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Journal ABSTRACTS

Acetaminophen

SEVERE HEPATOTOXICITY AFTER THERAPEUTIC DOSES OF ACETAMINOPHEN.

BACKGROUND: Acetaminophen overdose is a frequent cause of acute liver failure. Controversy exists over the rare association of severe hepatotoxicity or acute liver failure with therapeutic doses of acetaminophen. **CASE SUMMARY:** A 45-year-old white man weighing 85 kg with asymptomatic HIV, hepatitis B virus, and hepatitis C virus (HCV) infection presented with signs of severe hepatotoxicity: aspartate aminotransferase (AST), 8,581 IU/L; alanine aminotransferase (ALT), 5,433 IU/L; L-lactate dehydrogenase, 13,641 IU/L; and prothrombin international normalized ratio, 2.15. He reported taking acetaminophen 1,000 mg QID for the previous 4 days and 1,000 mg that morning because of a febrile illness. Immediate administration of continuous IV N-acetylcysteine 150 mg/kg for the first 90 minutes and then 50 mg/kg q4h for the next 3 days was followed by clinical improvement and a rapid decrease in AST and ALT. AST levels decreased from 8,581 to 42 IU/L within 11 days. Several potential risk factors for acetaminophen hepatotoxicity (ie, chronic alcohol, tobacco, and opiate consumption, malnutrition, illness-induced starvation, HIV infection, and HCV infection) were present in this patient. **CONCLUSIONS:** This patient with multiple risk factors and severe hepatotoxicity after therapeutic dosage of acetaminophen was successfully treated with N-acetylcysteine.

Clin Ther. 2006 May;28(5):755-60

ESTIMATES OF ACETAMINOPHEN (PARACETOMAL)-ASSOCIATED OVERDOSES IN THE UNITED STATES.

OBJECTIVE: To estimate the number of acetaminophen-associated overdoses in the United States and identify possible risk factors for intervention. **METHODS:** The investigators obtained estimates of acetaminophen-associated overdoses using different national databases. Two emergency room databases, a hospital discharge database, a national mortality file, and a poison surveillance database were used to identify cases. The FDA's spontaneous reporting system was searched to identify possible root causes for overdoses. **RESULTS:** Analysis of national databases show that acetaminophen-associated overdoses account for about 56,000 emergency room visits and 26,000 hospitalizations yearly. Analysis of national mortality files shows 458 deaths occur each year from acetaminophen-associated overdoses; 100 of these are unintentional. The poison surveillance database showed near-doubling in the number of fatalities associated with acetaminophen from 98 in 1997 to 173 in 2001. AERS data describe a number of possible causes for unintentional acetaminophen-associated overdoses. **CONCLUSIONS:** Each year a substantial numbers of Americans experience intentional and unintentional acetaminophen-associated overdoses that, in severe cases, lead to serious illness and possible death. This summary of a series of analyses highlights the need for strategies to reduce this public health burden.

Pharmacoepidemiol Drug Saf. 2006 Jun;15(6):398-405

ACETAMINOPHEN-INDUCED ACUTE LIVER FAILURE: RESULTS OF A UNITED STATES MULTICENTER, PROSPECTIVE STUDY.

Severe acetaminophen hepatotoxicity frequently leads to acute liver failure (ALF). We determined the incidence, risk factors, and outcomes of acetaminophen-induced ALF at 22 tertiary care centers in the United States. Detailed prospective data were gathered on 662 consecutive patients over a 6-year period fulfilling standard criteria for ALF (coagulopathy and encephalopathy), from which 275 (42%) were determined to result from acetaminophen liver injury. The annual percentage of acetaminophen-related ALF rose during the study from 28% in 1998 to 51% in 2003. Median dose ingested was 24 g (equivalent to 48 extra-strength tablets). Unintentional overdoses accounted for 131 (48%) cases, intentional (suicide attempts) 122 (44%), and 22 (8%) were of unknown intent. In the unintentional group, 38% took two or more acetaminophen preparations simultaneously, and 63% used narcotic-containing compounds. Eighty-one percent of unintentional patients reported taking acetaminophen and/or other analgesics for acute or chronic pain syndromes. Overall, 178 subjects (65%) survived, 74 (27%) died without transplantation, and 23 subjects (8%) underwent liver transplantation; 71% were alive at 3 weeks. Transplant-free survival rate and rate of liver transplantation were similar between intentional and unintentional groups. In conclusion, acetaminophen hepatotoxicity far exceeds other causes of acute liver failure in the United States. Susceptible patients have concomitant depression, chronic pain, alcohol or narcotic use, and/or take several preparations simultaneously. Education of patients, physicians, and pharmacies to

limit high-risk use settings is recommended.

Hepatology. 2005 Dec;42(6):1364-72

AMINOTRANSFERASE ELEVATIONS IN HEALTHY ADULTS RECEIVING 4 GRAMS OF ACETAMINOPHEN DAILY: A RANDOMIZED CONTROLLED TRIAL.

