PHARMACOLOGICAL DIGEST

Nisamanee Satyapan

Department of Pharmacology, Pramongkutklao College of Medicine, Bangkok 10400, Thailand.

Oral Misoprostol Less Effective When Given on The Same Day As Mifepristone

Administration of mifepristone and oral misoprostol on the same day is not as effective in causing abortion within 24 hours as when the medications are given 48 hours apart, University of Pittsburgh researchers report. After giving 600 mg of mifepristone to 86 women seeking termination of pregnancy, Dr. Mitchell D. Creinin and colleagues randomized the patients to receive oral misoprostol 400 µg 6 to 8 hours later (group 1) or 48 hours later (group 2). Women in group 1 who did not abort were provided with an additional dose of misoprostol to take 48 hours after mifepristone, according to the research team's report in the May issue of the *British Journal of Obstetrics and Gynaecology*. Twenty-four hours after receiving misoprostol, 50% of the women in group 1 had complete abortions compared with 91% of the women in group 2, the researchers report. Two weeks after mifepristone administration, 95% of the women in group 1 had had a complete abortion, as had 98% of the women in group 2. In group 2, 68% of the women reported nausea, 36% reported vomiting and 20% diarrhea, Dr. Creinin's team notes. Studies of mifepristone and vaginal misoprostol have resulted in higher rates of complete abortion and "more rapid expulsion compared with oral misoprostol," Dr. Creinin and colleagues note."It is possible," they say, "that a regimen with vaginal misoprostol may hold promise for same-day treatment."
Br J Obstet Gynaecol 2001;108:469-473.
(http://diabetes.medscape.com/reuters/prof/2001/06/06.06/20010605elin003.html)

Sulfonylurea Receptor Polymorphism Increases Risk of Type 2 Diabetes

In the French population, a common genetic variation in sulfonylurea receptor 1 (SUR1), a protein of the ATP-sensitive potassium channel that plays a central role in glucose-induced insulin secretion, is associated with an increased risk of non-insulin dependent diabetes mellitus (NIDDM). Dr. Philippe Amouyel, of Institut Pasteur in Lille, France, and a multicenter team report the finding in the June 1st issue of the *American Journal of Medical Genetics*. Their study included 122 subjects with NIDDM, 70 of whom were treated with sulfonylureas, and 1,250 nondiabetic controls. The subjects were genotyped for the SUR1 intron 16-3t/c polymorphism. Only 21% of controls were homozygous for the c allele (ie., cc genotype), compared with 30% of NIDDM patients. Subjects with the cc genotype had a 70% increased risk NIDDM compared with tt genotypes, Dr. Amouyel told Reuters Health.
A link between SUR1 polymorphism and response to sulfonylurea therapy also emerged in the study. "NIDDM patients bearing at least one c allele and treated with sulfonylurea agents had fasting plasma triglyceride concentrations 35% lower than non-c-allele bearers," according to the researcher. These findings may allow physicians to treat NIDDM according to a patient's genetic makeup. Such pharmacogenetic approaches "offer the best short-term applications of genetics to human health management," Dr. Amouyel said. "Indeed, in such situations, genotyping will have a clear interest for the patient: to increase the chances to receive the most efficient drug and to avoid deleterious side effects."
Am J Med Genet 2001;101:4-8.
(http://diabetes.medscape.com/reuters/prof/2001/06/06.07/20010606epid001.html)

Antiviral Activity of Lovastatin against Respiratory Syncytial Virus In Vivo and In Vitro

