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Special Articles

Adverse Interactions of Drugs in Critical Care Patients

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Adverse drug reactions are common and potentially lethal complications of modern medical treatment (1,2). According to a study by the Boston Collaborative Drug Surveillance Program (BCDSP), an estimated 29,000 drug-related deaths occur each year, and hospital patients account for 29% of them (2). In another study, the BCDSP monitored 9,900 patients with 83,200 drug exposures and found 3,600 reported adverse reactions (1). In 234 instances (6.5%), the adverse reactions were attributed to drug interactions.

Among hospital patients, those in critical care units are the most likely to have an adverse drug reaction. Often, these patients have multiple organ system failure or senescent organ dysfunction and require mechanical ventilation or other aggressive pulmonary intervention. Organ dysfunction affects drug metabolism and alters normal elimination characteristics (3). Because they may need mechanical ventilation with tracheal intubation and often have central nervous system dysfunction, they are unable to verbalize early symptoms of drug toxicity. Under these circumstances, a previous history of drug allergy or adverse drug effects is often difficult to elicit, especially if family members or previous records are not available.

Because critically ill patients usually require combinations of medications for the treatment of complicated medical disorders, prescribing for them is exceedingly complex. Sophisticated, multiple drug regimens are often required, both to treat primary diseases and to prevent complications of critical illness. Consequently, the number of medications such patients must be given increases the likelihood of adverse drug interactions. In fact, a logarithmic relationship between the number of errors and the number of prescriptions per patient has been demonstrated (4).

It is vital that the staff of critical care units be aware of reported drug interactions in order to reduce the potential hazards of multiple drug therapy. Guidelines for identifying potentially important drug interactions include:

1. understanding the sites and mechanisms of drug actions and the drugs that predictably interact at these sites;

2. understanding the pathophysiology of the patient's diseases and the pharmacology of the drugs being used to treat them;

3. using as few drugs as possible per patient regimen to minimize the potential for interactions; and

4. recognizing that differences between individual patients in their reactions to drugs can produce substantial variability in the pharmacological consequences of the interaction.

The Table on the following pages details 40 of the most frequently occurring drug interactions in critically ill patients. The drugs are listed in alphabetical order. This is by no means a comprehensive list of all relevant drug interactions; compendious lists are available elsewhere (5-8). Our purpose is to provide examples of drug interactions whose consequences are frequent and severe enough to warrant the attention of practitioners in the area.

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Table

Adverse Drug Interactions in Critical Care Patients

Drug	Drug	Effect	Mechanism	Comments/Recommendations	Reference
Aminoglycosides	Bumetanide	Increased risk of ototoxicity	Additive	Transient or permanent hearing loss	9
	Ethacrynic acid	Increased risk of ototoxicity	Additive	Increased risk with IV administration and preexisting renal failure	10-12
	Furosemide	Increased risk of ototoxicity	Additive		9
	Neuromuscular blocking agents	Neuromuscular blockade	Additive	Reversible with calcium	13,14
	Penicillins	Relative inactivation of both antibiotics	Formation of inactive conjugate	Separate administration times by 1-2 hrs	15-17
Aminophylline	see Theophylline				
Amphotericin B	Digitalis	Increased risk of digitalis toxicity	Amphotericin-induced renal potassium wasting	Monitor serum potassium closely	18
	Neuromuscular blocking agents	Increased curariform effect	Amphotericin-induced renal potassium wasting	Replace as needed	13,14,18,19
Antacids	Oral digoxin	Decreased digoxin effect	Decreased absorption	Separate administration times	20
	Salicylates	Decreased salicylate levels	Increased renal clearance	Increase salicylate dose as required	21
	Quinidine	Increased quinidine levels/effect	Decreased renal clearance	Monitor quinidine blood level; decrease quinidine dose as required	22
Aspirin	Antacids	Decreased salicylate levels	Increased renal clearance	Increase salicylate dose as required	21
	Heparin	Increased risk of bleeding	Inhibition of platelet function	Avoid combination	23
	Warfarin	Increased risk of bleeding	Additive	≥3 gm ASA/day may enhance hypoprothrombinemia ≤3 gm ASA/day inhibits platelet aggregation; AVOID	7
Barbiturates	Beta blockers	Decreased beta blockade	Induction of microsomal enzymes	Increase beta blocker dose as required	24
	Chloramphenicol	Increased barbiturate effect	Inhibition of microsomal enzymes	Significant, monitor barbiturate levels	25,26
	Corticosteroids	Decreased steroid effect	Induction of microsomal enzymes	Increase steroid dose as required	27
	Quinidine	Decreased quinidine effect	Induction of microsomal enzymes	Increase quinidine dose as required	28
	Rifampin	Decreased barbiturate effect	Induction of microsomal enzymes	Increase barbiturate dose as required	29,30

