Irrational Fixed Dose Combinations in Current Clinical Practice: A Need of Reconsideration or High Precautions

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Abstract:
Introduction: Fixed Dose Combinations (FDCs) play a crucial role in pharmaceuticals by incorporating multiple approved Active Pharmaceutical Ingredients (APIs) into a single dose. The intent is to enhance medication adherence, reduce poly-pharmacy, and promote cost-effectiveness. While the World Health Organization's Seventeenth Model List of Essential Medicines (March 2011) includes only 25 approved FDCs, India's National Essential Medicines List encompasses 354 essential medicines, featuring 14 FDCs. However, the irrational use of FDCs poses significant risks, leading to adverse effects, therapeutic failure, ineffective dosing, susceptibility to abuse, and increased costs. Identifying the causes of such side effects becomes challenging with FDCs, making a critical examination imperative. **Objective:** The primary objective of this study is to examine and discuss the irrationality of selected FDCs available in the market. **Methodology:** This study focuses on the irrationality of selected FDCs available in the market, including combinations such as Ramipril and Telmisartan, Aspirin and Clopidogrel, Rosuvastatin and Fenofibrate, Fluoxetine and Alprazolam, Amitriptyline and Chlordiazepoxide, Lovastatin and Nicotinic acid, Isoniazid and Rifampicin, Isoniazid and Ethambutol, Zidovudine and Lamivudine, Chlorpromazine and Trihexyphenidyl and Trifluoperazine, Domperidone and Rabeprazole, Atorvastatin and Amlodipine, Ezetimibe and Atorvastatin, Atenolol and Nifedipine, Salbutamol and Theophylline, Salbutamol and Ipratropium bromide, indicated for various diseases. The rationality of these FDCs is analyzed using authoritative resources such as AHFS drug information, BNF, Martindale: The complete drug reference, Stockley's drug interactions, among others. **Results:** The analysis reveals that the irrational use of FDCs may lead to adverse consequences, with potential risks such as side effects, therapeutic failure, and increased costs. By scrutinizing specific FDCs, including Ramipril and Telmisartan, Aspirin and Clopidogrel, Rosuvastatin and Fenofibrate, among others, evidence from authenticated resources is used to assess their rationality. Continuous monitoring and periodic clinical studies are deemed essential to justify the rationality of these FDCs, ensuring their safety and efficacy. **Conclusion:** In conclusion, the study underscores the need for a critical evaluation of FDCs to ensure their rational use in clinical practice. The presence of numerous FDCs in the market demands continuous monitoring and periodic clinical studies to validate their safety, efficacy, and cost-effectiveness. The results emphasize the importance of evidence-based assessments from authoritative drug information sources to guide healthcare professionals and policymakers in promoting rational FDC prescribing practices.
Keywords: Fixed Dose Combinations, FDCs, Rationality, Adverse Drug Reactions, Side-effects, Drug-Drug interactions.

Introduction:

Fixed dose combination (FDC) drugs contain more than one approved active pharmaceutical ingredient (API), are manufactured as a fixed dose, and are packaged in a single dosage form. FDCs are introduced to improve medication adherence and reduce poly-pharmacy and cost-effectiveness. Pharmaceutical industry's focused attention on FDCs as the CDSCO banned 328 irrational FDCs in September 2018.[1] Irrational fixed-dose combinations are combinations of medications that increase the risk of side effects, resulting in ineffective dosing, Therapeutic failure and susceptibility to abuse, and may also increase the costs. Identifying the causes of these side effects may be more difficult when using FDCs. In many cases, their stability is not always guaranteed, which reduces the effectiveness of some APC.[2] WHO's Seventeenth Model List of Essential Medicines (March 2011) contains only 25 approved FDCs, while India's National Essential Medicines List contains 354 essential medicines, including 14 FDCs. Nevertheless, the number of irrational FDCs has skyrocketed in the recent past, and many of them are available as Over-The-Counter (OTC) medications.[3]It is much required to analyze the available FDCs in the market. Hence, in this study, the selected FDC's rationality was assessed based on the evidence available in the authenticated primary, secondary and tertiary resources like AHFS drug information, BNF, Martindale: the complete drug reference, Stockley's drug interactions, PubMed, Medline, Embase, etc.

