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A STUDY ON SEVERITY OF DRUG INTERACTIONS AND THEIR INCLUSION IN VARIOUS DRUG INFORMATION COMPENDIA

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ABSTRACT

Medication incidents are a significant problem for all health systems in the world. Drug interactions are one cause of medication incidents. Drug interaction compendia can be used to populate clinical decision support systems. There has not been any comprehensive assessment of the validity of the severity classification used in the international drug interaction compendia. The current prospective observational study of six months duration was designed to assess the severity of drug interactions between various drug information compendia screened from prescriptions of general medicine department. The current study involved screening of 100 prescriptions, which belongs to 65 male and 35 female, out of which 27 prescriptions belongs to the age group of 41 - 50 years of age. Total numbers of drugs screened were 410 out of 100 prescriptions. The DDI's was assessed eventually in comparison with Stockley's, Medscape and BNF respectively based on the rating, severity and significance, and inferences. The main drug classes of DDI's were aminoglycoside gentamicin, ARB's, antacids, aspirin as analgesics, calcium channel blockers, beta blockers and NSAID's. In conclusion, In conclusion, the drug-drug interactions assessed in our study was majorly on 07 category of medications resembling in comparison to three standard international medications compendia but with certain considerable lack in ratings and severity of DDI's of other include drugs, which be rectified by continuous Continuing Medical Education (CME's) and series of advance learning with expertise on drug and its uses, preparing Hospital Formulary with extensive literature survey.

KEYWORDS: Clinical decisions, drug information compendia, drug interactions, severity.

INTRODUCTION

Adverse drug events (ADEs) may occur due to medication errors (MEs), pharmacokinetic alterations, drug-drug interactions (DDIs) and drug-disease interactions, with research revealing that both the incidence and severity of ADEs are heightened in intensive care unit (ICU) patients.[1], [2] Medication incidents are a significant problem for all health systems in the world. [3], [4], [5] Drug interactions are one cause of medication incidents. In a Danish study of 26,337 elderly patients, 4.4% received drug combinations carrying a risk of severe interactions. [6] In a recent prospective study in the United Kingdom, drug interactions accounted for 16.6% of adverse drug reactions causing hospitalization. [7] Wide implementation of computerized prescribing and dispensing with clinical decision support systems is recognized as a priority to reduce medication incidents.[5], [8]

However, several studies have shown that there is a considerable and potentially clinically important variability in the performance of dispensing and prescribing computer programs in detecting drug interactions.[9], [10], [11] Drug interaction compendia can be used to populate clinical decision support systems. There has not been any comprehensive assessment of the validity of the severity classification used in the international drug interaction compendia.[12]

Critically ill patients are at an increased risk for errors, such as drug-drug interactions (DDIs), due to an increased number of concomitant drugs, fluctuating organ function, altered drug disposition, and irregular protein binding.[13], [14],[15] An opportunity to identify and prevent medication-related errors such as DDIs and improve patient safety, especially in the critically ill,

occurred with the introduction of computerized provider order entry.[16]

MATERIALS AND METHODS

Study design: Prospective observational study.
Study duration: Six months.
Study site: General medicine department of a secondary care referral hospital in Andhra Pradesh, India.
Study sample: 100 Prescriptions.

Study criteria

Inclusion criteria

- Patients visiting to general medicine department for outpatient consultation
- Patient's medication profile of more than 3 - 5 drugs
- Medication profile of elderly patient.

Exclusion criteria: Patient's medication profile of less than 3 drugs.

Consent from hospital authority

A profoma of the study which included the objectives, methodology was submitted to the hospital authority for approval. The approval from the hospital was procured through the letter. The author was permitted to utilize hospital facilities for conducting the study.

RESULTS

In our study, which aimed at assessing the severity of drug interactions in prescriptions of a secondary care referral hospital, 100 prescriptions were screened within a study period of 06 months. Based on gender distribution there were 65 prescriptions of male and 35 of female and the prescriptions were also classified on the criteria of age groups, the results of which are reported in Table 1 (Demographic details of the prescriptions screened).

Table 1 Demographic details of the prescriptions screened.