Table

Adverse Drug Interactions in Critical Care Patients

Drug	Drug	Effect	Mechanism	Comments/Recommendations	Reference
Barbiturates (cont)	Valproic acid	Increased barbiturate effect	Inhibition of microsomal enzymes	Monitor barbiturate levels	31
Benzodiazepines	Cimetidine	Increased benzodiazepine effect (diazepam/chlordiazepoxide)	Inhibition of microsomal enzymes	Substitute lorazepam or oxazepam	32-35
	Neuromuscular blocking agents	Increased curariform effect (gallamine, tubocurarine, pancuronium)	Limits release of acetyl choline; additive	Not observed with depolarizing agents (decamethonium, succinlycholine)	36
Beta blockers	Anesthetics, general	Hypotension	Potentially additive	Monitor blood pressure closely	37
	Barbiturates	Decreased beta blockade	Induction of microsomal enzymes	Increase beta blocker dose as required	24
	Cimetidine	Increased beta blocker levels/ effect	Decreased hepatic clearance (mean 27%)	Observe closely	38
	Lidocaine	Increased lidocaine effect	Decreased hepatic clearance of lidocaine	May require lidocaine dosage reduction	39
	Neuromuscular blocking agents	Prolonged neuromuscular blockade	Potentially synergistic	Significant with large propranolol doses (120 mg/day oral)	7,40
	Theophylline	Increased theophylline levels/ effect	Decreased theophylline clearance (mean 40%)	Monitor theophylline levels; decrease dose as required	41
	Verapamil	Increased negative chronotropic and inotropic effects	Additive	May be significant in patients with impaired left ventricular performance and/or angina	42,43
Calcium channel blockers	Beta blockers	Increased negative inotropic and chronotropic effects	Additive	May be significant in patients with impaired left ventricular performance and/or angina	42,43
	Digoxin	Increased digoxin levels	Decreased renal and nonrenal clearance	May require digoxin dosage reduction	44
Carbenicillin	see Penicillins				
Chloramphenicol	Barbiturates	Increased barbiturate effect/ toxicity	Inhibition of microsomal enzymes	Monitor barbiturate levels and decrease dose as required	25,26
	Phenytoin	Increased phenytoin effect/ toxicity	Inhibition of microsomal enzymes	Monitor phenytoin levels and decrease dose as required	25,45
Chlordiazepoxide	see Benzodiazepines				

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Adverse Drug Interactions in Critical Care Patients