Methodology:

For this review, the key phrases utilized in the literature search were Fixed Dose Combinations, Rationality, Adverse Drug Reactions, Side-effects, Drug-Drug interactions, FDCs using, searching engines like ScienceDirect, PubMed, Google Scholar, CrossRef, Scopus,PubMed, Medline, Embase. All papers that contained the specified keywords have been included in this study. The rationality of the selected FDCs is reanalyzed by using AHFS drug information, BNF, Martindale: the complete drug reference, Stockley's drug interactions.

Results and Discussion:

The following FDCsare said to be irrational by assessing their Pharmacokinetics and pharmacodynamics properties based on existing evidence.

1. Ramipril and Telmisartan:

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor. Telmisartan is an angiotensin-II receptor blocker (ARB). These two drugs are available as FDCs with 40mg of Telmisartan and 5mg, or 2.5mg of Ramipril. Both Ramipril and Telmisartan indicated for hypertension, Cardio-vascular disease and renal impairment. It acts by inhibiting the angiotensin-II, producing a synergistic effect when administered as an FDC.

Yusuf S et al., 2008 conducted study with Ramipril 10 mg daily (8576 patients), Telmisartan 80 mg daily (8542 patients), or both drugs as FDC (8502 patients). Concluded that either administration of Ramipril with Telmisartan reduced mean systolic blood pressure by up to 5 mmHg but had no additive effect on the renin-angiotensin system. Without improving benefit, the FDC was linked to greater adverse events, such as severe hypotension, syncope, renal failure, and hyperkalemia. Compared to 149 patients using Ramipril alone and

229 patients receiving Telmisartan alone, 406 patients taking both medications had treatment termination due to severe hypotension. Combining the two medications decreased proteinuria in individuals with high vascular risk more than Ramipril by itself, but overall, FDC exacerbated renal impairment.[4]

Hence, this FDC may need to be reconsidered or the blood pressure, renal function, electrolyte, and fluid balance should be monitored to reduce these side-effects.

2. Aspirin and Clopidogrel:

Both Aspirin and Clopidogrel are used as anti-platelet agents and work by preventing platelets from sticking together and reducing the formation of harmful blood clots when given as FDC.These two drugs are available with dosage of 75mg or 150mg of Aspirin and 75mg of Clopidogrel.

Payne DA et al., 2002 concluded that, 26 patients with peripheral arterial disease were given either 325 mg of Aspirin daily or 75 mg of Clopidogrel daily with both drugs together for 14 days as part of a study to assess short-term prolongation of bleeding. When used concomitantly, bleeding time was prolonged compared to either drug alone (17.4 minutes for combination versus 6.6 minutes for Aspirin alone and 10.2 minutes for Clopidogrel alone). Similarly, in a study of 7 healthy volunteers, 75 mg Clopidogrel and 150 mg Aspirin daily for 2 days caused a 3.4-fold increase in bleeding time compared to baseline. When the Clopidogrel dose was increased to 300 mg, it occurred to a 5-fold increase in bleeding time.[5]

Diener HC et al., 2004 concluded that, patients with recent stroke or transient ischemic attack (MATCH) had a higher incidence of life-threatening bleeding events following the use of Clopidogrel 75 mg daily versus Aspirin 75 mg daily compared to Clopidogrel alone (2.6% and 1.3%, respectively).[6] Yende S et al., 2001, conducted a study of this drug combination and concluded thatincreased perioperative bleeding in patients taking both Aspirin and Clopidogrel.[7]

Hence, this FDC requires frequent monitoring of Prothrombin time and bleeding time. The patient must be educated regarding the risk of bleeding.