CONTEXT: During a clinical trial of a novel hydrocodone/acetaminophen combination, a high incidence of serum alanine aminotransferase (ALT) elevations was observed. **OBJECTIVE:** To characterize the incidence and magnitude of ALT elevations in healthy participants receiving 4 g of acetaminophen daily, either alone or in combination with selected opioids, as compared with participants treated with placebo. **DESIGN, SETTING, AND PARTICIPANTS:** A randomized, single-blind, placebo-controlled, 5-treatment, parallel-group, inpatient, diet-controlled (meals provided), longitudinal study of 145 healthy adults in 2 US inpatient clinical pharmacology units. **INTERVENTION:** Each participant received either placebo (n = 39), 1 of 3 acetaminophen/opioid combinations (n = 80), or acetaminophen alone (n = 26). Each active treatment included 4 g of acetaminophen daily, the maximum recommended daily dosage. The intended treatment duration was 14 days. **Main Outcomes** Serum liver chemistries and trough acetaminophen concentrations measured daily through 8 days, and at 1- or 2-day intervals thereafter. **RESULTS:** None of the 39 participants assigned to placebo had a maximum ALT of more than 3 times the upper limit of normal. In contrast, the incidence of maximum ALT of more than 3 times the upper limits of normal was 31% to 44% in the 4 treatment groups receiving acetaminophen, including those participants treated with acetaminophen alone. Compared with placebo, treatment with acetaminophen was associated with a markedly higher median maximum ALT (ratio of medians, 2.78; 95% confidence interval, 1.47-4.09; P<.001). Trough acetaminophen concentrations did not exceed therapeutic limits in any participant and, after active treatment was discontinued, often decreased to undetectable levels before ALT elevations resolved. **CONCLUSIONS:** Initiation of recurrent daily intake of 4 g of acetaminophen in healthy adults is associated with ALT elevations and concomitant treatment with opioids does not seem to increase this effect. History of acetaminophen ingestion should be considered in the differential diagnosis of serum aminotransferase elevations, even in the absence of measurable serum acetaminophen concentrations.

JAMA. 2006 Jul 5;296(1):87-93

DRUG-INDUCED CARDIOVASCULAR DISORDERS.

As the variety and range of pharmaceutical agents available to the medical profession continues to expand, one unavoidable effect will be an increase in drug-induced disease, including cardiovascular disorders. However, given the high rates of cardiovascular disease and prevalence of recognised cardiovascular risk factors in the population, it is sometimes impossible to conclusively attribute any individual patients' ill health to one particular drug. As a result, the relationship between drugs and cardiovascular disease is often difficult to quantify. This review discusses specific forms of drug-induced cardiovascular disease such as heart failure, left ventricular systolic dysfunction, hypertension and arrhythmia. Suspected culprit drugs for all disorders are highlighted. Specific attention is given to certain drug groups with a strong association with one or more forms of cardiovascular disease: these include anthracyclines, antipsychotics, NSAIDs and cyclo-oxygenase 2 inhibitors. Additionally, advice is offered on how physicians might distinguish drug-induced cardiovascular disorders from other aetiologies.

Drug Saf. 2007;30(9):783-804

HOW TO ADVISE ASPIRIN USE IN PATIENTS WHO NEED NSAIDS.

NSAIDs are widely used all over the world. NSAID use is rising due to increasing availability without a prescription, use of aspirin for prevention of thrombotic disorders and the ageing population. Aspirin is used as an analgesic drug in many countries, but the main current indication is low-dose aspirin for the prevention of cardiovascular events. However, NSAIDs and aspirin use account for approximately 20-25% of all reported drug adverse events. Most of those are gastrointestinal including dyspepsia, hemorrhage, perforation and even death. The COX-2- selective inhibitors (coxibs) have demonstrated equivalent efficacy to nonspecific NSAIDs in the management of arthritis and pain but have less gastrointestinal adverse events, although coxibs and probably all NSAIDs, significantly increase risk of serious thromboembolic events. Concomitant use of low-dose aspirin is present in more than 20% of all patients taking either NSAIDs or coxibs, thus increasing the risk of gastrointestinal side effects. Furthermore, at present, it is not known whether aspirin decreases the cardiovascular risks of COX-2 inhibitors or NSAIDs. Appropriate strategies for gastrointestinal risk reduction with NSAIDs and aspirin must consider the overall health status of our patients including the presence of cardiovascular and gastrointestinal risk factors. Use of the lowest possible dose of these drugs, gastroprotectants, especially proton pump inhibitors and Helicobacter pylori eradication will reduce the risk of gastrointestinal side effects in patients taking low-dose aspirin and NSAIDs or coxibs.

Curr Pharm Des. 2007;13(22):2248-60

N-ACETYLCYSTEINE--A SAFE ANTIDOTE FOR CYSTEINE/GLUTATHIONE DEFICIENCY.

Glutathione (GSH) deficiency is associated with numerous pathological conditions. Administration of N-acetylcysteine (NAC), a cysteine prodrug, replenishes intracellular GSH levels. NAC, best known for its ability to counter acetaminophen toxicity, is a safe, well-tolerated antidote for cysteine/GSH deficiency. NAC has been used successfully to treat GSH deficiency in a wide range of infections, genetic defects and metabolic disorders, including HIV infection and COPD. Over two-thirds of 46 placebo-controlled clinical trials with orally administered NAC have indicated beneficial effects of NAC measured either as trial endpoints or as general measures of improvement in quality of life and well-being of the patients.