Drug	Drug	Effect	Mechanism	Comments/Recommendations	Reference
Cimetidine	Beta blockers	Increased beta blockade	Decreased hepatic clearance	Observe closely	38
	Benzodiazepines	Increased benzodiazepine levels/effect	Inhibition of microsomal enzymes	Substitute lorazepam or oxazepam	32-35
	Lidocaine	Increased lidocaine levels/effect	Decreased lidocaine's hepatic clearance	May require lidocaine dosage reduction	32,46
	Narcotic analgesics	Increased narcotic effect, respiratory depression	Inhibition of microsomal enzymes	Monitor patients closely	47
	Phenytoin	Increased phenytoin effect	Inhibition of microsomal enzymes	Monitor phenytoin levels	48,49
		Increase in hematological abnormalities	Possible additive	Monitor hematologic values	34
	Theophylline	Increased theophylline levels/ effect	Inhibition of microsomal enzymes (mean clearance decrease of 40%)	Monitor theophylline levels; effect occurs within 48 hrs	50,51
	Warfarin	Enhanced hypoprothrobinemic effect of warfarin	Inhibition of microsomal enzymes	Monitor prothrombin time; significant; decrease warfarin dose as required	34,52
Corticosteroids	Barbiturates	Decreased corticosteroid effect	Induction of microsomal enzymes	Increase steroid dose as required	27
	Phenytoin	Decreased corticosteroid effect	Induction of microsomal enzymes	Increase corticosteroid dose as required	53-55
	Rifampin	Decreased corticosteroid effect	Induction of microsomal enzymes	Increase corticosteroid dose as required	56
Curariform drugs	see Neuromuscular blocking agents				
Dextran	Heparin	Increased bleeding	Synergistic anticoagulation	Avoid combination	57
Dialtiazem	see Calcium channel blockers				
Digoxin	Amphotericin B	Increased digoxin toxicity	Hypokalemia	Monitor serum potassium and replace as required	7,18
	Antacids	Decreased digoxin levels/effect	Decreased oral digoxin absorption	Separate administration times	20
	Antibiotics (oral)	Increased digoxin effect	Inactivation of gut flora by antibiotic	May occur in 10-20% of population	58

Table

Adverse Drug Interactions in Critical Care Patients

Drug	Drug	Effect	Mechanism	Comments/Recommendations	Reference
Digoxin (cont)	Calcium channel blockers	Increased digoxin levels/effect	Reduced renal and nonrenal clearance	Monitor patient closely; reduce digoxin dose as required	44
	Cholestyramine	Decreased digoxin levels/effect	Reduced oral absorption	Separate administration times by 4-6 hrs	59
	Diuretics	Increased digoxin toxicity	Hypokalemia	Monitor serum potassium and replace as required	60
	Kaolin pectin	Decreased digoxin levels/effect	Reduced oral absorption	Separate administration times by 4-6 hrs	20
	Procainamide Quinidine	Increased digoxin levels/effect	Altered excretion and tissue binding	Monitor closely; may require 30-50% reduction in digoxin dosage	61-63
	Vasodilators	Decreased digoxin levels/effect	Increased renal clearance (mean 50%)	May require digoxin dosage increase; observed with hydralazine, nitroprusside	64
Diuretics	Aminoglycosides	Increased risk of ototoxicity	Additive	Increased risk with IV administration and preexisting renal disease	10,11
	Digoxin	Increased digoxin toxicity	Hypokalemia	Monitor serum potassium and replace as required	60
Erythromycin	Digoxin	Increased digoxin effect	Inactivation of gut flora by erythromycin	May occur in 10-20% of population	58
	Theophylline	Increased theophylline levels/effect	Inhibition of theophylline clearance (mean 25%)	Occurs at 5-7 days; monitor theophylline levels and reduce dose as required	65-68
Ethacrynic acid	see Diuretics				
Furosemide	see Diuretics				
Heparin	Aspirin	Increased risk of bleeding	Inhibition of platelet function	Avoid combination	23
	Dextran	Increased risk of bleeding	Synergistic anticoagulation	Avoid combination	57
Lidocaine	Barbiturates	Decreased lidocaine levels/effect	Induction of microsomal enzymes	Increase lidocaine infusion rate as required	69
	Beta blockers	Increased lidocaine levels/effect	Decreased hepatic blood flow and clearance	Reduce lidocaine infusion rate as required	39
	Neuromuscular blocking agents	Increased curariform effect	Potentiation	Monitor patient closely	19
Narcotic analgesics	Beta blockers	Central nervous system depression	Unknown	Monitor patient closely	70
	Cimetidine	Increased narcotic effect	Decreased hepatic clearance	Monitor patient closely	34,47

