DRUG-DRUG INTERACTIONS IN MEDICAL ICU

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INTRODUCTION

Drug –drug interaction is a specific term for adverse effect which is used when efficacy or toxicity of one drug is modified by another drug.[1]Potential drug interactions can be predicted based on various properties of interacting drugs like bioavailability, mechanism of action, route of elimination etc. Thus, it is very important to prevent drug interactions which can affect patient management and should be recognized early and managed appropriately by selecting alternative therapeutic strategies. It is very common when multiple drugs are used especially in intensive care unit(ICU). The complex regimen of drugs in the ICU predisposes the critically ill patients to serious drug interactions. Drugs may affect the absorption, distribution, metabolism and elimination of interacting drug with suspected drug. Critically-ill patients are at an increased risk of adverse events from drug-drug interactions due to the large number of medications being taken and their effects on organ function.[1]

EPIDEMIOLOGY

The incidence and prevalence of drug-drug interactions in ICUs are variable which depends upon the methodology of data collection (Prospective cohort or retrospective chart review) by auditing medication chart and presence of surveillance system in ICU.[1] Polypharmacy is one of the most important cause of drug-drug interactions in ICUs, while daily scrutiny of drugs prescribed and keeping it to minimum is essential step to prevent potential drug interactions in ICUs.[1] In another retrospective study, it was reported that medication errors were significantly more in ICUs than in general medical unit, thereby emphasizing the need for a surveillance system for detecting clinically significant drug interactions in order to pre-empt these adverse effects and take corrective measures to change route, time and dose of interacting drug.[2]

Severity of Drug-Drug interactions[2]

Type I: Unknown: No known interaction
Type II: Minor: No action needed: It would have limited clinical effects.
Type III: Moderate: Monitor Therapy: The interaction may result in exacerbation of the patients' condition and require an alteration in therapy.
Type IV: Major: Consider therapy modification: It may be life-threatening and require medical intervention to minimize or prevent serious adverse events.
Type V: Contraindicated: Avoid combination: The drugs are contraindicated for concurrent use2.

Risk factors of drug-Drug interactions[2]:

1. Number of Medications received
2. Duration of treatment
3. Age (Very young or very old)
4. Number of Prescribing Physicians
5. Stage of Disorder
6. Multiple Diseases
7. Previous drug interactions
8. Overweight
9. Dehydration
10. Poor Nutrition
11. Hypotension
12. Congestive Heart Failure
13. Liver and Kidney Damage
14. Genetic Make-up
15. High Alert Medication

Mechanism of Drug-Drug Interactions:[3]

Drug interactions may be either Pharmacokinetic or Pharmacodynamics. A Pharmacokinetic
Interaction occurs when one drug alters the

absorption, distribution, metabolism or elimination of another drug.

A Pharmacodynamics interaction arises when one drug changes the pharmacologic response of another drug in an Additive, Synergistic or antagonistic way. Potential drug interaction is a situation in which a drug action is likely to be altered by the concurrent administration of another drug. Clinically relevant Drug interaction means where unwanted drug reaction alters the course of treatment and intervention of any form is required.

Effects- Hospital Stay and Cost:

In a study of hospitalized cancer patients, there was a strong positive association between length of stay and potential drug-drug interactions.[2] Interactions between drugs and subsequent laboratory tests also led to an increase in the duration of hospital stay.[3] Longer ICU stay may require extra laboratory tests, medications and utilisation of healthcare resources, all leading to added cost to the patient.[3] According to studies, potential Drug-Drug interactions are very frequent among hospitalized patients. The rate of Drug-Drug interactions are directly related to number of prescribed drugs and length of hospital stay and cost among other factors.[3] The Development and implementation of Guidelines/Protocols and computer based screening could help Physicians and Pharmacists to prevent potentially dangerous drug interactions and help patients. Many Drug-Drug interactions have adverse drug consequences which results in prolonged hospital stay and healthcare burden on society. Many studies shows that hospital admissions of Elderly population for drug toxicity usually occurs due to drug-drug interactions. The healthcare professional must develop their own system of approach to prevent undesirable drug-drug interactions to reduce healthcare burden[3].