S. no	Demographic Particulars	N = 100
Gender Distribution		
01	Male	65
02	Female	35
Age Distribution (in years)		
03	10 – 20	09
04	21 – 30	16
05	31 – 40	18
06	41 – 50	27
07	51 – 60	20
08	> 61	10

In our study, we compared three international drug interactions compendia to assess the severity of drug - drug interactions.

1. The drug interactions appendix of British National Formulary (BNF)
   - BNF uses a bullet to mark interactions that are potentially hazardous and where combined administration of the drugs involved should be avoided.
   - BNF may also state specifically whether a drug combination may be avoided or whether may be contraindicated by the manufacturer.
2. The Stockley's Drug Interactions is used to précis the mass of literature into a concise and easy-to-read form, the text has been organized into a series of individual monographs, all with a common format.
   - To inform busy healthcare professionals, of the facts about drug interactions, without their having to do the time-consuming literature searches and full assessment of the papers for themselves.

These therefore are the practical questions which this book attempts to answer:

- Are the drugs and substances in question known to interact or is the interaction only theoretical and speculative?
- If they do interact, how serious is it?
- Has it been described many times or only once?
- Are all patients affected or only a few?
- Is it best to avoid these two substances altogether or can the interaction be accommodated in some way?
- And what alternative and safer drugs can be used instead?

3. Clinical Pharmacology Database
4. Medscape Database.

The drugs and its classes selected for the assessment were reported in Table. 2 (Medications and its classes selected for the assessment)

Table 2 Medications and its classes selected for the assessment.

S. no	Class of drugs	Drugs
01	Calcium Channel Blockers	Amlodipine Diltiazem
02	Anticoagulant	Aspirin Clopidogrel
03	Antacids	Aluminium hydroxide Magnesium trisilicate
04	Antibiotics	Amikacin Gentamicin Ciprofloxacin Cefixime Ampicillin
05	Angiotensin Receptor Blockers (ARB's)	Losartan Telmisartan
06	Beta blockers	Atenolol Propranolol
07	Cardiac glycosides	Digoxin
08	Diuretics	Furosemide Spiranolactone Hydrochlorothiazide
09	H2 receptor blockers	Ranitidine Famotidine
10	NSAID's	Paracetamol Diclofenac Aceclofenac Ibuprofen

In our study, categories of medications mentioned above were classified based on its clinical significance by comparative study with the four international compendia BNF, Stockley's drug interaction tertiary source and Medscape databases.

According to Stockley's drug interactions: Each monograph has been assigned a rating symbol to offer guidance to the user on the clinical significance of the interaction. These ratings are the same as those used in Stockley's Interaction Alerts. The Alerts are rated using three separate categories: *action, severity and evidence.* These ratings are combined to produce one of four symbols.

- For interactions that have a life-threatening outcome, or where concurrent use is contraindicated by the manufacturers. (X)
- For interactions where concurrent use may result in a significant hazard to the patient and so dosage adjustment or close monitoring is needed. **!**
- For interactions where there is some doubt about the outcome of concurrent use, and therefore it may be necessary to give patients some guidance about possible adverse effects, and/or consider some monitoring. **?**
- For interactions that are not considered to be of clinical significance, or where no interaction occurs. √

The drug - drug interactions in our study was compared to Stockley's, and the following results were reported in Table 3 (Comparison and rating of Drug - drug interactions with Stockley's)

Table 3 Comparison and rating of Drug - drug interactions with Stockley's

S. no	Drugs	Drugs	Rating scale
01	Gentamicin	Digoxin	**!**
		Diuretics	√
		NSAID's	**!**
		Penicillin's	**!**
02	Angiotensin Receptor Blockers (ARB's)	Aspirin	**?**
		Digoxin	**?**
		Diuretics	**!**
		NSAID's	**?**
03	Antacids	Aspirin	**!**
		Cephalosporin's	**!**
		Corticosteroids	**!**
		Diuretics	**!**
		Azithromycin	**!**
		NSAID's	√
04	Aspirin	Furosemide	√
		Spiranolactone	**?**
		NSAID's	**?**
05	Calcium Channel Blockers	Corticosteroids	**!**
		Digoxin	**!**
		Diuretics	**!**
		NSAID's	**?**
		Theophylline	**!**
06	Beta Blockers	Diltiazem	**!**
		Digoxin	**?**
		H 2 receptor blockers	**?**
		NSAID's	**?**

Comparison of Drug - drug interactions severity with BNF was reported in Table 4 (Comparison and rating of Drug - drug interactions severity with B N F)

Table 4: Comparison and rating of Drug - drug interactions severity with B N F.

