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Review Article

Drug Interaction Exposures in an Intensive Care Unit: Antihypertensive Population

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Introduction

Drug-drug interaction is an event that occurs when the effects of one drug modified by another drug or food when taken concurrently or concomitantly. This interaction either reduced the effect or no effect or increased drug effect [Hartshorn, 2006]. Patient in intensive care unit (ICU) are highly susceptible to drug interactions because of the complexity of the drugs regimens they receive. Drugs may affect the Pharmacokinetics of the critical ill patients and subsequently altered the pharmacological response, which potentially lead to serious adverse drug events. Drug-drug interaction (DDI) are considered predictable and thus avoidable and manageable [Cruciol-Souza et al., 2006].

Importance of DDI in ICU:

Risk factors for drug interactions can be related to patient, drug and medical prescription. Patient-related factors include people that are more vulnerable to drug interactions such as the elderly, patients undergoing surgical procedures, those receiving intensive care, and immunosuppressed patients. The drug interactions increasein proportionate as the number of drugs prescribed increases[Ceia, 2007]. It is assessed that drug interactions occur in 3% to 5% of patients receiving a 3-6 number of drugs, and increase to 10% to 20% in patients receiving 10 to 20 drugs [Bustamante et al, 2005]. It is estimated that potential DDI occurred in 11% of admissions to the general ICU, after limiting analysis to severe and relevant DDI types. The most frequently encountered drug classes were antithrombotic agents and antibacterial for systemic use. [Askari M et al, 2013]. In one of the studies, it has been identified that the average number of drugs used per patients was nine and potential DDIs found per patient were two [S Ray et al, 2009]

Classification of Drug Interaction:

There are different methods to classify the drug interactions.One of the data bank software DRUG-REAX (Klasco RK, 2008) identifies the interactions, provides information about the associated clinical consequences or adverse reactions to drugs and characterizes the interaction mechanism. Furthermore, this database provides information about clinical consequences or adverse drug reaction (ADR) that could result from a DDI, describe the interaction mechanism and classifies onset, severity and scientific knowledge of adverse reactions caused by the DDI.

I – Classification according to the time of onset

1. Rapid (effects expected within 24 hours of drug administration)
2. Delayed (effects not expected to appear within the first 24 hours following drug administration)
3. Unknown (effects expected to appear any time after drug administration).

II – Classification according to the severity

1. Contraindicated or ‘X’
2. Severe or ‘D’
3. Moderate or ‘C’
4. mild or ‘B’
5. unknown or ‘A’

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III - Classification based upon scientific documentation categories

1. Excellent
2. Good
3. Fair
4. Poor
5. unlikely and
6. unknown

IV – Classification according to the mechanism

1. Pharmacokinetic
2. Absorption
3. Distribution
4. metabolism or
5. excretion
6. Pharmacodynamic

Table – 1 Ten Most Potential DDI in ICU [Adriano Max et al, 2011]

Drug Interaction	First 24 Hours		50th length of stay of percentile		Discharge	
	n	%	n	%	n	%
Severe						
Fentanyl + Midazolam	103	36.1	62	19.1	36	15.6
Captopril + Potassium Chloride	24	8.4	67	20.6	71	30.7
Acetylsalicylic Acid + Heparin	16	5.6	26	8	25	10.8
Clonazepam + Morphine	14	4.9	16	4.9	6	2.6
Clopidogrel +Enoxaparin	10	3.5	-	-	5	2.2
Fentanyl + Morphine	10	3.5	-	-	-	-
Midazolam + Morphine	10	3.5	-	-	-	-
Fentanyl + Morphine	10	3.5	-	-	-	-
Fentanyl + Promethazine	10	3.5	14	4.3	-	-
Morphine + Promethazine	6	2.1	-	-	-	-

Commonly used drugs in ICU are vasoconstrictors and cardiotonic agents, antimicrobials, coronary vasodilators, direct vasodilators, anti-secretory drugs, anticoagulants, sedatives- hypnotics agents, anti-emetics, anti-diabetics agents, analgesics-antipyretics and anti-inflammatory drugs.Classification of DDI involving antihypertensive drugs in medical prescriptions of adult inpatients in ICU has been summarized in Table 2.