3. Rosuvastatin and Fenofibrate:

Rosuvastatin is an HMG-CoA reductase inhibitor (statins). Fenofibrate belongs to fibrates and work by lowering the rates of triglycerides in the blood, preventing the body from making LDL while administered as FDC. These two drugs are available as FDCs with a dosage of 10mg, 20mg of Rosuvastatin, and 160mgof Fenofibrate.

Kipnes MS et al.,2010 concluded that, in an extension study of patients who completed a 12-week controlled trial, 174 patients received Fenofibrate 135 mg daily with 20 mg for 2 years or longer Rosuvastatin taken daily. Three patients experienced elevation of creatinine phosphokinase concentrations10 times than the normal range, one suffered from myalgia. However, none of these patients discontinued treatment. Two additional patients discontinued Fenofibrate with Rosuvastatin due to myalgia.[8]

Dedhia V et al., 2007 reported that, a 68-year-old man taking 10 mg of Rosuvastatin daily, developed Myopathy about 03 weeks after adding 160 mg of Fenofibrate. Rhabdomyolysis was diagnosed, and both medications were discontinued, resulting in significant clinical improvement within 24 hours.[9]

Buyukhatipoglu H et al., 2010 concluded that, other cases of muscle toxicity have been described shortly after taking Rosuvastatin 10 mg daily and Fenofibrate 250 mg daily.[10] The patients who administered the FDC must be educated regarding the risk of Myopathy and spontaneous reporting of ADR.

4. Fluoxetine and alprazolam:

Fluoxetine is an antidepressant and works by increasing levels of serotonin (a chemical messenger that improves mood). Alprazolam is a benzodiazepine and works by increasing the effects of GABA (a neurotransmitter that suppresses the abnormal activity of nerve cells in the brain). Both medications have an anti-anxiety and mood-enhancing effect. These two drugs are available as FDC with a dosage of 20mg of Fluoxetine and 0.25mg of Alprazolam.

Lasher TA et al.,1991, concluded that Fluoxetine 60 mg daily for 4 days reduced the clearance of Alprazolam 1 mg four times daily by about 21% and increased its plasma concentration by about 30%. These changes were associated with increased psychomotor impairment.[11]

Hence, this FDC leads to severe side-effects and increased psychomotor impairment. Educate thepatients about the potential effects and counsel them against undertaking skilled tasks (e.g., driving). Monitoring the symptoms such as agitation, tremors, rapid heart rate, and confusion which may leads to Serotonin syndrome. Exploring the alternative treatment options, such as psychotherapy or other medications, to address the patient's mental health condition while minimizing the need of this FDC.

5.Amitriptyline and Chlordiazepoxide:

Amitriptyline is a tricyclic antidepressant which works by increases chemical messengers in the brain that help regulate mood and treat depression. Chlordiazepoxide is a benzodiazepine which works by enhancing the effects of GABA. These two drugs are available as FDCs with a dosage of 12.5mg or 25mg of Amitriptyline and 5mg or 10mg of Chlordiazepoxide.

ABDOU FA et al., 1964 concluded that, two other patients taking Amitriptyline and Chlordiazepoxide suffered from drowsiness, memory impairment, slurred speech, and difficulty concentrating. Both were incapacitated, and one described himself as drunk.[12]

Beresford TP et al., 1981 concluded that, four individuals who were using Limbitrol, (a medication that contains both chlordiazepoxide and amitriptyline) displayed certain toxic effects, including delusions, confusion, restlessness, disorientation, mouth dryness, and impaired vision. Enhanced CNS depression (perhaps additive) and enhanced anti-muscarinic side effects of the tricyclic anti-depressant appear to be some of these effects.[13]

Hence, this FDC causes severe side-effects. Hence, the patients are advised regarding the degree of sedation and potential effects of the drug. The patients are warned about the caution while driving or undertaking other skilled tasks.

