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Drug Interaction Exposures in an Intensive Care Unit: Population Under Antihypertensive Use

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1. Introduction

A potential drug-drug interaction (DDI) is related to the possibility of a drug to alter the effect of another drug simultaneously administered. It can occur before or after drug administration (Almeida et al., 2007). DDI are considered predictable and thus avoidable and manageable (Cruciol-Souza et al., 2006).

Many of these interactions have slow onset clinical manifestations that can be diagnosed as new diseases and handled wrongly (Correr et al., 2007). Drug interactions are estimated to occur between 3% and 5% in patients to whom few drugs are prescribed and 20% among those who use 10 to 20 drugs simultaneously (Ferreira Sobrinho et al., 2006). The incidence of drug interactions is directly proportional to the increase in the number of drugs prescribed (Matos et al., 2009). It is known that a prescription containing eight or more drugs will present at least one interaction (Almeida et al., 2007).

Drug interactions incidence in Intensive Care Unit (ICU) is higher than hospital rates in general probably due to patient disease severity admitted in this unit (Almeida et al., 2007). ICU patients usually need great number of administered drugs and they are under risk of 44.3% to 95.0% of potential drug interactions occurrence (Sierra et al., 1997; Meneses & Monteiro, 2000). New drugs availability and prescription of fixed drug combinations difficult potential interactions identification (Trato, 2005). Thereby, this study aimed to discuss the risk of DDI in medical prescriptions of adult inpatients in ICU under use of antihypertensive drugs.

Commonly used drugs in ICU are vasoconstrictors and cardiotoxic agents, antimicrobials, coronary vasodilators, direct vasodilators, antisecretory drugs, anticoagulants, sedatives-

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hypnotics agents, antiemetics, antidiabetics agents, analgesics-antipyretics and antiinflammatory drugs.

Micromedex® DrugReax® System (Klasco, 2011) is one of the most used database to describe interactions. The DrugReax System contains a dictionary of more than 8,000 unique drug terms. This system distinguishes trade names from equivalent generic names and it analyses specific drug instead of drug class. This database provides information about clinical consequences or adverse drug reactions that could result from a DDI, describe the interaction mechanism and classifies onset, severity and scientific knowledge of adverse reactions caused by the DDI.

Onset is classified as rapid (effects expected within 24 hours of drug administration), delayed (effects not expected to appear within the first 24 hours following drug administration) or unknown (effects expected to appear any time after drug administration).

Severity is classified as minor (limited clinical effects including increased frequency or severity of adverse effects and generally no major alteration in therapy), moderate (exacerbation of patient's condition and/or an alteration in therapy), major (life-threatening interaction and/or medical intervention to minimize or prevent serious adverse effects) or contraindicated (life-threatening interaction).

Scientific knowledge is classified considering how well DDI is documented in the literature that means excellent (controlled studies clearly established the existence of the interaction), good (documentation strongly suggests the interaction exists but well-controlled studies are lacking), fair (available documentation is poor but pharmacologic considerations lead clinicians to suspect about interaction existence or documentation is good for a pharmacologically similar drug) or unknown (no documentation about the interaction).

Table 1 presents the classification of DDI involving antihypertensive and the most frequent used drugs in ICU.

Antihypertensives	Drug Classes	Severity	Onset	Scientific knowledge	DDI Outcome
Calcium channel blockers	Histamine H2-antagonists (cimetidine)	Moderate	Rapid	Good	Increased concentrations of calcium channel blockers and possible cardiovascular toxicity
	Benzodiazepinics	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).

Antihypertensives	Drug Classes	Severity	Onset	Scientific knowledge	DDI Outcome
	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, atrioventricular 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
	Sympathomimetics	Major	Rapid	Excellent	Hypertension, bradycardia and resistance to epinephrine in anaphylaxis
	Hypoglycemic	Moderate	Delayed	Good	Hypoglycemia, hyperglycemia or hypertension
	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)
	Lopp diuretics	Moderate	Rapid	Fair	Hypotension, bradycardia
	Thiazide diuretics	Moderate	Delayed	Fair	Hyperglycemia, hypertriglyceridemia
	Fluoroquinolone	Minor	Delayed	Fair	Bradycardia, hypotension
Lopp diuretics	Nonsteroidal antiinflammatory agents	Moderate	Delayed	Good	Decreased diuretic and antihypertensive efficacy
	Beta-blocker drugs	Moderate	Rapid	Fair	Hypotension, bradycardia
	Glucocorticoids	Moderate	Delayed	Fair	Hypokalemia