Curr Opin Pharmacol. 2007 Aug;7(4):355-9. Epub 2007 Jun 29

WHEY PROTEIN CONCENTRATE PROMOTES THE PRODUCTION OF GLUTATHIONE (GSH) BY GSH REDUCTASE IN THE PC12 CELL LINE AFTER ACUTE ETHANOL EXPOSURE.

Excessive ethanol consumption may increase the production of reactive oxygen species (ROS), which results in the damage of tissues, especially the neurons and glial cells in the central nervous system (CNS). The purpose of this study is to evaluate the effects of whey protein concentrate (WPC) on the glutathione (GSH) status after acute ethanol exposure in the pheochromocytoma (PC12) cell line. In this study, we assayed the cell viability, the percentage of lactate dehydrogenase released (% LDH released), the level of GSH, and the activity of GSH reductase (GRx). The results showed that with the supplement of WPC, the cell viability displayed no significant difference after acute exposure of ethanol in groups with or without ethanol treatment. The ethanol-induced cytotoxicity showed a slight decrease, and the level of GSH showed a significant increase. The activity of GRx significantly increased when 0.1, 10mg/ml of WPC was supplied. In conclusion, these results suggest that WPC in a moderate concentration should be a precursor agent to promote the production of GSH and will enhance the antioxidant capacity in the PC12 cell line.

Food Chem Toxicol. 2006 Apr;44(4):574-8. Epub 2005 Dec 19

SILYMARIN PROTECTS AGAINST PARACETAMOL-INDUCED LIPID PEROXIDATION AND LIVER DAMAGE.

The effect of silymarin on liver damage induced by acetaminophen (APAP) intoxication was studied. Wistar male rats pretreated (72 h) with 3-methylcholanthrene (3-MC) (20 mg kg⁻¹ body wt. i.p.) were divided into three groups: animals in group 1 were treated with acetaminophen (APAP) (500 mg kg⁻¹ body wt. p.o.), group 2 consisted of animals that received APAP plus silymarin (200 mg kg⁻¹ body wt. p.o.) 24 h before APAP, and rats in group 3 (control) received the equivalent amount of the vehicles. Animals were sacrificed at different times after APAP administration. Reduced glutathione (GSH), lipid peroxidation and glycogen were measured in liver and alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGTP) and glutamic pyruvic transaminase (GPT) activities were measured in serum. After APAP intoxication, GSH and glycogen decreased very fast (1 h) and remained low for 6 h. Lipid peroxidation increased three times over the control 4 and 6 h after APAP treatment. Enzyme activities increased 18 h after intoxication. In the group receiving APAP plus silymarin, levels of lipid peroxidation and serum enzyme activities remained within the control values at any time studied. The fall in GSH was not prevented by silymarin, but glycogen was restored at 18 h. It was concluded that silymarin can protect against APAP intoxication through its antioxidant properties, possibly acting as a free-radical scavenger.

J Appl Toxicol. 1992 Dec;12(6):439-42

PHOTO-THERMAL TUMOR ABLATION IN MICE USING NEAR INFRARED-ABSORBING NANOPARTICLES.

The following study examines the feasibility of nanoshell-assisted photo-thermal therapy (NAPT). This technique takes advantage of the strong near infrared (NIR) absorption of nanoshells, a new class of gold nanoparticles with tunable optical absorptivities that can undergo passive extravasation from the abnormal tumor vasculature due to their nanoscale size. Tumors were grown in immune-competent mice by subcutaneous injection of murine colon carcinoma cells (CT26.WT). Polyethylene glycol (PEG) coated nanoshells (approximately 130 nm diameter) with peak optical absorption in the NIR were intravenously injected and allowed to circulate for 6 h. Tumors were then illuminated with a diode laser (808 nm, 4 W/cm², 3 min). All such treated tumors abated and treated mice appeared healthy and tumor free >90 days later. Control animals and additional sham-treatment animals (laser treatment without nanoshell injection) were euthanized when tumors grew to a predetermined size, which occurred 6-19 days post-treatment. This simple, non-invasive procedure shows great promise as a technique for selective photo-thermal tumor ablation.

Cancer Lett. 2004 Jun 25;209(2):171-6

THERMAL DOSIMETRY PREDICTIVE OF EFFICACY OF ¹¹¹IN-CHL6 NANOPARTICLE AMF—INDUCED THERMOABLATIVE THERAPY FOR HUMAN BREAST CANCER IN MICE.