6. Lovastatin and Nicotinic acid:

Lovastatin is an HMG CoA reductase inhibitor, which works by inhibiting the production of cholesterol in the body by blocking an enzyme called HMG Co-A reductase, which is essential for cholesterol synthesis. It thus lowers LDL and triglyceride levels and increases the HDL. Nicotinic acid is essential vitamin for regular body

function and also reducing the cholesterol and triglycerides levels. These two drugs are available as FDCs with a dosage of 40mg or 20mg of Lovastatin and 1000mg or 750mg of Nicotinic acid.

Reaven P et al., 1988 concluded that, the addition of Nicotinic acid titrated up to 2.5 g daily caused rhabdomyolysis in a 43-year-old man receiving 40 mg of high-dose Lovastatin twice a day. Another brief report of myositis in a patient receiving lovastatin and nicotinic acid was made.[14]

In a 52-week study to assess the efficacy and tolerability, Kashyap ML et al. (2002) concluded that, a combination product of lovastatin and nicotinic acid is on the market (Advicor, USA), and none of the 814 patients experienced this drug-induced myopathy (myalgia and elevated creatine kinase concentrations above 10 times the upper limit of normal). 7 individuals, however, have been excluded from the research because their creatine kinase levels were too high.[15]

Yim BT et al., 2003 concluded that, a review of the use of extended-release Niacin along with Lovastatin found that myalgia, which occurred in 3% of patients, tended to be associated with one higher baseline doses of statins were associated.[16] Omar MA et al., 2002 concluded that, a review of FDA spontaneous reports of statin-associated rhabdomyolysis from November 1997 to March 2000 identified Nicotinic acid as a potentially interacting drug 1 of 40 cases for Lovastatin.[17]

Hence,the Patients must be educated regarding Myopathy and spontaneous reporting of ADR.Adjust the doses based on the patient's response and individual cholesterol levels. The dosage may need to be titrated to achieve the desired lipid-lowering effects.

7. Isoniazid and Rifampicin:

Isoniazid, a drug used to treat Tuberculosis. Rifampicin is a semi-synthetic antibiotic that is used in combination with Isoniazid to treat TB to eradicate the bacteria and eliminate the infection. These two drugs are available as FDCs with a dosage of 75mg, 150mg, or 300mg of Isoniazid and 150mg, 300mg, 450mg, or 600mg of Rifampicin.

Steele MA et al., 1991, reported that the evidence of frequency and severity of hepatotoxicity increases when both drugs are administered together.[18]

Askgaard DS et al., 1995 concluded that, a case report appears to prove that both drugs can quickly lead to hepatotoxicity. The patient tolerated both medications individually, but hepatotoxicity recurred when used concurrently.[19]

Pessayre D et al., 1977concluded that, although the causes of hepatotoxicity are not entirely known, Rifampicin or Isoniazid by themselves might harm the liver due to their toxic effects. One hypothesis is that Rifampicin modifies the metabolism of isoniazid, causing the production of the hepatotoxic compound hydrazine.[20]

The manufacturers of Rifampicin advise that caution should be exercised, especially in patients with impaired liver function, the elderly, malnourished patients, and children under 2 years of age. In patients with normal liver function before treatment, further testing after basic liver function tests is only required if fever, vomiting, or jaundice occurs or if the patient's condition worsens. However, one of the manufacturers of Isoniazid suggests that liver function tests should be checked monthly in patients receiving both drugs.

Since, both the drugs are primary options for the treatment of Tuberculosis, these drugs cannot be avoided. Instead of FDC, drugs can give in alternative day or two drugs can be administered with longest time-interval.

8. Isoniazid and Ethambutol:

Both Isoniazid and Ethambutol are anti-tuberculosis agents. These two drugs are available as an FDC with a dosage of 300mg of Isoniazid and 800mg of Ethambutol.