Table 2 Classification of DDI involving antihypertensive drugs in medical prescriptions of adult inpatients in ICU

Antihypertensives	Drug Classes	Severity	Onset	Scientific Knowledge	DDI Out come
Calcium Channel blockers	Histamine H2-antagonists (cimetidine)	Moderate	Rapid	Good	Increased concentration of calcium channel blockers and possible cardiovascular toxicity
	Benzodiazepines	Moderate	Rapid	Good	Increased / prolonged sedation
	Opioid analgesics	Major	Rapid	Good	Severe hypotension and an increased risk of respiratory depression
	Antifungals	Moderate	Delayed	Good	Increased calcium channel blockers concentrations and toxicity (dizziness, hypotension, flushing, headache, peripheral edema.)
	Glucocorticoids	Moderate	Rapid	Good	Increased glucocorticoids concentrations and enhanced adrenal- suppressant effects
	Calcium Channel blockers	Moderate	Rapid	Good	Toxicity (headache, peripheral edema, hypotension, tachycardia)
	Beta- blocker drugs	Major	Rapid	Good	Increased risk of hypotension, bradycardia, atrio-ventricular, conduction disturbances
	Alpha 1-adrenergic blockers	Moderate	Rapid	Fair	Hypotension
	Alpha 2-adrenergic agonistic drug	Major	Not Specified	Good	Increased incidence of sinus bradycardia requiring hospitalization and insertion of a pacemaker
Beta - blockers	Calcium Channel blockers	Moderate	Rapid	Good	Hypotension and /or bradycardia
	Sympathomimetic	Major	Rapid	Excellent	Hypertension, bradycardia and resistance to epinephrine in anaphylaxis
	Hypoglycemic	Moderate	Delayed	Good	Hypoglycemia, hyperglycemia or hypertension

Antihypertensives	Drug Classes	Severity	Onset	Scientific Knowledge	DDI Out come
Beta - blockers	Alpha 1- adrenergic blockers	Moderate	Rapid	Good	Exaggerated hypotensive response to the first dose of the alpha blocker
	Direct vasodilators	Moderate	Delayed	Fair	Increased risk of propranolol adverse effects (bradycardia, fatigue, bronchospasm)
	loop diuretics	Moderate	Delayed	Fair	Hypotension , bradycardia
	Thiazide diuretics	Moderate	Delayed	Fair	Hyperglycemia, hypertriglyceridemia
	Fluoroquinolone	Minor	Delayed	Fair	Bradycardia, hypotension
Loop diuretics	Non-steroidal anti-inflammatory agents	Moderate	Delayed	Good	Decreased diuretic and antihypertensive efficacy
	Beta- blocker drugs	Moderate	Rapid	Fair	Hypotension, bradycardia
	Glucocorticoids	Moderate	Delayed	Fair	Hypokalemia
	Direct vasodilators	Minor	Rapid	Good	Enhanced diuretic response to loop diuretic
Potassium - sparing diuretics	Non-steroidal anti-inflammatory agents	Moderate	Delayed	Good	Reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity
	Angiotensin converting enzyme inhibitors	Moderate	Delayed	Good	Hyperkalemia
	Angiotensin II Receptor Blockers	Moderate	Delayed	Fair	Hyperkalemia
Thiazide diuretics	Glucocorticoids	Moderate	Delayed	Fair	Hypokalemia and subsequent cardiac arrhythmias
	Non-steroidal anti-inflammatory agents	Moderate	Delayed	Good	Decreased diuretic and antihypertensive efficacy
	Beta- blocker	Moderate	Delayed	Fair	Hyperglycemia, hypertriglyceridemia

Antihypertensives	Drug Classes	Severity	Onset	Scientific Knowledge	DDI Out come
Angiotensin converting enzyme inhibitors	Non-steroidal anti-inflammatory agents	Moderate	Not Specified	Excellent	Decreased antihypertensive efficacy
	loop diuretics	Moderate	Rapid	Good	Postural Hypotension (first dose)
Catecholamine synthesis or release blockers	Beta - Blockers	Moderate	Rapid	Fair	Exaggerated hypertensive response,tachycardia, or arrhythmias during physiologic stress or exposure to exogenous catecholamine
	Oxazolidinone	Contraindicated	Rapid	Good	Hypertensive crisis (headache, palpitation neck stiffness)
Direct vasodilators	loop diuretics	Minor	Rapid	Good	Enhanced diuretic response to loop diuretic
Alpha 2-adrenergic blockers	Beta blockers	Major	Not Specified	Fair	Increased risk of sinus bradycardia, exaggerated clonidine withdrawal response (acute hypertension)