Antibody (mAb)-linked iron oxide nanoparticles (bioprobes) provide the opportunity to develop tumor specific thermal therapy (Rx) for metastatic cancer when inductively heated by an externally applied alternating magnetic field (AMF). To evaluate the potential of this Rx, in vivo tumor targeting, efficacy, and predictive radionuclide-based heat dosimetry were studied using (¹¹¹In)-ChL6 bioprobes (ChL6 is chimeric L6) in a human breast cancer xenograft model. METHODS: Using carbodiimide, (¹¹¹In)-DOTA-ChL6 (DOTA is dodecanetetraacetic acid) was conjugated to polyethylene glycol-iron oxide-impregnated dextran 20-nm particles and purified as (¹¹¹In)-bioprobes. (¹¹¹In) doses of 740-1,110 kBq (20-30 μCi) (2.2 mg of bioprobes) were injected intravenously into mice bearing HBT3477 human breast cancer xenografts. Pharmacokinetic (PK) data were obtained at 1, 2, 3, and 5 d. AMF was delivered 72 h after bioprobe injection at amplitudes of 1,410 (113 kA/m), 1,300 (104 kA/m), and 700 (56 kA/m) oersteds (Oe) at 30%, 60%, and 90% "on" time (duty), respectively, and at 1,050 Oe (84 kA/m) at 50% and 70% duty over the 20-min treatment. Treated and control mice were monitored for 90 d. Tumor total heat dose (THD) from activated tumor bioprobes was calculated for each Rx group using (¹¹¹In)-bioprobe tumor concentration and premeasured particle heat response to AMF amplitudes. Tumor growth delay was analyzed by Wilcoxon rank sum comparison of time to double, triple, and quintuple tumor volume in each group, and all groups were compared with the controls. RESULTS: Mean tumor concentration of (¹¹¹In)-bioprobes at 48 h was 14 +/- 2 percentage injected dose per gram; this concentration 24 h before AMF treatment was used to calculate THD. No particle-related toxicity was observed. Toxicity was observed at the highest AMF amplitude-duty combination of 1,300 Oe and 60% over 20 min; 6 of 10 mice died acutely. Tumor growth delay occurred in all of the other groups, correlated with heat dose and, except for the lowest heat dose group, was statistically significant when compared with the untreated group. Electron microscopy showed (¹¹¹In)-bioprobes on tumor cells and cell death by necrosis at 24 and 48 h after AMF. CONCLUSION: mAb-guided bioprobes (iron oxide nanoparticles) effectively targeted human breast cancer xenografts in mice. THD, calculated using empirically observed (¹¹¹In)-bioprobe tumor concentration and in vitro nanoparticle heat induction by AMF, correlated with tumor growth delay.

J Nucl Med. 2007 Mar;48(3):437-44

BACTERIALLY DERIVED 400 NM PARTICLES FOR ENCAPSULATION AND CANCER CELL TARGETING OF CHEMOTHERAPEUTICS.

Systemic administration of chemotherapeutic agents results in indiscriminate drug distribution and severe toxicity. Here we report a technology potentially overcoming these shortcomings through encapsulation and cancer cell-specific targeting of chemotherapeutics in bacterially derived 400 nm minicells. We discovered that minicells can be packaged with therapeutically significant concentrations of chemotherapeutics of differing charge, hydrophobicity, and solubility. Targeting of minicells via bispecific antibodies to receptors on cancer cell membranes results in endocytosis, intracellular degradation, and drug release. This affects highly significant tumor growth inhibition and regression in mouse xenografts and case studies of lymphoma in dogs despite administration of minute amounts of drug and antibody; a factor critical for limiting systemic toxicity that should allow the use of complex regimens of combination chemotherapy.

NANOPARTICLES AS IMAGE ENHANCING AGENTS FOR ULTRASONOGRAPHY.

Nanoparticles have drawn great attention as targeted imaging and/or therapeutic agents. The small size of the nanoparticles allows them to target cells that are beyond capillary vasculature, such as cancer cells. We investigated the effect of solid nanoparticles for enhancing ultrasonic grey scale images in tissue phantoms and mouse livers *in vivo*. Silica nanospheres (100 nm) were dispersed in agarose at 1-2.5% mass concentration and imaged by a high-resolution ultrasound imaging system (transducer centre frequency: 30 MHz). Polystyrene particles of different sizes (500-3000 nm) and concentrations (0.13-0.75% mass) were similarly dispersed in agarose and imaged. Mice were injected intravenously with nanoparticle suspensions in saline. B-mode images of the livers were acquired at different time points after particle injection. An automated computer program was used to quantify the grey scale changes. Ultrasonic reflections were observed from nanoparticle suspensions in agarose gels. The image brightness, i.e., mean grey scale level, increased with particle size and concentration. The mean grey scale of mouse livers also increased following particle administration. These results indicated that it is feasible to use solid nanoparticles as contrast enhancing agents for ultrasonic imaging.

Phys Med Biol. 2006 May 7;51(9):2179-89. Epub 2006 Apr 10

Thyroid

HYPERTHYROIDISM

Hyperthyroidism is a clinical situation where there is excess thyroid hormones in the circulation due to increased synthesis of hormone from a hyperactive thyroid gland. Common causes are Graves' disease, toxic multinodular goitre and toxic solitary nodule. Excess thyroid hormones in the circulation are also found in thyroiditis (hormone leakage) and excess exogenous thyroxine intake. Thyrotoxicosis is the term applied when there is excess thyroid hormone in the circulation due to any cause. Thyrotoxicosis can be easily diagnosed by high serum level of thyroxine (T4) and triiodothyronine (T3) and low serum level of thyroid stimulating hormone (TSH). Hyperthyroidism is confirmed by high isotope (I 131 or Tc99) uptake by the thyroid gland, while in thyroiditis it will be low. Treatment of hyperthyroidism depends on the underlying cause. Antithyroid drugs, 1131 therapy and surgery are the options of treatment of hyperthyroidism. Surgery is the preferred treatment for toxic adenoma and toxic multinodular goitre, while 1131 therapy may be suitable in some cases. Antithyroid drugs and 1131 therapy are mostly preferred for Graves' disease. Beta-adrenergic blockers are used for symptomatic relief in most patients of thyrotoxicosis due to any cause. Other rare causes of hyperthyroidism like, amiodarone induced thyrotoxicosis, choriocarcinoma, thyrotropin secreting pituitary tumour are difficult to diagnose as well as to treat.