Class of drugs having drug interactions is as under:

A. Antimicrobials
B. Anticoagulants
C. Autocoids and related drugs
D. Antidiabetics
E. Cardiovascular drugs
F. Cytotoxic drugs
G. Gastrointestinal drugs
H. Drugs acting on nervous system
I. Respiratory drugs
J. Miscellaneous drugs

S.No.	Drugs	Interacting drugs	Clinical effect	Precautions
(I) Antimicrobials				
1	Ampicillin	Allopurinol	Increases incidence of skin rashes	Monitor the patient for symptoms if symptoms appears use alternate antibiotics.
		Probenecid	Retards renal excretion of ampicillin	**Avoid** concurrent use and monitor the patient and reduce ampicillin dose if required
		Hydrocortisone	Inactivates ampicillin in IV solution	**Don't** use in same IV solution
2	Aminoglycosides: Eg- Gentamycin, Tobramycin	Loop diuretics: Furosemide	Produces additive toxicity (ototoxic, nephrotoxic)	Reduce the dose and **Avoid** concurrent use

3	Bacteriostatics: Tetracycline, Erythromycin, Clindamycin	Bactericidal: Beta lactum antibiotics (eg-Penicillin G)	Decrease in bactericidal action	Don't use concurrently
4	Cefoperazone, ceftriaxone	Oral anticoagulants: Warfarin	Additive hypoprothrombinaemia that leads to bleeding	Monitor **INR** and reduce dose of anticoagulant
5	Ciprofloxacin Norfloxacin Perfloxacin	Theophylline, Warfarin	Toxicity of theophylline and warfarin	Reduce the dose of theophylline and warfarin
6	Chloramphenicol	Warfarin, phenytoin, Sulfonylurea	Concentration of warfarin, phenytoin and sulfonylurea increases that leads to toxicity.	**Avoid** concurrent use or monitor and reduce dose of object drugs
7	Clarithromycin, Ciprofloxacin, Erythromycin, Metronidazole, Cotrimoxazole	Warfarin	Increased effect of warfarin.	Select alternative antibiotics
8	Clindamycin	Erythromycin, Clarithromycin, Chloramphenicol	Mutual antagonism of antibacterial action	**Avoid** concurrent use
		Pancuronium	Exaggregated neuromuscular blockade	**Avoid** concurrent use
9	Metronidazole, Tinidazole, cefoperazone	Alcohol	Bizarre or disulfiram like reactions	**Avoid** Alcohol by patient
10	Sulphonamide, Cotrimoxazole	Phenytoin	Phenytoin toxicity due to metabolism inhibition	**Avoid** concurrent use
11	Fluoroquinolones, Tetracycline	Sucralfate, Divalent/ trivalent cations	Decreased absorption of fluoroquinolones	Space administration by 2-4 hours
		NSAID's	Increase CNS toxicity and seizures are reported	**Avoid** concurrent use
12	Tetracycline	Diuretics: Furosemide	Blood urea rises	Should be **Avoided or** don't use concurrently
13	Isoniazid	Aluminium hydroxide	Inhibit isoniazid absorption.	**Avoid** combination or space administration by 2-4 hours
		Isoflurane	Hepatotoxicity is potentiated by isoflurane	Must be **Avoided**
14	Rifampin	Anti-seizure drugs: phenytoin, Phenobarbital, Carbamazepine	Decrease in level of phenytoin, Phenobarbital, Carbamazepine	Monitor drug level regularly
		HIV protease inhibitors (efaviraenz)	Decreased activity of HIV protease	Can use other rifamycins eg-rifabutin
15	Amphotericin B	Rifabutin, Minocycline	Increase in renal impairment caused by amphotericin B	Use other antifungal agent or reduce the dose of amphotericin B
		Tacrolimus	Synergestic effect	Use with caution and adjust the dose as per requirement
16	Griesofulvin	Phenobarbitone	Phenobarbitone reduces oral absorption and induces metabolism of Griseofulvin.	**Avoided** as failure in griesofulvin therapy

