, unnecessary financial burden to patients. It has become troublesome to those practitioners who endorse the habit of prescribing such combination leads to controversies through the litigations in consumer form [1,6,12]. To be in safer side with this regard one must possess an adequate knowledge on drug combinations, its rationale, information on banned drug combinations, update on ban / irrational combinations by DCGI. This article deliberately discusses about the FDC's, frequently prescribed FDC's in dental practice, rule of rational combinations, reason for continued use of banned FDC's in our country and compare the merits and demerits of drug combinations.

II. RATIONALE OF FDC

The FDC's are considered to be rational when it satisfies the following requirement

- The drugs included in the combination must act by diverse mechanisms i.e ., their mechanism of action should not be same , if two drugs are combined in a fixed dose each drug should act on its own mechanism
- The pharmacokinetics & pharmacodynamics of a combined drug should not differ by a wide gap form each other.
- The FDC's combined should never have supra-additive toxicity of the ingredients. [3,5,7,10].

III. MERITS OF FIXED DRUG COMBINATIONS

- ✓ Cost efficiency
- ✓ Reduced pill burden
- ✓ Improved compliance
- ✓ Therapeutic effect of one drug can be increased by another drug in combination
- ✓ Enhanced effect on combination
- ✓ Only one expiry simplifies dosing
- ✓ prevent or slows the accomplishment of resistance
- ✓ Frequency related to drug consumption is minimal and there is a less chance for a patients to miss a dose
- ✓ Improved shelf life [1,5,12]

IV. FIXED DRUG COMBINATIONS OFTEN PRESCRIBED IN DENTAL PRACTICE:

Antimicrobials, analgesics, steroids, antiseptics, muscle relaxant, antihistamines, antidepressant, nutritional supplements, antioxidants, sialagogue and anti-sialagogue, antacids, anaesthetic agents and dentifrices are the most common class of drugs been prescribed by the various dental practitioner on a day -to -day practice, these classes of drugs are available either in a single drug form or as a combinations to produce the desired therapeutic effect [10]. The drug combinations commonly prescribed in dental practice include

- Amoxicillin + clavulanic acid
- Ornidazole + ofloxacin
- Sulfamethoxazole + Trimethoprim
- Ampicillin + Cloxacillin
- Norfloxacin + Metronidazole
- Fluconazole + tinidazole
- Ibuprofen + paracetamol
- Diclofenac + paracetamol
- Ibuprofen + paracetamol + hydrocodone
- Aceclofenac + paracetamol + serratopeptidase
- Chlorzoxazone + Diclofenac sodium + Paracetamol
- Chlorzoxazone + Diclofenac sodium
- Cox -2 inhibitors + paracetamol
- Multivitamins + antioxidants
- Pantoprazole + domperidone
- Pantoprazole + ondansetron
- Immunosuppressive + corticosteroid
- Fluoride containing dentifrices
- Montelukast + levocetirizine
- LA + adrenaline etc.,

Besides these combinations various other combinations has been seen emerging frequently and is been promoted. Some of them are rational and highly advantageous in attaining the desired therapeutic effect, but potentially inappropriate fixed drug combinations are also flooded in market which on prescription might lead to adverse serious side effects on the consumers.

Table: 1 Rational and Irrational Combinations Prescribed in Dental Practice.

Rational combinations	Irrational combinations
<ul style="list-style-type: none"> • Amoxicillin + clavulanic acid • Sulfamethoxazole + trimethoprim • Chlorzoxazone + Diclofenac sodium/Acetaminophen <ul style="list-style-type: none"> • Multivitamins + antioxidant • Local anaesthetics + adrenaline • Fluoride containing tooth paste/mouthwashes 	<ul style="list-style-type: none"> • Ornidazole + ofloxacin • Norfloxacin + metronidazole • Ampicillin + Cloxacillin • Fluconazole + Tinidazole • Ibuprofen + paracetamol • Diclofenac + paracetamol <ul style="list-style-type: none"> • Ibuprofen + paracetamol + hydrocodone • Aceclofenac + paracetamol + serratopeptidase • Chlorzoxazone + diclofenac sodium + paracetamol <ul style="list-style-type: none"> • Cox -2 inhibitors + paracetamol • Pantoprazole + domperidone • Pantoprazole + ondansetron • Immunosuppressive + corticosteroid • Montelukast + levocetirizine

EVALUATING THE RATIONALITY OF FDC's PRESCRIBED IN DENTAL PRACTICE: AMOXICILLIN + CLAVULANIC ACID:

Amoxicillin is an aminopenicillin with extended spectrum of action. Clavulanic acid is a progressive/suicide inhibitor, it permeates the outer layer of gm-ve organism and inhibits the peri-plasmically located beta-lactamase. In this combination action of clavulanic acid enhances the therapeutic effect – thus considered as rational combination.

SULFAMETHOXAZOLE + TRIMETHOPRIM:

When given as a single drug both act as bacteriostatic, but on combination they become bactericidal. Trimethoprim

prevents the conversion of PABA to DHFA, sulfamethoxazole inhibits the production of THFA from DHFA. This combination act by a diverse mechanism, it is considered to be rational.

