PHARMACOLOGICAL DIGEST

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Lipodystrophy Syndrome in Children Infected With Human Immunodeficiency Virus

Lipodystrophy syndrome (LDS) is a fat-wasting condition associated with abnormalities of lipid metabolism and impaired glucose tolerance. It is commonly reported in adults infected with human immunodeficiency virus (HIV) and has been linked to the use of protease inhibitors and possibly other antiretroviral agents. Whereas little is known for certain about this syndrome's occurrence in children, case reports recently have emerged from the pediatric population. The occurrence of LDS reported in the literature has a wide range of 1.5-83% of HIV-infected adults. The first reports of LDS prompted the Food and Drug Administration to issue a warning on June 11, 1997, stating that there was a risk of diabetes mellitus in patients receiving protease inhibitors. Fat redistribution, first known as "Crix belly" due to its association with indinavir (Crixivan), also was reported at that time.

Although no standard definition or generally accepted mechanism of pathophysiology exists, a working case definition of HIV-associated LDS has been proposed, attempting to encompass all possible aspects of the condition-physical features, fat redistribution, and metabolic features. Physical features and fat redistribution are defined as one or more of the following after starting antiretroviral therapy: fat wasting of the arms, legs, or buttocks, and fat accumulation in the abdomen or over the dorsocervical spine. Metabolic abnormalities commonly associated with LDS are as follows : fasting hyperlipidemia (total cholesterol > 214 mg/dl and/or triglycerides >174 mg/dl); fasting C peptide (> 7.5 mg/ml); impaired fasting blood glucose (110-126 mg/dl) or diabetes mellitus (fasting blood glucose > 126 mg/dl, or fasting blood glucose > 200 mg/dl on 2-hr blood glucose by oral glucose tolerance test); impaired glucose tolerance (blood glucose 140-200 mg/dl); lipid profile alterations such as elevated very low-density lipoprotein (VLDL) or low-density lipoprotein (LDL), or decreased high-density lipoprotein (HDL).

Several risk factors for LDS have been identified, including duration of HIV infection, duration of antiretroviral therapy, baseline body mass index, CD4+ cell count nadir and rebound from nadir, abnormal lipid levels before protease inhibitor treatment, and age. In addition, patients with LDS are concerned about increased risk of cardiac disease and the characteristic cosmetic changes identifying them as HIV infected. Because of these concerns and the possible long-term effects associated with LDS, causes of and strategies for treatment of LDS must be identified. *Pharmacotherapy 2001; 21(7):861-866.*

Indinavir Impairs Insulin Sensitivity and B-Cell Function

Indinavir-based therapy impairs insulin sensitivity and B-cell function in HIV-infected patients, according to the results of a study conducted at a university-based outpatient clinic. Though treatment of HIV infection with protease inhibitors has been associated with the development of diabetes, no prospective studies have examined their impact on insulin sensitivity or B-cell function.

Dr. Michael P. Dube, now with the Willard Memorial Hospital in Indianapolis, and colleagues from the University of Southern California School of Medicine in Los Angeles used oral and intravenous glucose tolerance testing to evaluate the impact of the initiation of indinavir-based therapy on insulin secretion and sensitivity in 11 HIV-infected subjects. All subjects responded to indinavir treatment with increases in CD4+ cell counts and decreases in HIV RNA plasma loads. Fasting plasma glucose rose significantly (but not to diabetic levels) during the course of the 8-week study, the report indicates, and insulin resistance increased, but not significantly.

Insulin sensitivity declined by nearly 31% during the study, the researchers note, but B cells failed to respond with a significant increase in insulin secretion. The serial development of reduced insulin sensitivity in a group of individuals who were initiating indinavir-based antiretroviral therapy was

documented. "The finding that plasma glucose concentration rose significantly and insulin secretion failed to increase commensurate with increases in insulin resistance suggests that protease inhibitor use may also be associated with defects in B-cell function".
These short-term findings may contribute to the development of diabetes mellitus and other clinical syndromes of insulin resistance in protease inhibitor-treated HIV-infected patients. Further studies are needed to explore the implications and pathogenesis of these abnormalities.
J Acquir Immune Defic Syndr 2001;27:130-134. (http://diabetes.medscape.com/41354.rhtml?srcmp=endo-081001)