J Indian Med Assoc. 2006 Oct;104(10):563-4, 566-7

AUTOIMMUNE THYROID DISEASES.

PURPOSE OF REVIEW: Interesting clinical and basic studies have been published in the field of autoimmune thyroiditis (represented by Graves' disease and Hashimoto's thyroiditis) since January 2005. The review is organized into four main areas: genetics, environment, adaptive immune system, and innate immune system. **RECENT FINDINGS:** The quest continues for the identification of susceptibility genes for autoimmune thyroiditis. In addition to the classical major histocompatibility complex class II genes and cytotoxic T cell antigen-4, new studies have appeared on CD40 the protein tyrosine phosphatase-22. Too much iodine increases the incidence of Hashimoto's thyroiditis, perhaps by augmenting the antigenicity of thyroglobulin. T regulatory cells, Toll-like receptors and presentation of lipid antigens by CD1 molecules are new areas of basic immunological investigation that have been applied to autoimmune thyroiditis. **SUMMARY:** Overall, the studies have greatly expanded our understanding of the pathogenesis of thyroiditis. They have opened new lines of investigations that will ultimately result in a better clinical practice.

Curr Opin Rheumatol. 2007 Jan;19(1):44-8

MUSCLE CARNITINE IN HYPO- AND HYPERTHYROIDISM.

Weakness is common in both hyper- and hypothyroidism, and skeletal muscle L-carnitine may play a role in this regard, as suggested by studies indicating abnormal levels of carnitine in serum and urine of patients with thyroid dysfunction. Skeletal muscle samples were obtained for carnitine analysis from control subjects, and from hyperthyroid and hypothyroid patients before and after treatment. There was a significant reduction in carnitine, especially the esterified portion, in hyperthyroid individuals, with a return to normal as euthyroid status was regained. In hypothyroid patients, there was a trend for carnitine to be lower than normal and for improvement once euthyroid status was attained. Our data indicate that muscle carnitine levels are affected by both hypo- and hyperthyroidism. A decrease in muscle carnitine in both conditions may contribute to thyroid myopathy.

Muscle Nerve. 2005 Sep;32(3):357-9

THYROTOXICOSIS AND THYROID STORM.

Thyroid storm represents the extreme manifestation of thyrotoxicosis as a true endocrine emergency. Although Grave's disease is the most common underlying disorder in thyroid storm, there is usually a precipitating event or condition that transform the patient into life-threatening thyrotoxicosis. Treatment of thyroid storm involves decreasing new hormone synthesis, inhibiting the release of thyroid hormone, and blocking the peripheral effects of thyroid hormone. This multidrug, therapeutic approach uses thionamides, iodine, beta-adrenergic receptor antagonists, corticosteroids in certain circumstances, and supportive therapy. Certain conditions may warrant the use of alternative therapy with cholestyramine, lithium carbonate, or potassium perchlorate.

After the critical illness of thyroid storm subsides, definitive treatment of the underlying thyrotoxicosis can be planned.

Endocrinol Metab Clin North Am. 2006 Dec;35(4):663-86

CARNITINE IS A NATURALLY OCCURRING INHIBITOR OF THYROID HORMONE NUCLEAR UPTAKE.

Carnitine (3-hydroxy-4N-trimethylammoniumbutanoate) is a naturally occurring quaternary amine that is ubiquitous in mammalian tissues (concentrations in the order of mM). Based on limited studies of approximately 40 years ago, carnitine was considered to be a peripheral antagonist of thyroid hormone (TH) action. These interesting observations have not been explored. To study the biologic basis of this effect, we tested the following possibilities in three TH-responsive cell lines: (1) inhibition of TH entry into cells; (2) inhibition of TH entry into the nucleus; (3) inhibition of TH interaction with the isolated nuclei; and (4) facilitated efflux of TH from cells. On a preliminary basis we had verified that these cell lines (human skin fibroblasts, human hepatoma cells HepG2, and mouse neuroblastoma cells NB 41A3) take up ¹⁴Ccarnitine; however, there was no ¹⁴Ccarnitine uptake into the nuclei. Concentrations of unlabeled carnitine as high as 100 mM did not affect (125I)T3 binding to isolated nuclei or exit of TH from cells, thus excluding possibilities numbered 3 and 4. At 10 mM carnitine, (125I)T3 and (125I)T4 whole-cell uptake was inhibited by approximately 20% in fibroblasts and in HepG2, but by approximately 5% in NB 41A3 cells. Inhibition of T3 nuclear uptake was evaluated in HepG2 and NB 41A3 cells. At 10 mM carnitine, inhibition of T3 nuclear uptake was disproportionately higher, namely approximately 25% in neurons and 35% in hepatocytes. At 50 mM carnitine, there was a minimal additional decrease in whole-cell uptake of either hormone but a marked decrease in T3 nuclear uptake. The latter inhibition was approximately 60% in neurons and 70% in hepatocytes. We are aware of no inhibitor of TH uptake that has such a markedly different effect on the nuclear versus whole-cell uptake. Our data are consistent with carnitine being a peripheral antagonist of TH action, and they indicate a site of inhibition at or before the nuclear envelope.