CHLORZOXAZONE + DICLOFENAC SODIUM/ACETAMINOPHEN:

Chlorzoxazone is used to relieve stiffness caused by muscle strains and muscle sprains , act as a muscle relaxant, combining any analgesic especially diclofenac sodium or acetaminophen aids in relieving the pain associated with muscle sprains and hence this combination is considered to be rational.

MULTIVITAMINS + ANTI-OXIDANTS:

As per WHO guidelines vitamin combination are a part of nutrition and vitamin combination should not be used indiscriminately. Still this combination is a matter of discussion whether it is rational / irrational.

LOCAL ANAESTHETICS + ADRENALINE:

Adrenaline act as vasoconstrictor thus provides the blood less field for surgery, prolong the action of local anaesthetics, reduce systemic toxicity. These combinations are beneficial and are considered to be rational.

FLUORIDE CONTAINING DENTRIFICES/MOUTHWASHES:

Since from the year 1960 fluoride containing tooth paste has been proven to reduce caries significantly, fluoride aid in remineralizing the enamel layer and might reverses the earlier signs of tooth decay and hence they are considered to be rational.

OFLOXACIN + ORNIDAZOLE:

This Combination most commonly used in gingivitis and periodontitis. Ornidazole interrupt the formation of microbial DNA. Ofloxacin inhibit the formation of bacterial DNA gyrase, more or less the target action of this combination is on DNA. Even prescribing any one of the above drug will be sufficient to attain a therapeutic effect. Addition of these drugs does not provide any enhanced synergistic effect, thus it is considered to be irrational.

NORFLOXACIN + METRONIDAZOLE:

Fluoroquinolones is effective in broad range of infections; the most susceptible ones are aerobic gm-ve bacilli. But the metronidazole is toxic to anaerobic organism. These types of mixed infections rarely co-exist. Prescribing this combination may add to cost, adverse side effects and may favour resistance.

AMPICILLIN + CLOXACILLIN:

Ampicillin is effective against gm-ve bacilli but not against beta-lactamase. Cloxacillin is an antistreptococcal penicillin with no effect on gm-ve bacilli. These two bacterial infections rarely co-exist and marked to be irrational.

FLUCONAZOLE + TINIDAZOLE

Combination of these two antimicrobial agents for the purpose of increasing the spectrum of activity is considered to be irrational, as the patient might require only one drug. The important point is to come up with a correct diagnosis.

NSAIDS/MUSCLE RELAXANT + PARACETAMOL:

- Ibuprofen + paracetamol
- Diclofenac + paracetamol
- Ibuprofen + paracetamol + hydrocodone
- Aceclofenac + paracetamol + serratopeptidase
- Chlorzoxazone + diclofenac sodium + paracetamol
- Cox -2 inhibitors + paracetamol

Addition of paracetamol to other NSAIDS does not provide any additional therapeutic effect – so, this combination is considered to be irrational.

PANTOPRAZOLE + DOMPERIDONE/ONDANSETRON:

Combination of peptic ulcer drugs with antiemetic is considered to be irrational because peptic ulcer is not always associated with vomiting.

NSAIDS + OPIOD ANALGESIC:

Combining these two classes of drug is considered irrational. Because the primary action is to control the pain, but the way they act differ. This combination may pose severe adverse side effects.

MONTELUKAST + LEVOCETIRIZINE

Montelukast, belong to the class of leukotriene antagonist with a half-life of about 2.7-5.5 hours while ,Levocetirizine, a 2nd generation antihistaminic with a half-life of about 6 -10 hours. There is no justification for the use of this combination and hence considered irrational.

IMMUNOSUPPRESSIVE + CORTICOSTEROIDS:

Addition of steroids to immunosuppressive agent leads to additional immunosuppression and is considered to be unsafe combination and is considered to be irrational in terms of adverse side effects. [2,4,8,12,]

V. GUIDELINES REGARDING INAPPROPRIATE / IRRATIONAL COMBINATIONS:

DCGI, Department of Health and Family Welfare has issued a notification in public interest in order to regulate, make restriction and prohibition regarding manufacture, sale and distribution of drug under section 26-A of drug and cosmetic act. According to this notification the following combinations are considered to be irrational and is been banned from use in India.

- 1) Vitamins + Anti- inflammatory / Tranquilizer
- 2) Atropine + Analgesics/Antipyretics
- 3) Anti-histaminic + Anti-Diarrhoeal
- 4) Penicillin + Sulphonamide
- 5) Vitamin C + Tetracycline
- 6) Corticosteroid + Any drug (except for MDI / dry powder formulations)
- 7) Vitamins + anti – tubercular drug except for isoniazid + pyridoxine
- 8) Oestrogen + Progestin (other than oral contraceptive every other formulations are irrational
- 9) Sedative /Hypnotic + Analgesic/ Antipyretic
- 10) H2 receptor antagonist + antacid
- 11) Broncho-dilator + Antihistamine/ Antitussive
- 12) Anti-diarrhoeal + electrolytes
- 13) Anti-spasmodic + NSAID's
- 14) Tooth powders/pastes + tobacco products
- 15) Analgin + other drugs.
- 16) Vitamin B1 +B6+B12 [11].

