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Increasing Drug Resistance And Irrational Pediatric Fixed Dose Combinations: Is There A Correlation?

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ABSTRACT

Formulations containing two or more drugs in combination in a fixed ratio are called fixed dose combinations (FDCs). FDCs can be both rational as well as irrational. These irrational FDCs have numerous consequences associated with them like increased and unnecessary drug adverse reactions due to harmful &/or useless components, increased medication cost, poor clinical response in patients due to inappropriate dosage of individual components and above all increase in antibiotic resistance due to overuse or unnecessary use of antibiotic(s) present in FDC. We have highlighted certain irrational FDCs commonly prescribed to pediatric population and described the basis of their irrationality to enable the pediatricians to make well informed decisions of not prescribing these irrational drugs. It is high time that comprehensive efforts are made to curb this increasing menace of irrational pediatric FDCs; which would help tackle issue of increasing drug resistance as well.

Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, at the lowest cost to them and their community as per the conference of experts on the rational use of drugs, convened by the World Health Organization (WHO) in Nairobi in 1985.[1]

Formulations containing two or more drugs in combination in a fixed ratio are called fixed dose combinations (FDCs). FDCs can be both rational as well as irrational. The 16th essential medicines list of WHO have 351 essential medicines, including 26 FDCs whereas the national list of essential medicines of India has 354 essential drugs, including 14 drug combinations.[2,3] Despite the information and concern over increasing drug resistance, over 70 non approved dangerous FDCs are being sold in India under more than 1000 brand names.[4]

These irrational FDCs have numerous consequences associated with them like increased and unnecessary drug adverse reactions due to harmful &/or useless components, increased medication cost, poor clinical response in patients due to inappropriate dosage of individual components and above all increase in antibiotic resistance due to overuse or unnecessary use of antibiotic(s) present in FDC.

Many physiologic differences between neonates, infants, children, and adults can affect the absorption, distribution, metabolism, and excretion (pharmacokinetics) of drugs increasing risk of adverse drug reactions from irrational FDCs in pediatric patients. Gastric acid secretion, bile salt formation, gastric emptying time, intestinal motility, bowel length and microbial flora vary with age. Reduced gastric acid secretion increases bioavailability of acid-labile drugs (eg, penicillin) and decreases bioavailability of weakly acidic drugs (eg, phenobarbital). Reduced bile salt formation decreases bioavailability of lipophilic drugs (eg, diazepam). Reduced gastric emptying and intestinal motility increase the time it takes to reach therapeutic concentrations when enteral drugs are given to neonates. Drug-metabolizing enzymes present in the intestines of young infants are another cause of reduced drug absorption. Infants with congenital atretic bowel or surgically removed bowel or who have jejunal feeding tubes may have specific absorptive defects depending on the length of bowel lost or bypassed and the location of the lost segment.

Transdermal absorption may be enhanced in neonates and young infants because the stratum corneum is thin and because the ratio of surface area to weight is much greater than for older children and adults. Many drugs bind to proteins (primarily albumin, α_1-acid glycoprotein, and lipoproteins); protein binding limits distribution of free drug throughout the body. Albumin and total protein concentrations are lower in neonates but approach adult levels by 10 to 12 mo. The net result may be increased free drug concentrations, greater drug availability at receptor sites, and both pharmacologic effects and higher frequency of adverse effects at lower drug concentrations. Drug metabolism and elimination also vary with age. Phenytoin, barbiturates, analgesics, and cardiac glycosides have plasma half-lives 2 to 3 times longer in neonates than in adults. Moreover, elimination of drugs is also slower in children than adults.

Despite all these concerns, innumerous irrational FDCs are still marketed in India to continue sale of banned drugs as FDCs or to increase sale of drugs which are not prescribed as single compounds. These irrational FDCs reach the consumers either directly as over the counter medications from chemists or at times even prescribed by qualified health care professionals due to lack of basic pharmacological knowledge or as a result of inappropriate promotion of medicines.