Thyroid. 2000 Dec;10(12):1043-50

USEFULNESS OF L-CARNITINE, A NATURALLY OCCURRING PERIPHERAL ANTAGONIST OF THYROID HORMONE ACTION, IN IATROGENIC HYPERTHYROIDISM: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL.

Old studies in animals and unblinded studies in a few hyperthyroid patients suggested that L-carnitine is a peripheral antagonist of thyroid hormone action at least in some tissues. This conclusion was substantiated by our recent observation that carnitine inhibits thyroid hormone entry into the nucleus of hepatocytes, neurons, and fibroblasts. In the randomized, double-blind, placebo-controlled 6-month trial reported here, we assessed whether 2 or 4 g/d oral L-carnitine were able to both reverse and prevent/minimize nine hyperthyroidism-related symptoms. We also evaluated changes on nine thyroid hormone-sensitive biochemical parameters and on vertebral and hip mineral density (bone mineral density). Fifty women under a fixed TSH-suppressive dose of L-T₄ for all 6 months were randomly allocated to five groups of 10 subjects each. Group 0 associated placebo for 6 months; groups A2 and A4 started associating placebo (first bimester), substituted placebo with 2 or 4 g/d carnitine (second bimester), and then returned to the association with placebo. Groups B2 and B4 started associating 2 and 4 g/d carnitine for the first two bimesters, and then substituted carnitine with placebo (third bimester). Symptoms and biochemical parameters worsened in group 0. In group A, symptoms and biochemical parameters worsened during the first bimester, returned to baseline or increased minimally during the second bimester (except osteocalcin and urinary OH-proline), and worsened again in the third bimester. In group B, symptoms and biochemical parameters (except osteocalcin and urinary OH-proline) did not worsen or even improved over the first 4 months; they tended to worsen in the third bimester. In both the A and B groups, the two doses of carnitine were similarly effective. At the end of the trial, bone mineral density tended to increase in groups B and A (B > A). In conclusion, L-carnitine is effective in both reversing and preventing symptoms of hyperthyroidism and has a beneficial effect on bone mineralization. Because hyperthyroidism depletes the body deposits of carnitine and since carnitine has no toxicity, teratogenicity, contraindications and interactions with drugs, carnitine can be of clinical use.

J Clin Endocrinol Metab. 2001 Aug;86(8):3579-94

EFFECTS OF CARNITINE ON THYROID HORMONE ACTION.

By experiments on cells (neurons, hepatocytes, and fibroblasts) that are targets for thyroid hormones and a randomized clinical trial on iatrogenic hyperthyroidism, we validated the concept that L-carnitine is a peripheral antagonist of thyroid hormone action. In particular, L-carnitine inhibits both triiodothyronine (T₃) and thyroxine (T₄) entry into the cell nuclei. This is relevant because thyroid hormone action is mainly mediated by specific nuclear receptors. In the randomized trial, we showed that 2 and 4 grams per day of oral L-carnitine are capable of reversing hyperthyroid symptoms (and biochemical changes in the hyperthyroid direction) as well as preventing (or minimizing) the appearance of hyperthyroid symptoms (or biochemical changes in the hyperthyroid direction). It is noteworthy that some biochemical parameters (thyrotropin and urine hydroxyproline) were refractory to the L-carnitine inhibition of thyroid hormone action, while osteocalcin changed in the hyperthyroid direction, but with a beneficial end result on bone. A very recent clinical observation proved the usefulness of L-carnitine in the most serious form of hyperthyroidism: thyroid storm. Since hyperthyroidism impoverishes the tissue deposits of carnitine, there is a rationale for using

L-carnitine at least in certain clinical settings.

Ann N Y Acad Sci. 2004 Nov;1033:158-67

PHASE I AND PHARMACOKINETIC STUDY OF APLIDINE, A NEW MARINE CYCLODEPSIPEPTIDE IN PATIENTS WITH ADVANCED MALIGNANCIES.

PURPOSE: To establish the safety, pharmacokinetic parameters, maximum-tolerated dose, and recommended dose of aplidine, a novel marine cyclodepsipeptide, in patients with advanced cancer. **PATIENTS AND METHODS:** Using a modified Fibonacci method, we performed a phase I and pharmacokinetic study of aplidine administered as a 24-hour intravenous infusion every 2 weeks. **RESULTS:** Sixty-seven patients received aplidine at a dose ranging from 0.2 to 8 mg/m². Dose-limiting myotoxicity corresponding to grade 2 to 3 creatine phosphokinase elevation and grade 1 to 2 myalgia and muscle weakness occurred in two of six patients at 6 mg/m². No cardiac toxicity was observed. Electron microscopy analysis showed the disappearance of thick filaments of myosin. Grade 3 muscle toxicity occurred in three of 14 patients at the recommended dose of 5 mg/m² and seemed to be more readily reversible with oral carnitine (1 g/10 kg). Therefore, dose escalation was resumed using carnitine prophylactically, allowing an increase in the recommended dose to 7 mg/m². Other toxicities were nausea and vomiting, diarrhea, asthenia, and transaminase elevation with mild hematologic toxicity. Aplidine displayed a long half-life (21 to 44 hours), low clearance (45 to 49 L/h), and a high volume of distribution (1,036 to 1,124 L) with high interpatient variability in plasma, whereas in whole blood, clearance ranged from 3.0 to 6.2 L/h. Minor responses and prolonged tumor stabilizations were observed in patients with medullary thyroid carcinoma. **CONCLUSION:** Muscle toxicity was dose limiting in this study. Recommended doses of aplidine were 5 and 7 mg/m² without and with carnitine, respectively. The role of carnitine will be further explored in phase II studies.