Karmon G et al., 1979 concluded that, Isoniazid may increase optic neuropathy caused by Ethambutol and that any effects disappear more slowly after withdrawal of these medications.[21]

Sivakumaran P et al., 1998concluded that, if severe optic neuritis manifests, one set of writers advises stopping Ethambutol and Isoniazid right away. In addition, they advise stopping Isoniazid if less severe ocular neuritis does not get better after 6 weeks of stopping Ethambutol.[22]

This FDC produces serious adverse effects like optic neuropathy. Patient are advised to stop both the drugs if severe optic neuritis occurs.

9. Zidovudine and Lamivudine:

Both Zidovudine and Lamivudine belong to the class of Anti-retroviral medication. These two drugs are available as FDC with a dosage of 300mg of Zidovudine and 150mg of Lamivudine. This combination of medications prevents the HIV from multiplying, thereby reducing the virus in the body. They also increase the numberofCD4 cells (white blood cells that protect against infections).

Tseng A. et al., 1998 concluded that, there are case reports of blood dyscrasias with concurrent use. Zidovudine 500 to 600 mg daily was administered with Lamivudine 300 mg daily to 13 HIV-positive patients. 9 of these 13 patients had previously received Zidovudine or Lamivudine alone without any problems. However, when both drugs were administered, all patients developed blood dyscrasias within 7 weeks. All patients experienced significant anemia with a steep decline in hemoglobin concentration, and one patient developed leukopenia and thrombocytopenia. Both medications were discontinued, blood transfusions were given, and all patients improved or recovered. Later, 8 individuals were started on Zidovudine or Lamivudine alone, and two of them tolerated the combination without additional hematologic difficulties (with the Zidovudine dose lowered in one patient and the medications administered sequentially in the other).[23]

Hester EK et al., 1998 concluded that, two other patients who received Lamivudine 300 mg daily in addition to their long-term Zidovudine therapy also exhibited a dramatic reduction in hemoglobin. Oncethe drug was withdrawn and blood was donated, both individuals recovered.[24] The combination of zidovudine and lamivudine is not currently a recommended acceptable dual NRTI backbone option as it has been associated with mitochondrial and other toxicities.

This FDC causes severe side-effects like blood dyscrasias. Monitoring the patient's viral load and CD4 cell count regularly to assess treatment effectiveness which helps determine whether adjustments to the antiretroviral regimen are necessary.

10. Chlorpromazine, Trihexyphenidyl and Trifluoperazine:

Chlorpromazine is a conventional antipsychotic. Trihexyphenidyl is an anti-muscarinic. These two drugs are available as FDC with a dosage of 50mg of Chlorpromazine, 2mg of Trihexyphenidyl, and 5mg of Trifluoperazine. Chlorpromazine and Trifluoperazine work by blocking the effects of dopamine, a chemical messenger in the brain that influences thoughts and mood. Trihexyphenidyl acts on the nervous system and corrects some of the side effects that occur during treatment with antipsychotics.

Warnes H et al., 1967 concluded that, a 49-year-old woman with schizophrenia was hospitalized for four months. She was treated with Chlorpromazine 1600 mg and Trihexyphenidyl hydrochloride 6 mg daily (average). After a phase of chronic constipation, acute diarrhea occurred after the enemas were administered. She was highly dehydrated before her death. Physical examination revealed fecal impaction. The patient suffered a fatal shock. An autopsy was not performed.[25]

Rivera-Calimlim L et al., 1973 concluded that, a study of psychiatric patients given 300 to 800 mg of Chlorpromazine daily found that when 6 to 10 mg of Trihexyphenidyl was added daily, plasma concentrations of Chlorpromazine increased by one range of 100 to 300 nanograms/ml reduced to less than 30 nanograms/ml. When Trihexyphenidyl was discontinued, plasma concentrations of Chlorpromazine increased again, and clinical improvement was observed.[26]

Patients should be closely monitored for any adverse effects, especially extrapyramidal symptoms, sedation, and cardiovascular issues. Dose adjustments may be necessary to minimize side effects and maintain therapeutic efficacy.