Respiratory syncytial virus (RSV) is an important human pathogen that can cause severe and life-threatening respiratory infections in infants and immunocompromised adults. We have recently shown that the RSV F glycoprotein, which mediates viral fusion, binds to RhoA. One of the steps in RhoA activation involves isoprenylation at the carboxy terminus of the protein by geranyl-geranyltransferase. This modification allows RhoA to be attached to Phosphatidyl serine on the inner leaflet of the plasma membrane. Treatment of mice with lovastatin, a drug that inhibits prenylation pathways in the cell by

directly inhibiting hydroxymethylglutaryl coenzyme A reductase, diminishes RSV but not vaccinia virus replication when administered up to 24 h after RSV infection and decreases virus-induced weight loss and illness in mice. The inhibition of replication is not likely due to the inhibition of cholesterol biosynthesis, since gemfibrozil, another cholesterol-lowering agent, did not affect virus replication and serum cholesterol levels were not significantly lowered by lovastatin within the time frame of the experiment. Lovastatin also reduces cell-to-cell fusion in cell culture and eliminates RSV replication in HEp-2 cells. These data indicate that lovastatin, more specific isoprenylation inhibitors, or other pharmacological approaches for preventing RhoA membrane localization should be considered for evaluation as a preventive antiviral therapy for selected groups of patients at high risk for severe RSV disease, such as the institutionalized elderly and bone marrow or lung transplant recipients.
Antimicrob Agents Chemother 2001 Apr;45 (4):1231-7.

Efficacy of Zanamivir Against Avian Influenza A Viruses That Possess Genes Encoding H5N1 Internal Proteins and Are Pathogenic in Mammals

In 1997, an avian H5N1 influenza virus, A/Hong Kong/156/97 (A/HK/156/97), caused six deaths in Hong Kong; and in 1999, an avian H9N2 influenza virus infected two children in Hong Kong. These viruses and a third avian virus [A/Teal/HK/W312/97 (H6N1)] have six highly related genes encoding internal proteins. Additionally, A/chicken/HK/G9/97 (H9N2) virus has PB1 and PB2 genes that are highly related to those of A/HK/156/97 (H5N1), A/Teal/HK/W312/97 (H6N1), and A/Quail/ HK/G1/97 (H9N2) viruses. Because of their similarities with the H5N1 virus, these H6N1 and H9N2 viruses may have the potential for interspecies transmission. We demonstrated that these H6N1 and H9N2 viruses are pathogenic in mice but that their pathogenicities were less than that of A/HK/ 156/97 (H5N1). Unadapted virus replicated in lungs, but only A/HK/156/97 (H5N1) was found in the brain. After three passages (P3) in mouse lungs, the pathogenicity of the viruses increased, with both A/Teal/HK/W312/97 (H6N1) (P3) and A/Quail/HK/G1/97 (H9N2) (P3) viruses being found in the brain. The neuraminidase inhibitor zanamivir inhibited viral replication in Madin-Darby canine kidney cells in virus yield assays (50% effective concentration, 8.5 to 14.0 μM) and inhibited viral neuraminidase activity (50% inhibitory concentration, 5 to 10 nM). Twice daily intranasal administration of zanamivir (50 and 100 mg/kg of body weight) completely protected infected mice from death. At a dose of 10 mg/kg, zanamivir completely protected mice from infection with H9N2 viruses and increased the mean survival day and the number of survivors infected with H6N1 and H5N1 viruses. Zanamivir, at all doses tested, significantly reduced the virus titers in the lungs and completely blocked the spread of virus to the brain. Thus, zanamivir is efficacious in treating avian influenza viruses that can be transmitted to mammals.
Antimicrob Agents Chemother 2001 Apr;45 (4):1216-24.