17	Itraconazole, Fluconazole, Ketoconazole	Simvastatin, Lovastatin	Risk of myopathy and rhobdomyolysis	Monitor for myopathy and myoglobinuria(dark urine) if symptoms persists choose another antifungal like terbinafine
18	Chloroquine	Antiepileptics	Antagonism of antiepileptic effect	**Avoid** Combination
		Neostigmine, Pyridostigmine	Antagonism action	**Avoid** Combination
19	Mefloquine	Quinidine, Quinine,	Qtc lengthening that leads to cardiac arrest	Must be **Avoided**
(II) Anticoagulants				
1	Warfarin	Ciprofloxacin, Clarithromycin, Erythromycin, Metronidazole, Cotrimoxazole	Increased effect of warfarin	Select alternative antibiotics
		Amiodarone, Antifungal, Isoniazid, Omeprazole, Tramadol, Tamoxifen, Statins, Griesofulvin	May increase **INR** in plasma	Dose of warfarin should be **reduced**
		Aspirin	Increased INR and bleeding	**Reduce** dose of warfarin
		Ampicillin	Risk of bleeding due to decrease in vitamin k production in gut	Use with caution
2	Heparin	Vitamin k	Antagonism action with each other	Combination must be **Avoided**
(III)Autacoids and related drugs				
1	Aspirin	Probenecid	Uricosuric action of probenecid (inhibit tubular secretion of uric acid)	Use other NSAID's
		Spironolactone	Aspirin block spironolactone action	Use other NSAID's
2	Acetaminophen (Paracetamol)	Anti T.B drugs eg-Rifampicin, Isoniazid	Increase risk of liver disease	Use alternate NSAID's
		Zidovudine	Increased zidovudine levels	Use alternate NSAID's like aspirin
3	Azathioprine	Rifampicin	Organ Transplants rejections can happen.	**Avoid** Combination
4	Probenecid	Acyclovir	Probenecid may decrease renal clearance of acyclovir	Monitor Acyclovir if toxicity persists reduce the dose
5	Diclofenac sodium	Furosemide	Diclofenac counteract diuretic effect of furosemide	Better to replace diclofenac with other analgesic like paracetamol
6	NSAID's eg-Aspirin,Ibuprofen, ketoprofen,Naproxen	Methotrexate, Cyclosporine, Digoxin	Reduces kidney clearance of methotrexate, cyclosporine and digoxin	Monitor the patient for toxicity
(IV) Antidiabetic drugs				

