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DRUG-DRUG INTERACTIONS: NEW TRENDS

Review

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ABSTRACT

The modification of the action of one drug by the other had been noticed for a long time. For example, in 19995, Williams (1) discovered that there was an enhanced metabolism of oestrogens caused by phenabarbital and rifampicin (all of which are now known to be inducers of drug metabolism). Chloroquine was found to interact with Ampicillin and decreased peak plasma concentration of the former from 29 to 19 %. This effect was considered significant in reducing the bioavailability of Ampicillin (2).

Such interactions were discovered coincidentally and the most important drug-drug interactions are those reported from cimeditine (Tagamet). Cimetidine is a h1 receptor antagonist widely used in peptic ulcer disease. Other mwmbers of cimetidine family especially ranitidine, also cause some significant drug inmteractions.

Recent findings (3) have shown that the mechanism by which cimetidine caused drug interactions might not be the well- known inhibition of the microenzymes P450 complex, rather through a direct action on the gut muscle which directly slow down its movement and decreased gastric emptying process (4).

Other findings were also considered especially the ones produced by anticholigergics like propentheline. These have involved many compounds and in clinical practice have greater implications of drug-drug interactions.

A survey was carried out of the contribution of cimetidine in clinically relevent interactions and also the interactions by other mechanism of cimetidine and all the relevant clinical cases are reported in this literature review.

Cimetidine, a histamine-receptor antogonist, was found to be a powerful inhibitor of microsomal enzyme (P450 isoenzyme fraction) and was found to produce 20- 60% decrease in the clearance of about 25 drugs such as warfarin, theophylline etc (Table 1). This has been found to be very significant in clinical practice. Co-admistration of cimetidine with suspected drugs therefore has to be done with caution and strict monitoring of plasma concentration of the affected drugs. The literature survey of cimetidine-drug interactions which were found to be significant are summarized in Tables 1-4. Pharmacokinetic interactions which are significant and detectable require the affected drugs to have a narrow therapeutic margins and produce more than 20-25% change in drug absorption, distribution or elimination. This degree of change is necessary to overcome the normal intrapatient variation in drug disposition. Also it should be noted that drug interactions are generally important only in transient times when the interacting drug (such as cimetidine) is started, stopped or the dosage is changed. By anticipating these occassions, the clinician can evaluate the patient to prevent therapeutic failure.

Table 1: Influence of cemetidine on the metabolism of drugs

Drug	**Remarks**
Acetaminophen	S
Antipyrine	S
Aminopyrine	S
Carbamezepine	S
Chlordiazepoxide	S
Clobazame	S
Clonidine	S
Coumarine	S
Diazepam	S
Desmethydiazepam	S
Flecainidine	S
Imipramine	S
Meparidine	S
Metronidazole	S
Morphine	S
Phenytoin	S
Amantadine	S
Triazolam	S
Theophylline	S
Propanolol	S

S= Significant pharmacokinetic interaction.

Table 2: Influence of cimetidine on clearance of drug

Drug	Type of Influence	Remarks
Creatinine	Renal inhibition	S
Procainamide	Renal inhibition	S
Triamtrene	Renal inhibition	S
Diazepam	Altered elimination	S
Labetolol	Decrease in oral clearance	S
Pethidine	Decrease in total body clearance	S
Carbamazepine	Decrease in clearance	S
Imipramine	Decrease in clearance	S
Aspirin	Increase in rate of elimination	S
Nifedipine	Decrease in systemic clearance	S

S= Significant pharmacokinetic interaction.

Table 3: Influence of cimetidine on the absorption of drugs

Drug	Influence	Remarks
Aspirin	Altered absorption	S
Benzyl penicillin	Altered absorption	S
Ketoconazole	Increased absorption	S
Prednisolone	Altered absorption	S
Tetracycline	Altered absorption	S
Digoxin	Decreased absorption	S

S= Significant pharmacokinetic interaction.