VI. DEMERITS OF FDC's:

- ✓ The price of FDCs may be hiked if redundant drugs are included in the combination.
- ✓ There are probabilities that one of the drugs in the combination might be lavish or excess.
- ✓ FDCs may lead to augmented incidence of adverse side effect.
- ✓ Merging of drugs with discordant pharmacodynamic/pharmacokinetic properties in a FDC's may evidence to be harmful to the health of a individual.
- ✓ If preparations with dissimilar pharmacokinetic properties are combined in a Fixed drug combinations it might lead to undesirable fluctuation in the plasma concentration of the component drug.
- ✓ Additional side effect, if occur, cannot be easily accredited to a specific drug causing it in a combinations.
- ✓ There might be a increased frequency of adverse side effect and drug-to-drug interactions by a FDC as compared to a single dose.
- ✓ Moreover, if the patient is allergic or has contraindication to one of the components of the FDC, the FDC cannot be prescribed [1, 6,7,15].

VII. SCHEMA OF FDC's IN INDIA:

Over the last few years, a massive market for the irrational FDCs has been flared up in India; this has been ascribed to the profile-raising activities of the pharmaceutical companies embattled directly towards the consumers or towards the Doctors. In India, **122E of Drug and Cosmetics Rule**, proposes that “a combination of two or more drugs is considered to be a “NOVEL DRUG” and all new combinations has to be officially permitted by Drugs Controller General, India (DCGI), this is made considerate due to the fact that by compounding two or more drugs, the safety, efficiency, and bioavailability of the discrete Active Pharmaceutical Ingredient might differ. In the present day scenario, the practice of approval is as follows - State Drug Controllers can/do offer certificate for approval and marketing of new combination although they don't possess this legal authority. Once the permission for FDC is permitted by a State Drug Controller it can be traded/sold in any state of the country, although it is neither approved by DCGI nor by other SDCs. The Indian laws governing the marketing and accreditation of FDCs are not appropriately defined. The pharmaceutical companies take advantage of this ambiguities and endure to market irrational FDCs and in turn get benefitted with high earnings. To overcome this issues an expert committee was formed by Central drug standard control organization (CDSCO) on March 4th, 2013 to frame a policies on FDCs. This is considered to be an vital phase in development of a standards for approval of FDCs in our country [4,6,13]. Whereas in UK , EUROPE ,BELGIUM and some other developed countries the drug approval process is completely different. For example in UK MHRA(medicines and health products regulatory agency) provides license based on clinical trial regulations, monitoring safety and efficacy of drugs, providing information to public and implement laws.

VIII. WHY THE IRRATIONAL COMBINATIONS ARE BEING PRESCRIBED IN CLINICAL PRACTICE:

Lack of training among dental graduates pertaining to Problem-based pharmacotherapy is not included in curriculum put forth by DCI. New curriculum should be devised including the concepts of Rational Drug Use, Essential Medicine List, Personal drug [1,4,5].

Nonexistence of data regarding indication and safety of drugs among dental professionals. Moreover, clinicians mostly trust on the information provided by a medical representatives, available literature and brochures from the pharmaceutical companies which provide the reasoning information relevant to the safety and efficacy of these irrational FDCs to be disclosed. Continuing Dental education (CDE) if conducted regarding this aspect, it is most often been sponsored by various pharmaceutical companies having their personal market interests [2,5,7].

Lack of investigative amenities and ambiguity of diagnosis among the clinicians is a major contributing factor the lead them to camouflage their uncertainty in diagnosis by prescribing FDCs that are irrational and illogical [1,4,6].

There is a necessity to carefully screen and censor ambiguous claims by the pharmaceutical company. Negligence on the part of the pharmaceutical industry and lack of vigilance from government part leads to increased fame of irrational combinations. Most billboards in many of the medical/dental journals in India flopped to indicate the important information regarding the right usage of drug combinations. There is a prerequisite to reinforce the mechanism for continuing professional development of dentist so, that they gain a adequate knowledge and skills to prescribe rational combination [12,13].

Other major reasons include, communication gap between state drug controller and DCGI, Non-availability of an appropriate/right drug at the right time and their increased cost, self-prescription is the other significant cause which should be intervened by public awareness programmes. Due to poverty level these combinations are easily marketed at low cost. Persistence of lengthy legal procedure to ban any irrational combinations in India, Trust factor on commercial advertisement by pharmaceutical companies, lack of transparency and answerability are the some of the factors leading to the prescription of irrational drugs [15].

IX. CONCLUSION

We are in hour of need to diminish the degree of this delinquent by creating awareness among dental residents and clinicians about the effectiveness, safety, appropriateness, rationality and price benefit of FDCs available for patient use. Irrational prescription of FDC not only results in adverse drug effect, drug interactions and impose unnecessary financial burden but also pose a problem to those practitioners who endorse the habit of

prescribing such combinations, which may lead to controversy when subjected to litigations in consumer form. Creating awareness among dental practitioner's is very vital regarding the advantages, disadvantages and rationality in prescribing of fixed dose combinations.

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