J Clin Oncol. 2005 Nov 1;23(31):7871-80

ADAPTOGENIC AND CENTRAL NERVOUS SYSTEM EFFECTS OF SINGLE DOSES OF 3% ROSAVIN AND 1% SALIDROSIDE RHODIOLA ROSEA L. EXTRACT IN MICE.

Rhodiola rosea L., or 'golden root', is a popular plant in traditional medicine in Eastern Europe and Asia, with a reputation for improving depression, enhancing work performance, eliminating fatigue and treating symptoms of asthenia subsequent to intense physical and psychological stress. Due to these therapeutic properties, R. rosea is considered to be one of the most active adaptogenic drugs. To confirm and extend results obtained in the few preclinical and clinical studies available in English language journals, the purpose of the present study was to re-investigate the effects produced by a single oral administration of an R. rosea hydroalcohol extract (containing 3% rosavin and 1% salidroside) on the central nervous system in mice. The extract was tested on antidepressant, adaptogenic, anxiolytic, nociceptive and locomotor activities at doses of 10, 15 and 20 mg/kg, using predictive behavioural tests and animal models. The results show that this R. rosea extract significantly, but not dose-dependently, induced antidepressant-like, adaptogenic, anxiolytic-like and stimulating effects in mice. This study thus provides evidence of the efficacy of R. rosea extracts after a single administration, and confirms many preclinical and clinical studies indicating the adaptogenic and stimulating effects of such R. rosea extracts. Moreover, antidepressant-like and anxiolytic-like activities of R. rosea were shown in mice for the first time.

Phytother Res. 2007 Jan;21(1):37-43

EXTRACT OF RHODIOLA ROSEA RADIX REDUCES THE LEVEL OF C-REACTIVE PROTEIN AND CREATININE KINASE IN THE BLOOD.

The effects of extracts of Rhodiola rosea radix on blood levels of inflammatory C-reactive protein and creatinine kinase were studied in healthy untrained volunteers before and after exhausting exercise. Rhodiola rosea extract exhibited an antiinflammatory effect and protected muscle tissue during exercise.

Bull Exp Biol Med. 2004 Jul;138(1):63-4

RHODIOLA ROSEA L. EXTRACT REDUCES STRESS- AND CRF-INDUCED ANOREXIA IN RATS.

Rhodiola rosea L. is one of the most popular adaptogen and anti-stress plants in European and Asiatic traditional medicine. Its pharmacological properties appear to depend on its ability to modulate the activation of several components of the complex stress-response system. Exposure to both physical and psychological stress reduces feeding in rodents. The aim of this work was thus to determine whether in rats an hydroalcoholic R. rosea extract standardized in 3% rosavin and 1% salidroside (RHO) reverses hypophagia induced by (1) physical stress due to 60 min immobilization; (2) intracerebroventricular injection of corticotrophin-releasing factor (CRF, 0.2 µg/rat), the major mediator of stress responses in mammals; (3) intraperitoneal injection of Escherichia coli Lipopolysaccharide (LPS, 100 µg/kg); (4) intraperitoneal administration of fluoxetine (FLU, 8 mg/kg). The effect of the same doses of the plant extract was also tested in freely-feeding and in 20 h food-deprived rats. RHO was administered acutely by gavage to male Wistar rats 1 h before the experiments. The results show that at 15 and 20 mg/kg, RHO reversed the anorectic effects induced both by immobilization and by intracerebroventricular CRF injection. Moreover, at the same doses, RHO failed to reduce the anorectic effect induced both by LPS and FLU, and did not modify food intake in both freely-feeding and food-deprived rats. These findings strongly demonstrated that RHO is able selectively to attenuate stress-induced anorexia, providing functional evidence of claimed adaptogen and anti-stress properties of Rhodiola rosea L.

J Psychopharmacol. 2007 Sep;21(7):742-50

ANTIOXIDATIVE EFFECTS OF CINNAMOMI CASSIAE AND RHODIOLA ROSEA EXTRACTS IN LIVER OF DIABETIC MICE.

Both Cinnamomi cassiae and Rhodiola rosea extracts are used as anti-diabetic folk medicines. Recently, increased oxidative stress was shown to play an important role in the etiology and pathogenesis of diabetes mellitus and its complications. This study was designed to examine the effects of Cinnamomi cassiae and Rhodiola rosea extracts on blood glucose, lipid peroxidation, the level of reduced glutathione and its related enzymes (glutathione reductase, glutathione S-transferase), and the activity of the antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase) in the liver of db/db mice.