11. Domperidone and Rabeprazole:

Domperidone is a dopamine antagonist that operates on the upper digestive system to enhance motility of the stomach and intestines, allowing food to pass more quickly through the stomach. Rabeprazole is a proton pump inhibitor, works by reducing the stomach's acid, relieving acid-related indigestion and heartburn. These two drugs are available as FDC with a dosage of 10mg or 30mg of Domperidone and 20mg or 40mg of Rabeprazole.

Bourlon S. et al., 2002 reported that a single case describes the development of Myopathy and rhabdomyolysis in a patient 2 days after Rabeprazole 20 mg daily and Domperidone 6 tablets daily (strength not specified) were started. The patient had a creatine kinase level of 12,700 units/L (range, 15 to 100 units/L) and a myoglobin level of 650 micrograms/L (usually less than 90 micrograms/L). The patient had no significant medical history, and Domperidone and Rabeprazole were prescribed for the treatment of epigastric pain following a hysterectomy.[27] This FDC produces side-effects like Myopathy and rhabdomyolysis. Required monitoring for side-effects mentioned.

12. Atorvastatin and Amlodipine:

Atorvastatin is an HMG-CoA reductase inhibitor or statin. Amlodipine is a calcium channel blocker. These two drugs are available as Fixed Dose Combination (FDC) with a dosage of 10mg of Atorvastatin and 2.5mg or 5mg of Amlodipine. Amlodipine and Atorvastatin treat high blood pressure associated with high cholesterol levels.

Khan S et al., 2018, reported that a 65-year-old man with chronic renal impairment who had taken Atorvastatin and Amlodipine (doses not specified) for at least 4 years developed Myopathy that progressed to rhabdomyolysis (creatine kinase 160,000 U/ L).[28]

The bioavailability of the Atorvastatin and Amlodipine is high, when administered during night and day respectively. Hence, the proper administration time for this FDC need to be identified.

13. Ezetimibe and Atorvastatin:

Ezetimibe is a cholesterol-lowering drug that works by inhibiting cholesterol absorption in the gastrointestinal tract. Atorvastatin is a statin that works by stopping the body from producing LDL while boosting HDL. They will work together to reduce cholesterol in your body. These two drugs are available as FDC with a dosage of 10mg of Ezetimibe and 10mg, 20mg, or 40mg of Atorvastatin.

Ballantyne CM et al., 2003 concluded that, in a 12-week efficacy study in patients with hypercholesterolemia, Ezetimibe did not worsen statin intolerance or toxicity when co-administered with Atorvastatin 10 to 80 mg daily (255 patients) compared to Atorvastatin alone (248 patients). In this study, a patient taking Atorvastatin and Ezetimibe 40 mg daily developed elevated creatine kinase concentrations and myalgia.[29]

A case report revealed a 43-year-old man who was taking 80 mg of Atorvastatin daily at a high dose and got acute muscular discomfort with raised serum creatine kinase concentrations three weeks after commencing Ezetimibe 10 mg daily, according to Fux R et al., 2004. When both prescriptions were stopped, the symptoms went away, and he was able to begin taking Atorvastatin 80 mg daily without incident.[30] Simard C et al., 2006 similar cases were reported in patients taking Ezetimibe 10 mg daily and Atorvastatin 40 mg or 80 mg daily.[31,32]

Patients must be educated regarding the risk of Myopathy and spontaneous reporting of ADR. Patients are advised to inform the healthcare provider of any existing liver issues or a history of liver disease before starting the medication.

14. Atenolol and Nifedipine:

Atenolol is a non-selective adrenergic beta-blocker indicated for Hypertension and other cardiovascular diseases. Nifedipine is a calcium channel blocker, works by relaxing blood vessels. These two drugs are available as FDC with a dosage of 10mg or 50mg of Atenolol and 20mg or 40mg of Nifedipine.