Table 4: Influence of cimetidine on duration of action of drugs

Drug	Influence	Remarks
Warfarin	Prolongation of t1/2	S
Flecainide	Increased Tmax	S
Carbamezapine	Increased t1/2	S
Caffeine	Increased t1/2	S
Theophylline	Increased t1/2	S
Misonidazole	Increased t1/2	S
Succinyl choline	Increased t1/2	S
Cifenline	Prolongation of t1/2	S

S= Significant pharmacokinetic interaction

Cimetidine-drug interactions have been attributed to the high potential of cimetidine to bind to the P450 isoenzymes (which are actively involved in the metabolism of drugs and other foreign compounds). Ranitidine (Zante) which is also used in treating peptic ulcer and is reckoned to be more effective than cimetidine (imidazole derivatibe) is a furanoid derivative (5). In clinicl practice ranitidine has fewer significant effects on the metabolism of other concommittantly administered drugs. Several drugs which are known to interact with cimetidine have been found not to interact with ranitidine (6). However, a few significant pharmacokinetic interactions have been reported and the possibility that these might be clinically relevant should be borne in mind. Example is the fatal interaction of ranitidine with theophylline. Ranitidine impaired the metabloism of theophylline and the resultant higher plasma concentration of theophylline caused the death of 2 patients. In all the tables above, the effects of cimetidine has been on various drugs and the implications might be serious and affect drug therapy. In all cases adjustments of the doses must be done in order to be out of danger of thereprutic failure and also a strict monitoring procedure has to be established in order to follow the hardazous effects.

NEW TRENDS

It was established that Gut movement directly affects peristalsis and gastric emptying time. This, in turn, directly affects the absorption of drugs. Nimmo and co-workers (7) have found out that anticholinergics directly affected the movement of gut smooth muscles and this caused delayed gastric emptying with the resultant decrease in the absorption of paracetamol. In a recent study, Kwanashie et al (8) showed that cimetidine, in a concentration range of 500-1000 µg/ml, caused relaxation of gut smooth muscles of guinea pig ileum. Finding out that this concentration resembles that of pharmacokinetic plasma level of cimetidine in Humans, I decided to look into this phenomenon quite closely. I theorized that if cimetidine at that concentration could be proved to cause relaxation of gut smooth muscles in humans as it did in guinea pig ileum, then certainly it will be able to cause relaxation in gut smooth muscles with resultant decrease in absorption of drugs (9). I tested this with chloroquine, metronidazole and paracetamol. In all these cases, I adminitered the test drugs an hour after the administration of cimetidine. This is because of the need to have cimetidine concentration enough atb the time of interaction with other drugs so that interactions at full concentrations (maximum interaction) can be observed (10). Table 5 gives a summarized account of the effects of cimetidine on absorption constatnts, lag times and maximumconcentrations of the test drugs.

Table 5: Effects of cimetidine on the absorption of paracetamol, metronidazole and chloroquine in Humans

Drugs	Drug alone			Drug + Cimetidine			Remarks
	Lag time (hr)	C_{max}	$K_{(ab)}$	Lag time (hr)	C_{max}	$K_{(ab)}$	
1. Metronidazole	0.45 ± 0.13	15.9 ± 0.9 ug.ml	1.7 ± 0.31 ug.ml	0.98 ± 0.06	3.14 ± 0.45	1.00 ± 0.07	P < 0.05
2. Chloroquine	0.36 ± 0.06	358.8 ± 9 ng.ml	1.647 ± 0.01 ug.ml	0.50 ± 0.001	264 ± 7	0.391 ± 0.005	P < 0.05
3. Paracetamol	0.15 ± 0.001	30.8 ± 1.4 ng.ml	0.89 ± 0.01 ug.ml	0.89 ± 0.70	16.02 ± 0.7	0.021 ± 0.001	P < 0.001

P< 0.05 significant

It can be seen that the lag time and concentrations of the affected drugs have a common relationship which is inversely proportional. If lag time increases, concentration is decreased. This means that if lag time increases then concentration decreases because the gut muscle is relaxed more and emptying time has also decreased with consequent decrease in drug absorbed (plasma concentration).

The new trend therefore pays attention not to only cimetidine's capacicity to impair metabolism of drugs but to actions of drugs and chemical substances directly on gut smooth muscles. There are quite many compounds which exhibit this action like anticholinergics, central narcotic agents, phenothiazines etc (11).

Recently (12,13), in a study Ukpe Ajima compared the effects of cimetidine and hyoscine-n-butyl bromide on paracetamol pharmacokinetics in Human volunteers and found out that cimetidine simulated the anticholinergic in reducing the concentration of paracetamol in the volunteers through prolomged lag time.

In conclusion, it was proved beyond doubt that any chemical or biological process that affects the gut smooth muscles would have high tendency to effect gastric emptying. If the rate of contraction of the gut is increasesd then emptying rate would be faster and more absortion of the orally administered drugs would take place leading to higher concentration of same in the plasma as typipied by penitoin while if the rate of contraction of the gut smooth muscles is delayed then the rate of emptying is reduced and less absorption would take place and less of the drugs would be available in the plasma as seen by many examples given.

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