Impact of Prophylaxis for Mycobacterium avium Complex on Bacterial Infections in Patients with Advanced Human Immunodeficiency Virus Disease

The epidemiology and natural history of bacterial infections among ambulatory patients with advanced human immunodeficiency virus (HIV) disease has not been well described. In this prospective study, 394 subjects were enrolled and followed at 8-week intervals for a median of 21 months. During follow-up, 164 (42%) of 394 patients developed at least 1 bacterial infection. The most common infections were sinusitis, bacterial pneumonia, skin and soft tissue infection, and bronchitis. Serious bacterial infections (defined as bacterial pneumonia, bacteremia, or deep visceral abscess) were reported in 56 subjects (14%). Female sex, age of <40 years, and Karnofsky score of ≤80 were independent risk factors for bacterial infections. Prophylaxis with clarithromycin, trimethoprim and sulfamethoxazole, or both, had significant protective effect. The occurrence of any confirmed bacterial infection was associated with a significantly increased risk of mortality. This study documents that bacterial infections are common among patients with advanced HIV disease, especially among women.
Clin Infect Dis 2001 Jun 1;32(11):1615-22.

Resistance to Trimethoprim - Sulfamethoxazole

Sulfonamides have a glorious history. In 1935, they were the first class of true antimicrobial agents with life-saving potency. Today, 66

agents with life-saving potency. Today, 66 years later, increased bacterial resistance to sulfonamides and to trimethoprim (TMP), a synthetic antimicrobial agent that is 30 years younger than sulfonamides, has limited their use to only a few indications. In the treatment and prophylaxis of patients with urinary tract infections, trimethoprim-sulfamethoxazole (TMP-SMZ) or TMP alone is still considered the first-line drug of choice, although increased bacterial resistance to these agents has been linked with treatment failure. TMP-SMZ has a possible role as a second- or third-line treatment for patients who have respiratory tract infections. In the developing world, where this inexpensive drug is widely used as first-line treatment, bacterial resistance has caused problems, especially with regard to the treatment of patients with severe respiratory tract infections. Use of TMP-SMZ as prophylaxis for *Pneumocystis carinii* infection has rapidly increased the multidrug resistance of bacterial pathogens found in human immu-nodeficiency virus-infected patients. Today, detailed and reliable knowledge on the resistance of bacterial pathogens to both TMP-SMZ and TMP is an essential requirement for the safe and effective use of these drugs in all clinical settings.
Clin Infect Dis 2001 Jun 1;32(11):1608-14.

Pseudomonas aeruginosa Reveals High Intrinsic Resistance to Penem Antibiotics: Penem Resistance Mechanisms and Their Interplay

Pseudomonas aeruginosa exhibits high intrinsic resistance to penem antibiotics such as faropenem, ritipenem, AMA3176, sulopenem, Sch29482, and Sch34343. To investigate the mechanisms contributing to penem resistance, we used the laboratory strain PAO1 to construct a series of isogenic mutants with an impaired multidrug efflux system MexAB-OprM and/or impaired chromosomal AmpC beta-lactamase. The outer membrane barrier of PAO1 was partially eliminated by inducing the expression of the plasmid-encoded *Escherichia coli* major porin OmpF. Susceptibility tests using the mutants and the OmpF expression plasmid showed that MexAB-OprM and the outer membrane barrier, but not AmpC beta-lactamase, were the main mechanisms involved in the high intrinsic penem resistance of PAO1. However, reducing the high intrinsic penem resistance of PAO1 to the same level as that of penem-susceptible gram-negative bacteria such as *E. coli* required the loss of either both MexAB-OprM and AmpC beta-lactamase or both MexAB-OprM and the outer membrane barrier. Competition experiments for penicillin-binding proteins (PBPs) revealed that the affinity of PBP 1b and PBP 2 for faropenem were about 1.8- and 1.5-fold lower, than the respective affinity for imipenem. Loss of the outer membrane barrier, MexAB, and AmpC beta-lactamase increased the susceptibility of PAO1 to almost all penems tested compared to the susceptibility of the AmpC-deficient PAO1 mutants to imipenem. Thus, it is suggested that the high intrinsic penem resistance of *P. aeruginosa* is generated from the interplay among the outer membrane barrier, the active efflux system, and AmpC beta-lactamase, but not from the lower affinity of PBPs for penems.
Antimicrob Agents Chemother 2001 Jul;45 (7):1964-71.