Opie L.H. et al., 1980 concluded that, when administered Nifedipine 10 mg twice daily together with Atenolol 50 mg daily as a diuretic for one month, one in fifteen patients with hypertension and exertional angina gradually acquired hypotension (90/60 mmHg).[33]

Robson RH et al., 1982 concluded that, heart failure developed in a patient with angina who took Atenolol (and several other drugs) when 20 mg of Nifedipine was administered three times daily.[34]

This FDC causes severe side-effects like hemodynamic effects like severe hypotension and heart failure on its concurrent use. This FDC needs close monitoring as it can be contraindicated in patients with certain medical conditions, such as severe bradycardia, heart block, or hypotension.

15. Salbutamol and Theophylline:

Both Theophylline and Salbutamol are bronchodilators, works by relaxing the muscles in the airways and widening the airways. These two drugs are available as FDC with a dosage of 2mg or 4mg of Salbutamol and 100mg, 200mg, or 300mg of Theophylline.

According to a case cited by Epelbaum S et al. in 1989, a 10-year-old girl who received theophylline and salbutamol inhaler, developed respiratory failure that may have been caused by hypokalemia.[35]

Dawson, KP et al., 1982 concluded that, heart rate was significantly higher (109 beats per minute) in 15 children with asthma given single doses of oral Theophylline and Salbutamol compared to a control group receiving oral Theophylline alone (91 beats per minute).[36]

Whyte KF et al., 1988 concluded that, an infusion of salbutamol (4 micrograms/kg loading dosage) followed by 8 micrograms/kg for an hour dramatically worsened the hypokalemia and tachycardia in healthy volunteers after 9 days of pretreatment with oral theophylline.[37]

This FDC produces side-effects like hypokalemia, tachycardia and some respiratory complications which leads to life threatening cases.Patients with severe asthma are recommended to monitor serum potassium.

16. Salbutamol and Ipratropium bromide:

Both Salbutamol and Ipratropium bromide are bronchodilators works by relaxing the muscles in the airways and widening the airways. These two drugs are available as FDC with dosages of 100mcg, 2.5mg, or 200mcg of Salbutamol and 20mcg, 40mcg or 500mcg of Ipratropium bromide.

Shah P et al., 1992 concluded that, five patients with an acute exacerbation of COPD who were given nebulized Ipratropium and Salbutamol developed acute angle-closure glaucoma (IOP: 45-64 mm Hg), four of which developed within one to 36 hours of starting treatment. Two of the patients had a history of angle-closure glaucoma.[38]

Kalra L et al., 1988 concluded that, an increase in intra-ocular pressure was also reported in other patients who were given both drugs via nebulizer.[39] According to Hall SK et al., a patient who received nebulized Salbutamol and inhaled Ipratropium through a metered dosage inhaler developed acute angle-closure

glaucoma.[40] Other similar cases of acute angle-closure glaucoma due to concomitant use of Salbutamol and Ipratropium are reported elsewhere.[41]

Patients are advised to regularly monitor the patient's respiratory status, including lung function and symptom control. Adjust the treatment plan as needed based on the patient's response. Hence, alternatives like long or short acting beta agonists or inhaled corticosteroids can be preferred.

Conclusion:

The FDCs are required for close monitoring of ADR, therapeutic failure and (non-beneficial). Hence, the FDC drugs induces side-effects, and it concluded that the drugs can be given alone whenever possible, providing enough effectiveness. Cost of medication when given as FDCs increases and it may resemble patient compliances.Most of the studies says that FDCs have lessevidences for their safety and effectiveness and also the available evidences are too old. No much recent study has been conducted in FDCs. The study is based on the rationality of the FDCs to ensure the ADR and effectiveness of the drugs. Time to time evaluation of FDCs towards risk and benefit is highly recommended.

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