EDITORIAL

Irrational fixed-dose drug combinations: a sordid story of profits before patients

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Anyone with even an elementary knowledge of medicine knows that, ideally, drugs should be administered as single molecules based on the specific requirement of each patient. This enables the prescriber to select specific drugs in specific doses for specific durations. Only under exceptional circumstances are fixed dose combinations (FDCs) are allowed. These are when (a) two or more drugs have a synergistic action, i.e. the combination acts to achieve a better therapeutic response than the individual drugs alone; (b) there is corrective action, and one drug acts to reduce the incidence and/or severity of adverse effects caused by the other; (c) two or more molecules are normally needed and taken by the patient concurrently – provided the dosage of each drug does not need to be individualised, or (d) prescribing two or more drugs separately could result in one of them not being ingested, and this would adversely affect the patient's health.

Even under such situations care has to be taken to ensure that there are no adverse interactions between the combined drugs, that the pharmacological behaviour (absorption, duration of action, elimination) is not grossly different, that the withdrawal of one of the agents does not lead to withdrawal symptoms and in any event sub-therapeutic doses are never used. Conversely medicines cannot be mixed if side effects are additive or they belong to the same group with similar mode of action, such as two NSAIDs.

Are these precise and scientifically sound guidelines being followed in permitting the combination of drugs in our country? Certainly not. All sorts of bizarre combinations have flooded the market. Many of them not only harm the patients, they can also damage the health of entire communities in the future by promoting the emergence of drug-resistant strains of micro-organisms. Take the example of combining quinolones (e.g. ciprofloxacin) with imidazoles (e.g. tinidazole). This combination is widely used, overused and misused for diarrhoea. Since most cases of diarrhoea are due to viruses, suboptimal use is giving rise to quinolone-resistant strains of typhoid germs.

Manufacturers' main motive behind mixing drugs is, of course, to generate prescriptions and make profits. One can hardly expect anything else if there are over 17,000 pharmaceutical manufacturers, some 40,000 brands but only around 450 basic medicines. When atenolol does not generate enough sales, it is mixed with alprazolam to create an expensive 'novel' product. In the absence of research, the pharmaceutical industry in India has been reduced to a purely commercial activity in which marketing is the name of the game. It is no wonder that the basic principles of pharmacology get pushed to the background.

As a result we have combinations such as nimesulide with paracetamol (both with hepato-toxic additive adverse effects); diclofenac (taken three times daily) with famotidine (taken once daily); mebendazole (taken twice daily for three days) with pyrantel (taken as a single dose), atenolol (taken once daily) with plain nifedipine (taken two-three times daily), and so on.

Cisapride is combined with omeprazole so that a patient who requires just omeprazole, a relatively safe medicine, is also made to consume cisapride, a far more dangerous drug which is banned in western countries.

Some of the most absurd fixed drug combinations are available in India. A few examples: nimesulide, paracetamol and tizanidine; amoxycillin,probenecid and tinidazole; diazepam, antacids and oxyphenonium. Over 70 dangerous FDCs are being sold in India under more than 1,000 brand names.

Who is responsible for this mess of mixing incompatible medicines? We must blame the total lack of accountability of the drug regulatory apparatus, and the existence of parallel drug control centres in our country.

All new molecules have to be approved by the Drugs Controller General, India (DCGI). Once a new molecule is licensed, the state drug controllers take over and monitor pharmaceutical manufacturing facilities located in their own jurisdictions.

Legally, when two or more individually approved drugs are combined, the mixed medicine is deemed to be a 'new' product and hence requires DCGI approval. In practice, state drug controllers merrily go on licensing such combinations -- even though they do not have the legal powers to do so. Once one state drug controller approves a combination, it can be sold all over the country. The result: a patient in, say, Maharashtra consumes a drug that is neither approved by the DCGI nor by the Maharashtra drug controller but by a drug controller in, say, Assam! Unless state drug controllers are made to obey the law, no improvement can occur.

The DCGI is no less culpable. In a federal set-up he may hesitate to move against erring state controllers but he has the power to ban such illegal combinations. He has failed to do so. If the Central Government does not move quickly, the day is not far off when courts will be compelled to move in to protect the health of the people.