1	Glibenclamide	Bosentas	Increase in hypoglycaemic effect	Use with caution
2	Insulin	Lithium	Increase in hypoglycaemia	Use with caution
(V) Cardiovascular drugs				
1	ACE inhibitors	K+(potassium) diuretics	Hyperkalemia	Monitor k+ level regularly
2	Amiodarone	Antimalarial drugs: Chloroquinine	Increase risk of ventricular arrythmia	**Avoided**
		Simvastatin	Increase in cocentration of simvastatin leads to myopathy and rhabdomyolysis	Use alternate statins like rosuvastatin
		Levofloxacin, Moxifloxacin, Ofloxacin	Increased risk of Qtc prolongation	Use alternative antibiotics like ciprofloxacin
3	Clonidine	Chlorpromazine Imipramine	Decrease in antihypertensive action of clonidine	Concurrent use **Avoided**
4	Cholestyramine	Coticosteroids like Methylprednisolone, Hydrocortisone	Raises blood sugar	Concurrent use **Avoided**
5	Digoxin	Calcium	Increased effect of digoxin	**Avoid concurrent use.**
		Quinidine	Plasma concentration of digoxin becomes double so toxicity can occur	Reduce the dose of Digoxin,can be reduced up to half
		Diuretics, Corticosteroids	Hypokalemia, digitalis arrythmia can be precipitated	Potassium may be given prophylactically
		Propanolol, Verapamil, Diltiazem, Disopyramide	May depress AV conduction and oppose positive Ionotropic action	**Avoid** the combination
6	Beta-blockers:Atenolol	Lidocaine	Bradycardia and Hypotension	**Avoid** concurrent use
7	Diuretics	Cotrimoxazole	Higher incidence of thrombocytopenia	Should be **Avoided**
8	Propranolol	Adrenaline with local anaesthetic	Rise in BP due to decrease in adrenaline vasodilation activity in systemic circulation.	**Avoid** adrenaline having local anaesthetics.
9	Nitrates: Glyceryl trinitrate, Isosorbide dinitrate, Isosorbide mononitrate	Sildenafil, Tadalafil	Dramatic hypotension	Must be **Avoided** onset of interaction effect soon after taking sildenafil
10	Thiazide diuretics: Hydrochlorothiazide, Indapamide, Chlorthalidone	Lithium	Increase in toxicity of lithium	Decrease lithium dose by 50% and monitor level of lithium
11	Verapamil,diltiazem	B-Blockers: Propanolol, Metoprolol, Atenolol	Additive sinus defects,marked bradycardia, AV-block	**Avoided**
S.No.	**Drugs**	**Interacting drugs**	**Clinical effect**	**Precautions**
(VI) Cytotoxic drugs				

1	Doxorubicin,daunorubicin, Epirubicin,idarubicin	Methadone	Acute cardiac toxicity,cumulative dose-dependent toxicity.	**Avoid** concurrent use
2	Daunorubicin Doxorubicin Epirubicin Sorafenib	Venlafaxine	Synergistic effect of QTc prolongation.	Increasing venlafaxine levels wil predispose patients to toxicity. Monitor for QTc prolongation
3	Cisplatin	Celecoxib, Amiloride, Vancomycin, Furosemide, Hydrochlorothiazide	Both potentiate nephrotoxicity and ototoxicity	If possible must be **Avoided** or use with caution
4	Cyclophosphamide	Chloramphenicol	Retard metabolism of cyclophosphamide	**Avoid** concurrent use
5	Geftinib,imatinib,desatinib	Tramadol	Increases tramadol concentration.	Monitor the patient for tramadol induced serotonin syndrome if symptoms persists use other alternatives of tramadol like NSAID's
S.No.	**Drugs**	**Interacting drugs**	**Clinical effect**	**Precautions**
6	Nilotinib	Morphine	Nilotinib may increase morphine concentration	Monitor closely morphine induced toxicity and reduce the dose if required
(VII) Gastrointestinal drugs				
1	Omeprazole	Phenytoin, Diazepam, Warfarin	Omeprazole increases the oxidation of Phenytoin, Diazepam, Warfarin	Monitor the patient
		Clarithromycin	Clarithromycin increases plasma concentration of omeprazole	Monitor the patient
2	Metoclopramide	Levodopa	Abolish therapeutic effect of levodopa	**Avoid** concurrent use
(VIII) Drug acting on Nervous System				
1	Amitryptiline	Phenytoin, Phenobarbital, Valproaic Acid, Carbamazepine	Antagonism of anticonvulsant effect	**Avoid** combination
		Haloperidol	Chances of ventricular arrythmia	**Avoid**
2	Baclofen	MAO inhibitors: Selegiline	Depression in brain function	Avoid combination
3	Antipsychotic(neuroleptics):eg-chlorpromazine, Haloperidol, Risperidone	Levodopa	Block action of levodopa	**Avoid** concurrent use
4	Benzodiazepine: Clonazepam	Sodium valproate	Provoked psychotic disorder	**Avoid** concurrent use
S.No.	**Drugs**	**Interacting drugs**	**Clinical effect**	**Precautions**
6	Clonazepam	Sodium valproate	Absence status may be precipitated	**Avoid** concurrent use
7	Duloxetine	Tamoxifen	Duloxetine inhibit conversion of tamoxifen to endoxifen that leads to toxicity	**Avoid** if possible. Venlafaxine can be used in place of duloxetine