Phase I Study Shows Fiber Can Reduce Side Effects of Orlistat

Ingestion of natural fiber can reduce the gastrointestinal side effects of anti-obesity prescription drug orlistat, according to study results reported in the *International Journal of Obesity*.
Orlistat, a gastrointestinal lipase inhibitor, is marketed by Swiss firm Roche. The diet aid is designed to prevent absorption of one third of consumed dietary fat and is usually prescribed for patients who are at least 30% overweight. Orlistat has been shown to "produce significant weight loss and reduction in metabolic risk factors" for a wide variety of obese patients. However, orlistat's side effects, including uncontrolled bowel movements, oily spotting and flatulence with discharge, have prevented a number of people from trying the drug.
Phase I study, conducted by Dr. Geraldo Medeiros-Neto and others at the University of Sao Paulo, explored the impact of a oncedaily dose of a fiber drink containing psyllium mucilloid on orlistat side effects. The researchers found that concomitant consumption of the orange-flavored fiber drink made orlistat "significantly more tolerable" for patients. In that study 60 patients received orlistat 120 mg three times daily with 6.0 g of fiber or with a placebo drink. After 30 days and a 2-week washout period, each group crossed over to the opposite regimen. Trial data showed that 29% of patients experienced orlistat side effects while receiving the fiber drink, compared with 71% while receiving placebo. In addition, patients seemed to experience orlistat side effects less intensely while receiving the fiber drink.
The results remained the same even when the protocol was changed later in the study so that patients received a nightly dose of 12.0 g of fiber, rather than a 6.0 g dose three times daily. The researchers theorize that psyllium mucilloid, a natural water-soluble fiber that has been shown to lower serum cholesterol levels, also helped to absorb the fat blocked by orlistat. All patients in the trial lost weight, regardless of their fiber intake.
(http://diabetes.medscape.com/reuters/prof/2001/08/08.27/20010824clin004.html)

Estrogen Improves Cognitive Function in Women With Alzheimer's Disease

High doses of estradiol delivered by skin patch appear to be able to improve memory and attention skills in women with Alzheimer's disease, according to the results of a pilot study reported in the August 28th issue of *Neurology*. There have been conflicting findings of estrogen effects in women with Alzheimer's disease, told Reuters Health. While some studies have shown positive results, three recent studies have shown negative results, Dr. Sanjay Asthana, of the University of Wisconsin School of Medicine in Madison noted.
Dr. Asthana and colleagues at the VA Puget Sound Health Care System in Tacoma and elsewhere randomly assigned 20 postmenopausal women diagnosed with probable Alzheimer's disease to receive 0.10 mg/day of 17-beta-estradiol by skin patch or placebo. Neuropsychologic tests were given at baseline and during week 3, 5 and 8 of treatment, and again 16 weeks after treatment ended. Women receiving estradiol showed an improvement from baseline in selective attention as demonstrated by results of the Stroop Color World Interference Test, which they were able to complete more quickly than patients receiving placebo. Improved performance from baseline in verbal and visual recent memory was also observed in estradiol-treated patients compared with placebo patients. In addition, women on estradiol were able to name more pictures on the Boston Naming Test compared with women on placebo. However, there was no general improvement in cognition, the beneficial effects of estrogen were targeted only to certain domains of cognition, Dr. Asthana said. The gains in attention, verbal, visual and semantic memory seen in the estradiol group deteriorated after treatment was stopped and most women returned to their pretreatment level, he added. Dr. Asthana believes that the form of estrogen used is important, and may

explain the various findings of previous studies. He also suggests that the results of this small study may be used to develop larger trials.
Neurology 2001;57:605-612.

One Million US Children May Use Performance Enhancing Drugs

One million US children between the ages of 12 and 17 years old may be taking performance-enhancing substances, according to a new survey. In addition, one in five young people between the ages of 10 and 17 years old report they know someone who has taken supplements or drugs to improve their athletic performance, build muscle or "look better". The survey, conducted by telephone with 785 randomly selected youth between 10 and 17 years old and 1,002 adults, was commissioned by the Blue Cross and Blue Shield Association (BCBSA).
Creatine was the performance enhancer cited most often, with 57% of the youth surveyed saying they knew someone who took it. Steroids were the next most frequently cited drugs, with 31% of youth knowing someone who had taken them. Creatine supplementation as a performance enhancer is based on the idea that extra creatine will help muscles work harder and longer. Creatine is available as an over-the-counter supplement, and has been added to some food products, including "Cookies n' Creatine", a "sports energy" bar. One web site sells "Teen Creatine Advantage", a supplement "developed especially for aspiring athletes 11 to 19 years of age".
Creatine's side effects include cramps, dehydration and nausea, and the supplement may cause kidney damage. Little research has been done on its effects in young people. "We think the supplements industry should not be allowed to market products to children under 18", said Iris Shaffer, executive director of the Healthy Competition Foundation, formed by BCBSA in September 1999 to provide the public with information on the potential dangers of performance-enhancing drugs and supplements.
The survey also found that 70% of children and 50% of adults could not name any dangerous side effects of performance enhancers, although 37% of the adults said the use of these substances was their greatest concern in youth sports. Four in five youths said they had not talked to their parents about performance enhancers. Among the adults, 45% said they did not know enough about these supplements and drugs to talk to their children about them, and 64% said they never talked to their kids about these substances. According to projections based on the survey results, 390,000 10- to 14-year-olds have taken performance enhancers. A similar survey commissioned by BCBSA in 1999 found no children under 14 who reported taking these substances.
(http://diabetes.medscape.com/ reuters/prof/ 2001/08/08.29/ 20010828publ001.html)

