ADVERSE REACTIONS DUE TO DRUG INTERACTIONS

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The list of drug interactions is ever increasing and very soon, for intelligent bedside therapeutics, we may require computer technology providing adequate data storage and quick retrieval of relevant information (Hill, Spicer & Weatherall, 1968). A handbook of drug interactions catalogues, in an alphabetical index, a formidable list of interactions (Swidler, 1971)). For rational and safe therapy, the medical students, the residents and the practicing doctors must be aware of probable drug interactions. An active educational program, organized by clinical pharmacology divisions in medical colleges, would be of an immense help in cultivating rational therapeutic practice (Sjoqvist, 1968). It is essential that drug interactions must, as a subcategory, be separately considered for documentation, analysis and reporting by the agencies monitoring adverse drug reactions (Westerholm, 1972). Such a vigilant and discriminated monitoring can only help in the discovery of new adverse drug interactions and an evaluation of their incidence. During the administration of every new drug, a careful documentation of the concurrently given drugs can also assist in evaluation of adverse drug interactions (Hunter, Stem & Laurence, 1970). The classification of drug interactions is often based on the mechanisms involved either pharmacokinetic or pharmacodynamic factors (Karandikar, 1973). The clinician, though helped in his basic understanding by such a pharmacological classification of drug interactions, would be inclined to appreciate a more clinical approach to drug interactions. When two drugs A and B interact, the individual components of therapeutic response - A ane B may get enhanced (+) or may be diminished (-) (Figure 1).

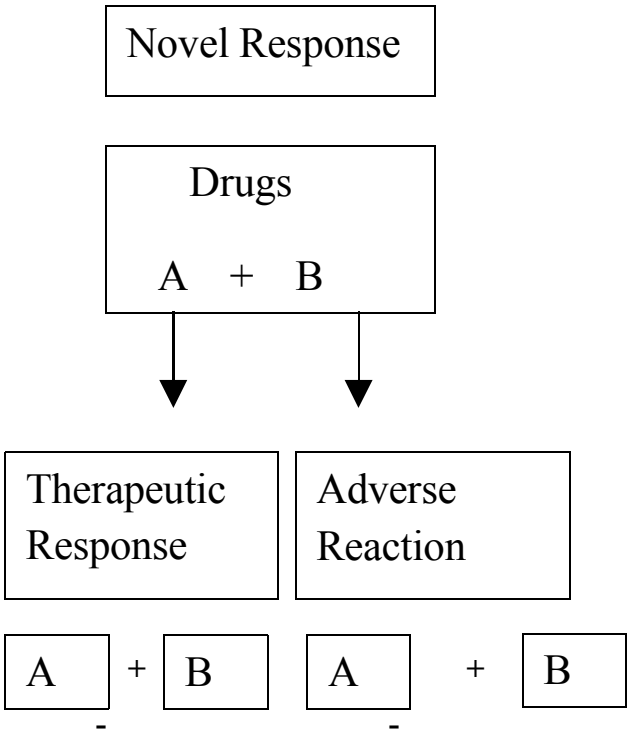

Figure-1 : DRUG INTERACTION

The profiles of adverse reaction of drug A and drug B may be altered by a drug interaction. The drugs may have an enhanced (+) or a diminished (-) adverse reaction. The drugs can also give rise to a novel response which may not have any adverse or therapeutic effect on the patient e.g. a modification of a laboratory value by interference in the analytical technique (Christian, 1970). For a clinical usage, the classification of the adverse drug interactions must be dynamic and in clinical terms. The clinician would also be interested in categorizing the severity, the predictability and the reversibility of the adverse drug interactions. A tentative classification of adverse drug interactions is as follows.

Classification of Adverse Drug Interactions

1. Diminished therapeutic response
2. Enhanced side effects
3. Relative over dosage toxicity
4. Intensified allergic reactions
5. Increased secondary effects
6. Severe idiosyncratic reactions
7. Greater teratogenicity
8. Additive addiction potential
9. Miscellaneous.

Diminished therapeutic response:

Diminished therapeutic response is likely to be more often detected if the clinician monitors the magnitude of therapeutic response according to preset quantitative criteria. A reduction in therapeutic response could be due to (1) a decreased plasma level of the drug, which in turn may be due to a diminished absorption, an increased protein-binding, an enhanced metabolism or a rapid excretion of the active drug. (2) a reduced response of the target tissue either due to a passive occupatio" of the receptors by the other drug or a" opposite pharmacodynamic effect of the other drug. There are many examples in literature of drug interaction causing diminished therapeutic response. The binding of terasyclines by antacids or calcium salts has been cited very often. However, in India, we must also consider the possibilities of decreased absorption of tetracyclines when a patient may be concurrently consuming a" Ayurvedic drug e.g. ***Kapardikn - Bhasma*** (Calcined seashells) containing calcium. Methyl-dopa and Levodopa may compete for the same enzyme and if given together may diminish their respective therapeutic response. Drugs stimulating the drug metabolism can decrease the plasma level of other drug and hence diminish therapeutic response. The clinical examples of such stimulations of drug metabolism have been reviewed by several authors (Mannering, 1969; Conney, 1971; Breckenridge & Orme, 1971).