Potential DDI with Major Severity:

All DDI including details of severity and outcome has been summarized in the Table 2. The major DDI, which constitutes a life-threatening (interaction and/or medical intervention to minimize or prevent serious adverse effects) and contraindicated DDI constituted a life-threatening interaction with high mortality rate, is discussed as follows

Calcium channel blockers + (Opioid or beta-blocker or alpha 2-adrenergic)

A severe DDI is present when calcium channel blockers combine with opioid analgesics, which is classified as majorseverity because it may result in severe hypotension and an increased risk of respiratorydepression caused by fentanyl toxicity.

For example, diltiazem HCL is a moderate CYP3A4inhibitor and fentanyl is a CYP3A4 substrate. The concurrent use may result in increasedfentanyl plasma levels and fatal respiratory depression. Caution is necessary if these agentsare givenconcurrently and use the lowest possible fentanyl dose. Patient should be carefullymonitored for an extended period of time for fentanyl adverse events. Any dosage increasesto either medication should be made carefully.

Co-administration of calcium channel blockers and beta-blocker drugs is also classified asmajor severity because it may result in an increased risk of hypotension, bradycardia,atrioventricular

conduction disturbances. If concurrent therapy is required, cardiac functionand blood pressure should be carefully monitored, particularly in patients predisposed toheart failure. A dosage adjustment for hepatically metabolized beta blockers may berequired.

The combination of calcium channel blockers with alpha 2-adrenergic agonistic drug isalso classified as major severity because it may result in increased incidence of sinus bradycardiarequiring hospitalization and insertion of a pacemaker. Therefore, heart rate should bemonitored when clonidine and verapamil or diltiazem are given concurrently.

Beta-blocker + sympathomimetic drugs

The concomitantuse of beta-blocker and sympathomimetic drugs should be evaded because it may result in hypertension, bradycardia and resistance to epinephrine in anaphylaxis. But, if concomitant therapy is necessary, patient should be carefully monitored for severe and prolonged hypertension.

Alpha 2-adrenergic blockers + beta-blockers

Alpha 2-adrenergic blockers and beta-blockers may result in increased risk of sinus bradycardia and exaggerated clonidine withdrawal response. Monitor heart rate when clonidine and atenolol are given concurrently. Patients to be withdrawn from clonidine who are concomitantly receiving a beta blocking agent, such as atenolol, should be withdrawn from the beta blocker several days before the gradual discontinuation of clonidine to avoid an excessive rise in blood pressure. In the case of a hypertensive crisis following discontinuation of clonidine, IV phentolamine or oral clonidine can be used to reverse the excessive rise in blood pressure. Patients to be withdrawn from clonidine who are concomitantly receiving a beta blocking agent should be monitored carefully for hypertension.

Antihypertensive and anti-inflammatory agents

NSAIDmay block the antihypertensive effects of thiazide and loop diuretics, β-adrenergic blockers, α-adrenergic blockers and angiotensin converting enzyme inhibitors. It seems to happen by NSAID interference with prostaglandins synthesis which may thus limit the ability of antihypertensive drugs to control blood pressure. When concomitant use of loop diuretics and NSAID is required, patient should be monitored for diuretic efficacy and for signs of renal failure.

Factors associated with the occurrence of potential DDI in the ICU:

It has been identified that only inducers of cytochrome P450, drugs that prolong the QT interval and drugs from group C of the ATC (cardiovascular system) were significantly associated with potential DDIs. In the first 24 hours in ICU, a potential DDI correlation discovered between drugs with a narrow therapeutic index and drugs from ATC group N. At the time of discharge, inhibitors of cytochrome P450, drugs that affect glycoprotein P and drugs from groups J and L were significantly correlated with potential DDIs [Adriano Max et al, 2011].

