DRUG-DRUG INTERACTIONS (13)

Drug	Possible Mechanism / Onset and severity	Adverse Effects	Management
Drugs that DECREASE tacrolimus (TAC) levels			
Anticonvulsants: ➢ Phenytoin ➢ Carbamazepine ➢ phenobarbital, primidone	Enzyme induction ↑TAC metabolism • delayed / major • delayed/ moderate • delayed / major	↓effectiveness of TAC which may lead to rejection	↑ TAC dose by 30% and monitor levels following addition, dose change or discontinuation
Antimicrobial: ➢ rifampin ➢ caspofungin	Induction of hepatic enzymes • delayed / major Mechanism is unknown • delayed / moderate	↓effectiveness of TAC which may lead to rejection	Monitor TAC levels following addition, dose change or discontinuation. Monitor tacrolimus level closely when capsofungin is initiated or dose changes and when capsofungin is discontinued.

[13]- Mecadon K. Managing Side Effects of Immunosuppressants. R I Med J. 2021;104(1):31-33.

Drug	Possible Mechanism / Onset and severity	Adverse Effects	Management
B) Drugs that INCREASE tacrolimus (TAC) levels			
Antimicrobial: ➢ erythromycin, clarithromycin ➢ azole antifungals (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole)	↓TAC metabolism, ↑rate of absorption, ↓volume of distribution • delayed / major ↓TAC metabolism • delayed/ moderate	↑TAC levels, ↑ risk of toxicity	Monitor TAC levels following addition, dose change or discontinuation. Monitor serum creatinine
Antidepressants: ➢ fluoxetine, fluvoxamine greater than sertraline, venlafaxine, mirtazapine, paroxetine	↓TAC metabolism • delayed/ moderate	↑TAC levels, ↑ risk of toxicity	Consider another antidepressant (citalopram, escitalopram) and/or monitor TAC levels closely
Cardiovascular: ➢ diltiazem, verapamil ➢ amiodarone	May inhibit hepatic metabolism of TAC •delayed / Major	↑TAC levels, ↑ risk of toxicity	Monitor TAC levels following addition, dose change or discontinuation

[13]- Mecadon K. Managing Side Effects of Immunosuppressants. R I Med J. 2021;104(1):31–3.

PHARMACODYNAMIC INTERACTIONS[13]

Drug	Proposed Mechanism and Possible effects	Management
Pharmacodynamic Interactions of Tacrolimus (TAC)		
➢ Aminoglycosides, Amphotericin B, NSAIDS, C0X-2 inhibitors	Additive nephrotoxicity	These drugs should be avoided in transplant recipients due to increased nephrotoxicity. The only exception is when the benefit clearly outweighs the potential risks and only used for short-term treatment. Renal function should be monitored closely while this drug is used
➢ HMG-CoA Reductase Inhibitors : Example: lovastatin, simvastatin, atorvastatin	TAC may ↓metabolism of these agents →accumulation of statin and toxicity: Myalgia, myopathy, rhabdomyolysis	Start with low dose of these agents and monitor very closely for toxicity
➢ Digoxin	↓volume of distribution of digoxin by 50-70%, ↑〈digoxin half-life by 30-40%, and increased digoxin levels Digoxin toxicity such as vomiting, cardiac arrhythmia's	Initiate low dose and follow up with serum digoxin levels Closely monitor for symptoms of digoxin toxicity

[13]- Mecadon K. Managing Side Effects of Immunosuppressants. R I Med J. 2021;104(1):31–3.