Enhanced side effects :

As late Lord Rosenheim, (1958) pointed out, the term side effects should be reserved for therapeutically undesirable but unavoidable, effects of drugs. When the drugs have similar profiles for side effects, even when given in lesser doses, the additive effect may be clinically a" adverse one, e.g. the nephrotoxicity of streptomycin and kanamycin. A knowledge of the profiles of side effects of the concurrently administered drugs would alert a clinician to watch for adverse reactions. Sometimes it might be essential to employ sensitive laboratory tests to detect the side effect at a subclinical level e.g. basal and serial leucocyte counts would be mandatory when two drugs with potential bone marrow suppressant effects arc being administered concurrently.

Adverse Reactions due to Drug Interactions

Some Ayurvedic physicians prescribe certain parts of the castor plant ***Ricinus communis*** to patients with rheumatoid arthritis (Arya Vaidya, 1901). If the patient is also taking other antiarthritic drugs with known gastro-intestinal side effects, the enhanced side effect due to castor plant can be severe. The possibility of enhanced side effects due to concomitant administration of Ayurvedic and modern drugs must be borne in mind.

Relative overdosage toxicity :

Drug interaction could lead to a relative overdosage toxicity when one drug converts a safe dose of another drug into a toxic dose by pharmacokinetic or pharmacodynamic mechanisms. Antacids increase the absorption of chloroquine and can be responsible for greater chloroquine toxicity. Hypoglycemia due to a sulphonylurea can be severe when the drug is displaced from the protein bound state by a sulphonamide. Allopurinol, by blocking the metabolism of mercaptopurine, can markedly enhance the toxicity of the latter drug. The example of toxicity of monoamine oxidase inhibitors & pressor amines has been notorious. However, theoretically an Ayurvedic drug can interact with M.A.O. inhibitor. A patient of depression may be receiving a M.A.O. inhibitor. The patient may also be consuming ***'Kaunch-pak',*** an Ayurvedic tonic to improve his libido. ***'Kaunch' -Mucuna pruriens*** is rich in catecholamine precursors and a severe hypertensive crisis could occur. In India a ***'Kounch'*** reaction may occur instead of a 'cheese reaction'. Though an allergic reaction is a very complex phenomenon, histamine release does play a significant role in the clinical manifestations of allergy. Drugs known to release histamine e.g. polymyxin, tubo-curarine, etc. (Lecomte, 1958) can markedly enhance a drug allergic reaction. The drugs inhibiting the biodegradation of histamine can also enhance the histaminemediated effects of drug allergy. Hydralazine inhibits diamine oxidase, the enzyme responsible for oxidative deamination of histamine (Vaidya & Levine, 1969). Chloroquine and a number of other antimalarial drugs inhibit the enzyme imidazole-N-methyl transferase, the other biodegradative enzyme for histamine (Cohn, 1965). Chloroquine and hydralazine can significantly enhance the histamine effects of an allergic drug reaction. More research in this area is called for.

Increased secondary effects :

Secondary effects have been defined as the indirect consequence of a primary drug action. (Rosenheim. 1958). Moniliasis or vitamin deficiency following the use of the broad spectrum antibiotics would be such secondary effects. An example of increased secondary effect is exacerbated moniliasis when a woman on the oral contraceptive pill also receives tetracyclines. Oral contraceptives, somehow, predispose a patient to monilial infection.

Severe idiosyncratic reactions :

True idiosyncrasy implies an inherent qualitatively abnormal reaction to a drug. Any sulphonamide and a nitrofuran, if given together, may precipitate a severe hemolysis in a patient with Glucose-b

phosphate dehydrogenase deficiency. This class of drug interactions can also occur in patients with other genetic & enzymic defects. Greater teratogenic effects or additive
addiction hazard can occur with drugs having potentially similar hazards or by the effect of one drug on the kinetics of the other drug. Lasty, miscellaneous drug interactions would include those phenomena which cannot be classified in any of the aforesaid categories. There have been several interesting reviews on drug interactions (Morrelli & Melmon, 1968; Hartshorn, 1971; Barranco, 1971). And it may not be long before we may also have a Journal of Drug Interactions

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