Phytoestrogen Intake of US Women Does Not Reduce Breast Cancer Risk

While several epidemiologic studies involving Asian populations have suggested that phytoestrogen consumption may lower the risk of breast cancer, levels of phytoestrogens commonly consumed by non-Asian women in the USA do not appear to protect against the disease.
Dr. Pamela L. Horn-Ross from the Northern California Cancer Center in Union City and colleagues compared the phytoestrogen intake of 1,326 women who developed breast cancer with that of 1,657 women randomly selected from the general population. The breast cancer group included African-American, Latina, and White US women, 35 to 79 years of age, who were diagnosed between 1995 and 1998.
The researchers found no correlation between total phytoestrogen intake and breast cancer risk; the odds ratio was 1.0 for the highest versus lowest quartiles of intake. This lack of association held true even after considering the woman's menopausal status, ethnic background, and the type of phytoestrogen consumed. Soy milk and soy burger consumption was linked to a reduced risk of breast cancer, but only a small percentage of case and control subjects consumed these products. The highest average intake of phytoestrogens in the study population was only 3 mg/day, a level equivalent to less than one serving of tofu per week. In contrast, the average intake of phytoestrogens in Asian countries has been estimated to range from about 15 to 30 mg/day. Thus, it is possible that non-Asian US women are not reaching a level of intake that may reduce the risk of breast cancer.
Am J Epidemiol 2001;154:434-441.

Endometriosis May Be an Autoimmune Disease

Immunomodulating therapy may be an alternative to traditional estrogens as a treatment for endometriosis. Dr. Warren B. Nothnick, of the University of Kansas Medical Center in Kansas City, said that in a review of the literature he found "overwhelming evidence" of a role for immunologic factors, particularly cytokines, in the pathophysiology and etiology of endometriosis.

In particular, research results show that levels of tumor necrosis factor alpha (TNF-alpha) are elevated in patients with endometriosis. Given the success of TNF-alpha inhibitors in treating other immunologic disorders, Dr. Nothnick proposed examining these therapies as an option for treating endometriosis. Disturbed levels of other cytokines, cell apoptosis, and T- and B-cell abnormalities have also been observed in patients with endometriosis. However, researchers and physicians need to be aware of that many factors and pathways can contribute to the growth and progression of endometriosis and the cytokines may be one commonality among these factors or pathways. While for now there is only a small amount of evidence to support an immunologic approach to treating endometriosis, it is need to explore all possibilities and take advantage of today's technologies. A treatment that could suppress the disease and its symptoms independently of compromising a women's reproductive cyclicity would hold great promise.

Fertil Steril 2001;76:223-231.

High-Dose Acetaminophen Associated With High Risk of Peptic Ulcer

Patients who take acetaminophen at dosages exceeding 2 grams per day are at nearly four times the risk of peptic ulcer compared with non-users. The risk skyrockets when non-steroidal anti-inflammatory drugs (NSAIDs) and high-dose acetaminophen are taken together.

Dr. Luis Alberto Garca Rodroguez, of the Centro Espanol de Investigation Farmacoepidemiologica in Madrid, Spain, and Dr. Sonia Hernondez-Daz, of Harvard School of Public Health in Boston, evaluated the association between acetaminophen and NSAIDs and upper GI complications. They also evaluated the effects of various gastroprotective agents. The cases were 2,105 patients, aged 40 to 79, diagnosed with peptic ulcer. The 11,500 control subjects were matched by age and gender. Use of acetaminophen at any dose was associated with a relative risk of 1.3. Adding NSAIDs to acetaminophen at less than 2 grams daily did not increase the 4.1-fold increased risk associated with NSAID use alone. When the daily dosage was more than 2 grams, the relative risk increased to 3.6. However, when NSAIDs were combined with acetaminophen at 2 grams per day or more, the relative risk was 13.2. Drs. Rodriguez and Hernandez-Diaz noted that "acetaminophen is a weak nonselective inhibitor of both isoforms of cyclooxygenase." The exacerbated risk associated with high-dose acetaminophen and NSAIDs is likely due to augmentation of cyclooxygenase inhibition. The researchers also reported for the first time that the risks associated with the newer NSAIDs etodolac, meloxicam and nabumetone were comparable to those of "the average NSAID effect". Dosage was the most significant factor associated with risk due to NSAIDs, although longer plasma half-life or slow-released formulation also increased the risk. Apazone was the only NSAID that at the daily doses used (600 mg to 1,200 mg) was associated with a relative risk of upper GI complications distinctively greater than the average NSAID relative risk.

H_2 receptor antagonists did not lower the risk of peptic ulcers. However, omeprazole, misoprostol, and nitrates decreased the risk among users of NSAIDs.

Epidemiology 2001;12:570-576.