Antihypertensives	Drug Classes	Severity	Onset	Scientific knowledge	DDI Outcome
	Direct vasodilators	Minor	Rapid	Good	Enhanced diuretic response to loop diuretic
Potassium-sparing diuretics	Nonsteroidal antiinflammatory 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
	Nonsteroidal antiinflammatory agents	Moderate	Delayed	Good	Decreased diuretic and antihypertensive efficacy
	Beta-blockers	Moderate	Delayed	Fair	Hyperglycemia, hypertriglyceridemia
Angiotensin converting enzyme inhibitors	Nonsteroidal antiinflammatory agents	Moderate	Not specified	Excellent	Decreased antihypertensive efficacy
	Loop diuretics	Moderate	Rapid	Good	Postural hypotension (first dose)
	Thiazide 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 catecholamines
	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)

Table 1. Classification of DDI involving antihypertensive drugs in medical prescriptions of adult inpatients in ICU

2. DDI of major severity

The combination of calcium channel blockers with opioid analgesics is classified as major severity because it may result in severe hypotension and an increased risk of respiratory depression caused by fentanyl toxicity. For example, diltiazem is a moderate CYP3A4 inhibitor and fentanyl is a CYP3A4 substrate. The concurrent use may result in increased fentanyl plasma levels and fatal respiratory depression. Caution is necessary if these agents are given concurrently and use the lowest possible fentanyl dose. Patient should be carefully monitored for an extended period of time for fentanyl adverse events. Any dosage increases to either medication should be made carefully.

Calcium channel blockers and beta-blocker drugs co-administration is also classified as major severity because it may result in an increased risk of hypotension, bradycardia, atrioventricular conduction disturbances. If concurrent therapy is required, cardiac function and blood pressure should be carefully monitored, particularly in patients predisposed to heart failure. A dosage adjustment for hepatically metabolized beta blockers may be required.

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

The abrupt discontinuation of vasodilators may lead to a hyper-adrenergic attack causing acute myocardial infarction, stroke and/or other complications due to rebound vasoconstriction. This effect is known as antihypertensive drugs withdrawal. The most commonly drugs involved in this effect are the beta-blockers, centrally acting agents, direct vasodilators and calcium channel blockers (Kirk & Johnson, 1995).

Concomitant use of beta-blockers and clonidine provide the rebound effect after abrupt withdrawal of therapy. Clonidine by an agonistic effect on presynaptic alpha-2 receptors decreases noradrenaline release from postganglionic sympathetic neurons. It is an excess of catecholamines in the synaptic clefts when the administration of clonidine is interrupted and this catecholamines are available for binding to the alpha and beta receptors. However, if the beta receptor, auxiliary in vasodilation, is blocked, the alpha effects are not counterbalanced. The result is vasoconstriction, rebound hypertension and risk of coronary and cerebral vasospasm. It is recommended that in patients who are on beta blockers and clonidine, the drug should be withdrawn gradually to avoid this adverse drug reaction. Moreover, the use of clonidine and beta-blocker raises the risk of sinus bradycardia (Goodman & Gilman, 2011).

The concurrent use of beta-blocker and sympathomimetic drugs should be avoided because it may result in hypertension, bradycardia and resistance to epinephrine in anaphylaxis. However, if concomitant therapy is necessary, patient should be carefully monitored for severe and prolonged hypertension. Glucagon has positive inotropic and chronotropic effects that are independent of adrenergic receptors. The use of this agent is of great importance in patients on beta blockers which are affected by an anaphylactic reaction. Glucagon increases cardiac output and coronary perfusion, decreasing myocardial hypoxia and a possible secondary cardiogenic shock (Lieberman, 1998).

Alpha 2-adrenergic blockers and beta-blockers may result in increased risk of sinus bradycardia; exaggerated clonidine withdrawal response (acute hypertension). 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.

3. Catecholamine synthesis or release blockers and oxazolidinone

The severity of the most frequent used drugs in ICU is moderate to minor. However, the combination of catecholamine synthesis or release blockers with oxazolidinone is contraindicated because it may result in hypertensive crisis, causing headache, palpitation and neck stiffness. Hypertension due to drugs can cause increase of blood pressure level, reduction of antihypertensive drug effectiveness or the worsening of a pre-existing hypertension.