8	Levodopa,Carbidopa	ACE inhibitors, Prazocin, Vasodilators	Excessive postural hypotension	Reduce dose of antihypertensive drugs
9	Lithium	Sulfonylurea, Insulin	Increased hypoglycaemia	**Avoid** concurrent use
		Succinylcholine, Pancuronium	Prolonged paralysis	Should be **Avoided**
10	MAO inhibitors:Selegiline	Selected Serotonin reuptake inhibitor(SSRI) :Fluoxetine, Escitalopam, Sertaline, Paroxetine, Luvoxamine	Hypertensive crisis (and cases of mania with fluoxetine)	**Avoid** as interaction effect occur soon after initiation
		Tricyclic Antidepressents: Imipramine Amitryptiline, Trimipramine, Doxepin, Clomipramine	Dangerous hypertensive crises with excitement and hallucinations	Must be **Avoided**
		Levodopa	Hypertensive crisis occurs	Use with caution or reduce the dose
S.No.	**Drugs**	**Interacting drugs**	**Clinical effect**	**Precautions**
(IX) Respiratory drugs				
1	Theophylline	Erythromycin, Ciprofloxacin	Tremors occurs	Reduce the dose of theophylline or choose alternate antibiotics
2	Aminophylline	Ascorbic acid, Chloropromazine Promethazine, Morphine, Penicillin G, Erythromycin, Tetracycline, Pethidine	Combination in same infusion is chemically unstable	**Avoid** using in same infusion
3	Salbutamol(albuterol)	Metoprolol	Antagonistic pharmacological action	**Avoid** combination if not possible must space the administration by 2-4 hours and monitor the patient
(X) Miscellaneous drugs				
1	Cyclosporine	Potassium Diuretics, ACE Inhibitors, Amiloride	Marked Hyperkalemia	Monitor the K+ level of patient if symptoms of hyperkalemia occurs reduce the dose
2	Pyridoxine(vitamin B6)	Levodopa	Reduce efficacy of levodopa	**Avoid** use of Vitamin B6 in patients on levodopa
3	Nicotinic acid Gemfibrozil	Statins: Simvastatin, Rosuvastatin, Fenofibrate, Clofibrate, Cholestyramine	Increase risk of Myopathy	Caution in concurrent use
4	Live Vaccines	Azathioprine, Bleomycin, Cyclophosphamide	Can leads to impairment in immune system	**Avoid** combination

5	Oral contaceptive pills	Rifampin, Antibiotics	Decreased oral contraceptive effectiveness	**Avoid** combination if possible.if necessary use high contraceptive dose(>35 mcg of ethinyl estradiol)or alternative method of contraception

PREVENTION:[4]

During multiple drug therapy some precautions must be considered:

(1)Concurrent administration of drug should be avoided, if not possible, care must be taken and therapeutic drug monitoring must be done to observe the patients for any interaction.

(2)Dose titration must be done in case of possibility of any drug interaction.

(3)Any suspicious new symptoms must be observed clinically and modification in therapy should be considered according to the situation.

(4)Do not ignore any symptoms if its due to interaction as they can lead to adverse outcomes.

CORRECTIVE MEASURES

Drug-Drug interaction knowledge base development should include patient specific information such as patient demographics, Risk factors, laboratory values, radiology reports, electrocardiogram information and Hemodynamic values. Physician and Pharmacist alerts may differ to find out the most clinically relevant information that would benefit patients.[4] additionally, in ICU set up the alert system should be more efficient. Importance of Pharmacokinetics in preventing Drug-drug interactions and the evaluation of Interactions with biological drugs should be considered in future direction to prevent drug interaction.

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