Table 3 - Factors associated with the occurrence of potential DIs in the

ICU [Adriano Max et al, 2011]

Predictive Factors	First 24 Hours			50th length- of - stay percentile			Discharge		
	OR	CI 95%	P Value	OR	CI 95%	P Value	OR	CI 95%	P Value
Narrow Therapeutic Index	4.4	1.4-3.9	0.006[1]	3.6	0.9-4.1	0.039[3]	2.3	0.9-5.7	0.099[1]
Cytochrome P450 Inducer	3	1.8-5.1	<0.001[1]	2	1.2-3.6	0.012[1]	2.2	1.3-3.9	0.003[1]
Cytochrome P450 inhibitor	1.5	0.2-11.0	0.651[3]	4.4	0.6-38.3	0.114[3]	6.6	2.3-20.0	<0.001[1]
Modulation of glycoprotein P	2.2	0.0-81.2	0.531[3]	8.8	0.8-223.0	0.056[3]	9.4	2.4-43.7	<0.001[3]
Drugs that Prolong the QT Interval	2.2	1.2-4.2	0.010[1]	1.9	1.1-3.5	0.030[1]	2.5	1.3-4.7	0.003[1]
ATC Group B	ND	ND	ND	8.8	0.8-223	0.056[3]	4	0.8-21.5	0.059[3]
ATC Group C	3.1	1.7-5.6	<0.001[1]	4.1	2.1-7.8	<0.001[1]	9.2	5.0-17.0	<0.001[1]
ATC Group J	1.3	0.8-2.3	0.293[1]	1.9	1.1-3.4	0.020[1]	1.8	1.1-3.1	0.029[1]
ATC Group L	1.7	0.6-4.4	0.359[1]	4.9	1.4-20.5	0.009[1]	9.3	2.1-57.3	0.001[1]
ATC Group N	6.4	3.3-12.5	<0.001[1]	2.8	1.5-5.2	0.001[1]	1.6	0.9-2.8	0.093[1]

ND - not determined because every Patient in the study used at least one medication of this ATC Group. CI-Confidence interval

1: Chi-square test with Yates correction; 2: Chi-square test; 3: Fisher's exact test. OR - adds ratio

The administration of drugs with a narrow therapeutic index was an important factor of DDIs. The pharmacotherapy of critically ill patients requires the use of cyclosporine, phenytoin, vancomycin and digoxin, in addition to other drugs with narrow therapeutic indexes. The identified association was likely due to the use of these drugs.

A strong association in terms of DDI has been discovered between drugs that prolong the QT interval and there is a growing concern regarding these drugs due to the risk of cardiotoxicity with cardiac events. [Letsas et al, 2009]. These adverse events can be determined by potential pharmacokinetic interactions that inhibit the metabolism of drugs with this property or by pharmacodynamic synergism. The metronidazol+amidorane, amiodarone+haloperidol etc. interactions detected, which can produce the potential adverse events.

Management of DDI in ICU:

There are many potential DDIs with high alleged relevance in the ICU that appear to require attention and follow-up. Different strategies can be adopted to manage the DDI in the ICU

1. Depute one dedicated Clinical Pharmacist to review the medication system in ICU
2. Prescription verification and validation should be mandatory
3. Patient Care Plan
4. All drugs should be dispensed after pharmacist verification
5. Patient Labs., organ system must be reviewed before initiation of any new therapy

6. Medication monitoring
7. Continuous liaison with the physician
8. Computerized decision support system may help reduce the number of potential DDIs but needs to be accustomed to the environment in which it operates.

CONCLUSION:

DDIs are common in the ICU population in the presence of poly-pharmacy, and a considerable proportion of drugs are clinically relevant. Critically ill patients may also augment an intended pharmacologic response and potentially result in an unintended effect.A team approach is important to identify, prevent, and address drug interactions in the intensive care setting and optimize patient outcomes. Additionally, a clinical decision support system is an important toll to identify potential interactions in the prescription and reduce the adverse drug events. The peer review meeting between the healthcare professional involved in prescribing, dispensing and administering the drugs are the main domain of risk factors, the education and updates regarding the most frequent and potential drug interactions an also help in the prevention of drug interactions.

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