Linezolid is an antibiotic used to treat infections caused by gram-positive bacteria but this drug is also a non-selective and reversible inhibitor of monoamine oxidase (MAO). The inhibitors of this enzyme block the oxidative deamination of three biogenic amines which are norepinephrine, dopamine and 5-hydroxytryptamine. When monoamine oxidase inhibitors (MAOI) are associated with sympathomimetic drugs or foods containing tyramine, hypertensive crisis may occur (Fuzikawa et al., 1999). The hypertensive crises are life-threatening and can also cause damage to susceptible organs as heart, brain and kidneys (Plavnik, 2002).

4. Calcium channel blockers and histamine H2-antagonists

The co-administration of calcium channel blockers and some histamine H2-antagonists, as cimetidine, result in increased concentrations of calcium channel blockers and possible cardiovascular toxicity. This effect happens because of Cytochrome P (CYP) 450 inhibition.

The Cytochrome P (CYP) 450 is a superfamily of hemoproteins that play an important role in the metabolism of steroid hormones, fatty acids and many drugs. Many agents used for management of cardiovascular diseases are substrates, inhibitors or inducers of CYP450 enzymes. When two agents that are substrates, inhibitors or inducers of CYP450 are administered together, drug interactions with significant clinical consequences may occur (Cheng et al., 2009). Monitoring cardiovascular response is necessary when the patient is in use of cimetidine and a calcium channel blocker. Dose reductions of up to 35% to 40% may be needed for diltiazem or nifedipine if co-administered with cimetidine.

5. Antihypertensive and antiinflammatory agents

5.1 Nonsteroidal antiinflammatory agents

Nonsteroidal antiinflammatory drugs (NSAID) may 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.

Potassium-sparing diuretics and NSAID co-administration may also result in hyperkalemia or possible nephrotoxicity. If this combination is necessary, patient should be monitored for blood pressure, weight changes, urine output, potassium levels, creatinine levels, decreased effectiveness of the diuretic and hyperkalemia.

In same way, when concurrently administration of thiazide diuretics and NSAID is necessary, blood pressure and weight should be monitored. It is important to follow the patient for signs of renal failure, including decreases in urine output and increased edema.

Caution is recommended when prescribing NSAID to patients taking ACE inhibitors. When concomitant use is required, patient should be monitored for ACE inhibitor efficacy and for signs of renal failure. NSAID may also promote the development of hyperkalemia in association with ACE inhibitors as a result of deterioration of renal function. They are also responsible for reducing the antihypertensive effects of ACEI by interfering in the synthesis of prostaglandins. Probenicid reduces captopril renal excretion and increases its plasma concentration. On the other hand, aspirin and antiacids may decrease or abolish the antihypertensive efficacy of captopril (Gonzaga et al., 2009).

The mechanism of the hypertensive effects caused by NSAID seems primarily to be related to their ability to block the cyclo-oxygenase pathway of arachidonic acid metabolism which results in decrease of prostaglandin formation. The prostaglandins are important in normal modulation of renal and systemic vascular dilatation, glomerular filtration, tubular secretion of salt and water reabsorption, adrenergic neurotransmission and the renin-angiotensin-aldosterone system. Blockade of beneficial effects of prostaglandins by NSAID results in complex events which culminate in attenuation of many antihypertensive agents effects. The risk is greatest in the elderly, blacks and patients with low-renin hypertension. (Houston, 1991).

Pharmacologically, it is thought that NSAID interact differently with antihypertensive drugs. However, the NSAID effects on newly initiated antihypertensive drug therapy remain unclear because few studies have included patients who were initially administered NSAID and then antihypertensives. Physiologically, the effects of renal prostaglandins on salt and water transport in the kidney are complementary to the actions of diuretics. Therefore, it is likely that the blocking of prostaglandins synthesis by NSAID attenuates the effect of diuretics. angiotensin-converting enzyme (ACE) inhibitors produce vasodilatation and lower blood pressure by inhibiting ACE which promotes the formation of angiotensin-2 and aldosterone. Bradykinin is an autacoid that produces vasodilatation and further reduces blood pressure. Blocking ACE decreases the inhibition of bradykinin-induced vasodilatation. However, the vasodilatory properties of bradykinin that contribute to the antihypertensive properties of ACE inhibition appear to be mediated through local release of prostaglandins and are therefore susceptible to interference by NSAID (Ishiguro et al., 2008).

