Clinical Pharmacology & Toxicology Pearl of the Week

~ Tacrolimus and Neuropsychiatric Side Effects ~

Case:

A 36-year-old male with a history of a kidney transplant on tacrolimus presents with new onset hallucinations and persecutory delusions with preserved insight. His immunosuppressive medications were changed recently with the addition of sirolimus to his existing therapy.

Background:

- ✓ Tacrolimus is an immunosuppressant that acts though binding to FKBP-12 and complexes with calcineurin dependent proteins to inhibit calcineurin phosphatase activity. Calcineurin normally acts to increase activity of genes coding for IL-2 and other cytokines.

- ✓ A common indication is immunosuppression in the context of organ transplantation, but other indications include graft versus host disease and myasthenia gravis.

- ✓ Tacrolimus is predominantly metabolized by CYP3A4 with a half life of 23 to 46 hours for the immediate release form and 38 hours for the extended-release formulation. It is also a substrate of p-glycoprotein.

Central Nervous System Adverse Effects:

- ✓ The underlying mechanisms resulting in central nervous system related side effects are not fully understood, but damage to the blood-brain barrier, cerebral vasospasm, mitochondrial dysfunction, and subcortical edema has been suggested.

- ✓ Reported neuropsychiatric effects include seizures, visual disturbance (including cortical blindness), dysarthria and akinetic mutism, severe psychomotor disturbance, stupor, coma, delusions, psychosis, hallucinations, cerebellar ataxia, or asthenia.

- ✓ Risk factors: Blood concentrations above therapeutic levels, including CYP 3A34 inhibition. However, neuropsychiatric side effects can occur at therapeutic concentrations as well. Immediate release formulations may result in higher peak concentrations and have higher risk. Other risk factors include increased age, elevated blood pressure or impaired kidney function.

- ✓ The onset is variable and can occur weeks into therapy.

Other notable side effects:

- ✓ Diabetes mellitus
- ✓ Drug-induced thrombotic microangiopathy
- ✓ Hyperkalemia
- ✓ Hypertension
- ✓ Infection
- ✓ Malignancy
- ✓ Nephrotoxicity
- ✓ Neurotoxicity

Case Discussion:

- ✓ Sirolimus is a mTOR kinase inhibitor that is metabolised through CYP 3A4 and p-glycoprotein as well. Studies have found that using the two medications leads to increased incidence of toxicity, including nephrotoxicity, dyslipidemia, hemolytic uremic syndrome, and post transplant diabetes. A pharmacokinetic interaction has also been documented, in which concomitant use of the two agents leads to a reduction in tacrolimus level.

- ✓ Interestingly, this patient was found to have a supratherapeutic level. This suggests that a pharmacodynamic interaction between the two drugs, along with elevated serum concentrations could have led to his symptoms. The patient had his immunosuppressant medications briefly held with the guidance of transplant nephrology, and his symptoms of hallucinations and delusions improved suggesting a tacrolimus related side effect.

References:

Varghese J, Reddy MS, Venugopal K, Perumalla R, Narasimhan G, Arikichenin O, Shanmugam V, Shanmugam N, Srinivasan V, Jayanthi V, Rela M. Tacrolimus-related adverse effects in liver transplant recipients: its association with trough concentrations. Indian Journal of Gastroenterology. 2014 May;33:219-25.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-1212 (SK).