Diabetic C57BL/Ks db/db mice were used as experimental models. Mice were divided into control (n=10), Cinnamomi cassiae (200 mg/kg/day, n=10), and Rhodiola rosea (200 mg/kg/day, n=10) treated groups for 12 weeks of treatment. These type II diabetic mice were used to investigate the effects of Cinnamomi cassiae and Rhodiola rosea on blood glucose, reduced glutathione, glutathione reductase, glutathione S-transferase, glutathione peroxidase, lipid peroxidation, catalase and superoxide dismutase. Cinnamomi cassiae and Rhodiola rosea extracts significantly decreased on blood glucose, increased levels of reduced glutathione and the activities of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase and superoxide dismutase in the liver. Extract treatment also significantly decreased lipid peroxidation. Cinnamomi cassiae and Rhodiola rosea extracts may be effective for correcting hyperglycemia and preventing diabetic complications.

Biofactors. 2006;26(3):209-19

RHODIOLA ROSEA: A POSSIBLE PLANT ADAPTOGEN.

Rhodiola rosea is a popular plant in traditional medical systems in Eastern Europe and Asian with a reputation for stimulating the nervous system, decreasing depression, enhancing work performance, eliminating fatigue, and preventing high altitude sickness. Rhodiola rosea has been categorized as an adaptogen by Russian researchers due to its observed ability to increase resistance to a variety of chemical, biological, and physical stressors. Its claimed benefits include antidepressant, anticancer, cardioprotective, and central nervous system enhancement. Research also indicates great utility in asthenic conditions (decline in work performance, sleep difficulties, poor appetite, irritability, hypertension, headaches, and fatigue) developing subsequent to intense physical or intellectual strain. The adaptogenic, cardiopulmonary protective, and central nervous system activities of Rhodiola rosea have been attributed primarily to its ability to influence levels and activity of monoamines and opioid peptides such as beta-endorphins.

Altern Med Rev. 2001 Jun;6(3):293-302

RHODIOLA ROSEA IN STRESS INDUCED FATIGUE—A DOUBLE BLIND CROSS-OVER STUDY OF A STANDARDIZED EXTRACT SHR-5 WITH A REPEATED LOW-DOSE REGIMEN ON THE MENTAL PERFORMANCE OF HEALTHY PHYSICIANS DURING NIGHT DUTY.

The aim of this study was to investigate the effect of repeated low-dose treatment with a standardized extract SHR/5 of rhizome Rhodiola rosea L, (RRE) on fatigue during night duty among a group of 56 young, healthy physicians. The effect was measured as total mental performance calculated as Fatigue Index. The tests chosen reflect an overall level of mental fatigue, involving complex perceptive and cognitive cerebral functions, such as associative thinking, short-term memory, calculation and ability of concentration, and speed of audio-visual perception. These parameters were tested before and after night duty during three periods of two weeks each: a) a test period of one RRE/placebo tablet daily, b) a washout period and c) a third period of one placebo/RRE tablet daily, in a double-blind cross-over trial. The perceptive and cognitive cerebral functions mentioned above were investigated using 5 different tests. A statistically significant improvement in these tests was observed in the treatment group (RRE) during the first two weeks period. No side-effects were reported for either treatment noted. These results suggest that RRE can reduce general fatigue under certain stressful conditions.

Phytomedicine. 2000 Oct;7(5):365-71

ACUTE RHODIOLA ROSEA INTAKE CAN IMPROVE ENDURANCE EXERCISE PERFORMANCE.

PURPOSE: The purpose of this study was to investigate the effect of acute and 4-week Rhodiola rosea intake on physical capacity, muscle strength, speed of limb movement, reaction time, and attention. **METHODS:** PHASE I: A double blind placebo-controlled randomized study (n= 24) was performed, consisting of 2 sessions (2 days per session). Day 1: One hour after acute Rhodiola rosea intake (R, 200-mg Rhodiola rosea extract containing 3% rosavin + 1% salidroside plus 500 mg starch) or placebo (P, 700 mg starch) speed of limb movement (plate tapping test), aural and visual reaction time, and the ability to sustain attention (Fepsy Vigilance test) were assessed. Day 2: Following the same intake procedure as on day 1, maximal isometric knee-extension torque and endurance exercise capacity were tested. Following a 5-day washout period, the experimental procedure was repeated, with the treatment regimens being switched between groups (session 2). PHASE II: A double blind placebo-controlled study (n = 12) was performed. Subjects underwent sessions 3 and 4, identical to Phase I, separated by a 4-week R/P intake, during which subjects ingested 200 mg R/P per day. **RESULTS:** PHASE I: Compared with P, acute R intake in Phase I increased (p <.05) time to exhaustion from 16.8 +/- 0.7 min to 17.2 +/- 0.8 min. Accordingly, VO₂peak (p <.05) and VCO₂peak (p<.05) increased during R compared to P from 50.9 +/- 1.8 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ to 52.9 +/- 2.7 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ (VO₂peak) and from 60.0 +/- 2.3 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ to 63.5 +/- 2.7 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ (VCO₂peak). Pulmonary ventilation (p =.07) tended to increase more during R than during P (P: 115.9 +/- 7.7 L/min; R: 124.8 +/- 7.7 L/min). All other parameters remained unchanged. PHASE II: Four-week R intake did not alter any of the variables measured. **CONCLUSION:** Acute Rhodiola rosea intake can improve endurance exercise capacity in young healthy volunteers. This response was not altered by prior daily 4-week Rhodiola intake.

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