Table

Adverse Drug Interactions in Critical Care Patients

Drug	Drug	Effect	Mechanism	Comments/Recommendations	Reference
Narcotic analgesics (cont)	Neuromuscular blocking agents	Respiratory depression	Additive	Monitor patient closely	19
Neuromuscular blocking agents	Aminoglycosides	Neuromuscular blockade	Additive	Reversible with calcium	13,14
	Amphotericin B	Increased curariform effect	Amphotericin induced renal potassium wasting	Monitor serum potassium and replace as required	13,14,18,19
	Clindamycin	Neuromuscular blockade	Additive	Monitor patient closely	13,19
	Diuretics	Increased curariform effect	Hypokalemia	Monitor serum potassium and replace as required	19
	Lidocaine	Increased curariform effect	Potentiation	Monitor patient closely	19
	Narcotic analgesics	Respiratory depression	Additive	Monitor patient closely	19
	Procainamide	Increased curariform effect	Additive	Monitor patient closely	19
	Quinidine	Increased curariform effect	Additive	Monitor patient closely	19,22
Nifedipine	see Calcium channel blockers				
Pancuronium bromide	see Neuromuscular blocking agents				
Penicillins	Aminoglycosides	Decreased blood levels of both drugs	Formation of an inactive conjugate	Separate administration times by 1-2 hrs	15-17
Phenytoin	Chloramphenicol	Increased phenytoin levels/toxicity	Inhibition of microsomal enzymes	Monitor phenytoin levels and decrease dose as required	25,45
	Cimetidine	Increased phenytoin levels/toxicity	Inhibition of microsomal enzymes	Monitor phenytoin levels	48,49
		Increase in hematological abnormalities	Possibly additive	Monitor hematological values	34
	Corticosteroids	Decreased cortico-steroid effect	Induction of microsomal enzymes		53-55
	Quinidine	Decreased quinidine effect	Induction of microsomal enzymes	May increase clearance by 50%; increase dose as required	28
Procainamide	Neuromuscular blocking agents	Increased neuro-muscular blockade	Additive	Monitor patient closely	19,71

Table

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Drug	Drug	Effect	Mechanism	Comments/Recommendations	Reference
Quinidine	Antacids	Decreased quinidine levels/effect	Increased renal clearance	Increase dose as required	22
	Barbiturates	Decreased quinidine levels/effect	Induction of microsomal enzymes	Increase quinidine dose as required	28
	Digoxin	Increased digoxin levels/effect	Altered excretion and tissue binding	Monitor closely; may require 30-50% reduction in digoxin dosage	61-63
	Neuromuscular blocking agents	Increased curariform effect	Additive	Monitor patient closely	19,71
	Phenytoin	Decreased quinidine effect	Induction of microsomal enzymes	May increase clearance by 50%; increase dose as required	28
	Sodium bicarbonate	Increased quinidine levels	Decreased renal clearance	Decrease dose as required	22
Succinyl-choline	see Neuromuscular blocking agents				
Theophylline	Allopurinol	Increased theophylline levels/effect	Decreased theophylline clearance (mean 25%)	Occurs with allopurinol doses ≥600 mg/day; reduce theophylline dose as required	72
	Cimetidine	Increased theophylline levels/effect	Decreased theophylline clearance (mean 40%)	Monitor theophylline levels and reduce dose; effect occurs within 48 hrs	50,51
	Erythromycin	Increased theophylline levels/effect	Decreased theophylline clearance (mean 25%)	Occurs at 5-7 days; monitor theophylline levels and reduce dose as required	65-68
	Phenobarbitol	Decreased theophylline levels/effect	Induction of microsomal enzymes (mean clearance increase of 25%)	Observe; increase dose if required	73
	Phenytoin	Decreased theophylline levels/effect	Induction of microsomal enzyme system (mean clearance increase 75%)	Interaction may result in loss of seizure control as well; increase doses *or* avoid combination	74
	Propranolol	Increased theophylline levels/effect	Decreased clearance (mean 40%)	Metoprolol has only a small effect on theophylline clearance; avoid propranolol	75
	Rifampin	Decreased theophylline levels/effect	Increased clearance (mean 25%)	May be caused by rifampin inducing hepatic microsomal enzymes; monitor patient	76
Tubocurarine	see Neuromuscular blocking agents				
Ticarcillin	see Penicillins				
Verapamil	see Calcium channel blockers				

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