5.2 Steroidal antiinflammatory agents

Glucocorticoids may increase blood pressure by increasing the concentration of sodium-potassium adenosine triphosphate in the cell membrane which could increase the concentration of extracellular sodium and therefore expand the plasma volume. Cortisol also stimulates the synthesis of mineralocorticoid aldosterone leading to sodium and water retention and, consequently, increased blood volume and cardiac output (Ortega et al., 1996; Brown, 2005). It also increases the sensitivity of the myocardium to endogenous catecholamine and increases the vascular response to endogenous vasopressors such as angiotensin II and norepinephrine (Ortega et al., 1996). In addition, glucocorticoids induce hepatic production of angiotensinogen resulting in an exacerbated response of the renin-angiotensin-aldosterone system (Dukes, 1992).

6. Beta-blockers and hypoglycemic drugs

The use of beta-blockers and hypoglycemic may result in hypoglycemia, hyperglycemia or hypertension. If the use of a beta blocker is required in a diabetic patient, glucose should be carefully monitored. Cardioselective beta blockers (atenolol, metoprolol) cause less disturbance of glucose metabolism and less masking of hypoglycemic effects. Propranolol accounts for the majority of positive reports of interactions and should clearly be avoided.

Hyperglycemia occurs frequently in critically ill patients and it is a marker of poor prognosis (Pitrowsky et al., 2009). The main complication of insulin therapy is hypoglycemia which is considered a potentially serious adverse event in these patients (Diener et al., 2006). The combination of a beta-blocker and insulin may impose a higher risk of blood glucose changes and lead to the development of hypoglycemia, hyperglycemia and hypertension.

Beta-blockers may inhibit some of the normal physiologic response to hypoglycemia. Symptoms of hypoglycemia such as tremors and tachycardia may be absent, making it more difficult for patients to recognize an oncoming episode. In addition, multiple effects on glucose metabolism have been reported, usually with the noncardioselective beta-blockers (e.g., propranolol, pindolol, timolol) but occasionally also with relatively beta-1 selective agents (e.g., metoprolol). Specifically, inhibition of catecholamine-mediated glycogenolysis and glucose mobilization in association with beta-blockade can potentiate insulin-induced hypoglycemia in diabetics and delay the recovery of normal blood glucose levels. Prolonged and severe hypoglycemia may occur, although these events have rarely been reported. Significant increases in blood pressure and bradycardia can also occur during hypoglycemia in diabetics treated with insulin and beta-blockers due to antagonism of epinephrine's effect on beta-2 adrenergic receptors, which leads to unopposed alpha-adrenergic effects including vasoconstriction. Other effects reported with various beta-blockers include decreased glucose tolerance and decreased glucose-induced insulin secretion (Goodman & Gilman, 2010).

7. Conclusion

The need of multiple drugs simultaneously used is common in the intensive care environment and contribute to the occurrence of drug interactions. The clinical

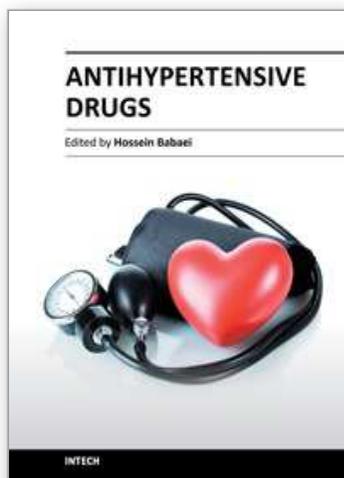
consequences of these interactions should be considered in order not to endanger ICU inpatients health once this population is under unfavorable conditions.

The presence of drug interactions is a permanent risk in the ICU and not all DDI can be prevented. The use of software is mentioned in the literature as an important toll in reviewing prescriptions to identify interactions and reduce adverse events. Also, the continuing education of professionals involved in the processes of prescribing, dispensing and administering medicines as the main risk factors for drug interactions, the dissemination of information regarding the more frequent and important in clinical practice about drug interactions are instruments in the prevention of drug interactions.

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Hypertension, known as a "silent killer" is widely prevalent and a major risk factor for cardiovascular diseases. It afflicts more than one billion population worldwide and is a leading cause of morbidity and mortality. The authors of the chapters look from different angles to hypertension, sharing their new knowledge and experience in the direction of deep understanding and more clarification of the disease providing an invaluable resource not only for clinicians, but also for all medical sciences students and health providers.

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