List of certain irrational FDCs commonly prescribed to pediatric population:

(i) FDCs containing banned drugs: The ministry of health and family welfare on February 10, 2011 prohibited the manufacture, sale and distribution of the "cough and cold" drug phenylpropanalamine that causes stroke, the analgesic anti-inflammatory drug nimesulide for children below 12 years which damages the liver, cisaspride that gives rise to cardiac problems and other drug formulations, with immediate effect.[5] Despite this, many FDCs sold as cough and cold remedies contain phenylpropanolamine as an ingredient. Similarly FDCs containing nimesulide (in combination with paracetamol, serratiopeptidase or diclofenac sodium) are still freely available despite serious concerns regarding liver damage.

(ii) FDCs containing irrational drug combinations: A number of combinations of nitroimidazole (antiamoebic) with fluoroquinolone (antibacterial) are available in the Indian market (norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole). These are irrational because patient suffers only from one type of diarrhea and therefore use of such a combination adds to the cost, adverse effects, and may encourage resistance.[6]

(iii) Polypharmacy: Drug Controller General India has banned combinations containing vitamins B1 + B6 + B12, but these are almost universally present in all multivitamin preparations available for children. Similarly it is well known that iron absorption is altered by vitamins and other minerals; hence its combination with multivitamins is again irrational. Anemia in children is usually either caused by iron deficiency or vitamin B12 deficiency; rarely both. Hence, combinations of iron salts with vitamin B12 are again uncalled for.

(iv) FDCs with combination of allopathic and ayurvedic formulations: Any combination of allopathic drug with other forms of medications like ayurvedic, homeopathic, etc are banned by DCGI. Despite this, products containing iron salts with ayurvedic medications are freely advertised and sold.

(v) FDCs containing inappropriate drug component dosages: All FDCs containing paracetamol are irrational as they prohibit from prescribing proper dose of acetaminophen which is weight based in children.

(vi) FDCs containing inappropriate salts of compounds: It is well known that ferrous salts are better absorbed than ferric salts. Then why supplements containing ferric salts should be marketed & prescribed when better alternatives are available.

It is high time that comprehensive efforts are made to curb this increasing menace of irrational pediatric FDCs; which would help tackle issue of increasing drug resistance as well. Drug regulatory bodies (national as well as local), physicians and consumers all need to cooperate to achieve this target. Various steps suggested in this regard include setting up of a central body along with subcommittees in districts & hospitals to coordinate medicine use policies, framing clear-cut treatment guidelines, availability of essential medicines list in all hospitals/ clinics, sensitization of undergraduates & graduates to rational drug use in the primitive and formative years of making of a doctor, continuing in-service medical education as a licensure requirement, provision of independent drug related information to physicians, public education about medicines and awareness regarding banned drugs, curb on of perverse financial incentives and above all regular supervision and audit of drug prescriptions. Stringent drug prescription regulations with strict implementation and heavy penalty to offenders is the need of the hour.

References:

(1) Core components. Geneva: World Health Organization; 2002. WHO policy perspectives on medicines-promoting rational use of medicines.

(2) WHO model list of essential medicines 16th list. Available from: http://whqlibdoc.who.int/hq/2010/a95060_eng.pdf [last updated on Mar 2010]

(3) National list of essential medicines 2003. Available at: http://www.searo.who.int/LinkFiles/Essential_Drugs_and_Medicines_India.pdf [last accessed on 2012 Apr 6]

(4) Gulhati CM. Irrational fixed-dose drug combinations: a sordid story of profits before patients. Issues Med Ethics. 2003;11:5.

(5) Health ministry bans Nimesulide and 2 other drugs. Hindustan Times New Delhi, January 27, 2011. Available at: http://www.hindustantimes.com/News-Feed/Health/Health-ministry-bans-Nimesulide-and-2-other-drugs/Article1-655448.aspx

(6) Gautam, Saha L. Fixed dose drug combinations (FDCs): rational or irrational: a view point. Br J Clin Pharmacol 2007;65(5):795–796.