S. no	Drugs	Drugs	Inference
01	Amino glycosides	Digoxin	Gentamicin increases the plasma concentration of digoxin
		Loop diuretics	Increased risk of ototoxicity
02	Antacids	Aspirin	Increased excretion of aspirin
		Digoxin	Decreased absorption of digoxin
03	Beta blockers	ARB's	Hypotensive effect
		CCB's	Increased hypotensive effect
		Digoxin	Bradycardia
		Diuretics	Increased hypotensive effect
04	CCB's	ARB's	Increased hypotensive effect
		Digoxin	Increased plasma concentration of digoxin
		Diuretics	Increased hypotensive effect
05	NSAID's	Beta blockers	Antagonise hypotensive effect of beta blockers
		CCB's	Antagonise hypotensive effect of CCB's
		Digoxin	Increased plasma concentration of digoxin
		Diuretics	Increased risk of nephrotoxicity

Comparison of Drug - drug interactions severity with Medscape Table 5 (Comparison of Drug - drug interactions severity with Medscape).

Table 5: Comparison of Drug - drug interactions severity with Medscape.

S. no	Drugs	Drugs	Inference
01	Gentamicin	Furosemide	Serious
02	Amikacin	Furosemide	Serious
03	Ciprofloxacin	Aluminium hydroxide	Serious
04	Famotidine	Digoxin	Serious
05	Diltiazem	Atenolol	Serious
06	Aluminium Hydroxide	Digoxin	Serious
07	Atenolol	Digoxin	Serious
08	Propranolol	Digoxin	Serious

DISCUSSION

The report of drug - drug interactions in the department of General medicine of secondary care referral hospital, was documented and compared with three standard international medications compendia, where:

- Gentamicin - Amino glycoside antibiotics was comparatively presenting similar results as of severity in Stockley's, severity of Medscape and inferences of B N F towards cardio glycoside - Digoxin specifically.
- Angiotensin Receptor Blocker (ARB's) drug - drug interaction with diuretics was significantly marked both in Stockley's and Medscape, but only with ethacrynic acid in Stockley's as very lethal not for furosemide and spiranolactone and severity as per Medscape was significant.
- Antacids drug - drug interactions with aspirin and digoxin was well marked as serious DDI's in both Medscape and B N F were it lowers the absorption of digoxin and increases the excretion of aspirin resulting reduced health outcome of patient, close monitoring is advisable.
- Aspirin was having significant severity of drug interaction with spiranolactone and gentamicin and other antibiotics as of Medscape and Stockley's with more literatures.
- In our study Calcium Channel Blockers showed drug interactions with B-blockers in major population proved more serious and significant with atenolol and propranolol (significant).
- The very frequent drug-drug interaction found in B-blockers was with cardiac glycosides (digoxin) resulting in hypotensive effects characterized by bradycardia in our study, which was the same found in all three standard international medications compendia resulting in more serious significant rating of ACC (associated cardiac complications).
- The Non Steroidal Anti Inflammatory Drugs (NSAID's) interaction with diuretic and cardiac glycoside was well pronounced in our study showing nephrotoxicity in some cases used along with diuretics and increased plasma concentration of digoxin as such in BNF and Stockley's.

CONCLUSION

In conclusion, the drug-drug interactions assessed in our study was majorly on 07 category of medications resembling in comparison to three standard international medications compendia but with certain considerable lack in ratings and severity of DDI's of other include drugs, which be rectified by continuous Continuing Medical Education (CME's) and series of advance learning with expertise on drug and its uses, preparing Hospital Formulary with extensive literature survey.

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Conflict of Interest: The author declares no conflict of interest.

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