

Acetaminophen Poisoning (Analgesic Toxicity)

ABSTRACTS

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Phospholipid association reduces the gastric mucosal toxicity of aspirin in human subjects.

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Am J Gastroenterol 1999 Jul;94(7):1818-22

OBJECTIVE: In previous studies on rats, we have shown that aspirin (ASA)-induced injury to the gastric mucosa is markedly reduced or completely abolished if ASA is chemically associated with the phospholipid, phosphatidylcholine (PC). We have also shown that the protective effect of PC does not influence the ability of ASA to inhibit mucosal cyclooxygenase (COX) activity in the stomach and other tissues. We therefore sought to assess the effect of PC-associated ASA (ASA/PC) on the gastric mucosa of normal volunteers and to compare the results with the use of ASA alone.

METHODS: Sixteen normal healthy subjects were administered ASA or ASA/PC in a randomized, double-blind, crossover study. The subjects received ASA in a dose of 650 mg three times a day for 3 days or an equivalent dose of ASA chemically associated with PC. Endoscopy was performed at baseline and again on the morning of day 4, after the subjects had taken the final dose of the test drug. On both occasions, antral biopsy specimens were obtained for the assessment of mucosal COX activity and prostaglandin concentration.

RESULTS: The number (mean SD) of gastric erosions seen with the ASA/PC formulation was significantly less than when ASA was used alone (8.7 10.7 vs 2.9 4.3; $p < 0.025$). A similar trend was seen in the duodenum but the difference was statistically not significant. The antral mucosal COX activity, as well as the level of prostaglandin 6-keto PGF1alpha, were reduced significantly (80-88%) and to a similar extent by both ASA and ASA/PC.

CONCLUSIONS: The present study shows that acute aspirin-induced damage to the gastric mucosa can be reduced by chemically associating ASA with PC. The mechanism of mucosal protection provided by this compound is not related to any alteration in the ability of ASA to inhibit mucosal COX activity. We believe this protection is attributable to the maintenance of the defensive hydrophobic barrier of the gastric mucosa.

Acute renal failure due to acetaminophen ingestion: a case report and review of the literature.

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J Am Soc Nephrol 1995 Jul;6(1):48-53

Acetaminophen is the most commonly reported drug overdose in the United States. Acute renal failure occurs in less than 2% of all acetaminophen poisonings and 10% of severely poisoned patients. At the therapeutic dosages, acetaminophen can be toxic to the kidneys in patients who are glutathione depleted (chronic alcohol ingestion, starvation, or fasting) or who take drugs that stimulate the P-450 microsomal oxidase enzymes (anticonvulsants). Acute renal failure due to acetaminophen manifests as acute tubular necrosis (ATN). ATN can occur alone or in combination with hepatic necrosis. The azotemia of acetaminophen toxicity is typically reversible, although it may worsen over 7 to 10 days before the recovery of renal function occurs. In severe overdoses, renal failure coincides with hepatic encephalopathy and dialysis may be required.

Acute hepatic and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency.

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Hepatology 1994 May;19(5):1141-8

A 67-yr-old man with chronic cardiopulmonary disease exhibited severe hepatic and moderately severe renal injury after short-term ingestion of therapeutic doses of acetaminophen (1 to 3 gm/day for 3 days). Drug metabolism and other studies, performed 5 mo after recovery from the acute insult, indicated that the patient had decreased rates of hepatic metabolism of acetaminophen to its primary, nontoxic metabolites and decreased kidney function that was compromised further by acetaminophen ingestion. He also had abnormally low concentrations of hepatic and plasma reduced glutathione. Alcohol abuse and malnutrition could not be implicated in the pathogenesis of injury; rather it appeared that advancing age with chronic renal, cardiac and pulmonary insufficiency contributed to acetaminophen toxicity in this patient.

Recommendations for treatment of paracetamol poisoning. Danish Medical Society, Study of the Liver

Clemmesen J.O.; Ott P.; Dalhoff K.P.; Astrup L.B.; Tage-Jensen U.; Poulsen H.E. Medicinsk Afdeling A-2101, Rigshospitalet, DK-2100 København O Denmark

Ugeskr Laeger (Denmark) Nov 25 1996, 158 (48) p6892-5

Based on recent reports concerning the efficacy of N-acetylcysteine (NAC) in paracetamol (acetaminophen) poisoning, guidelines for treatment and control of these patients are reviewed by a study group under the Danish Association for the Study of the Liver. It is recommended that NAC-treatment is initiated immediately after referral and continued for 36 hours in all cases. Further NAC-treatment should not be discontinued before a decrease in INR has been observed.

Protective activity of silipide on liver damage in rodents.

Conti M, Malandrino S, Magistretti MJ. Inverni della Beffa Research and Development Laboratories, Milan, Italy.

Jpn J Pharmacol 1992 Dec;60(4):315-21

The activity of silipide, a silybin-phosphatidylcholine complex (IdB 1016), was tested in different models of liver damage in rodents. After oral administration, silipide exhibited a significant and dose-related protective effect against the hepatotoxicity induced by CCl₄, praseodymium, ethanol and galactosamine. The ED₅₀ values for inhibition of the rise in ASAT and ALAT levels caused by CCl₄ and praseodymium and for antagonism of the increase in liver triglycerides caused by ethanol ranged from 93 to 156 mg/kg (as silybin). At a dose of 400 mg/kg (as silybin), silipide was also active in protecting against paracetamol-induced hepatotoxicity. Silybin and phosphatidylcholine at doses equivalent to those contained in the active doses of silipide failed to show any significant protective activity in these models. The liver protective effect of silipide is probably related to its antioxidant activities and to a stimulating effect on the hepatic synthesis of RNA and proteins.

Glutathione Metabolism and Its Role in Hepatotoxicity

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Pharmacologic Therapy, 1991;52:287-305

Glutathione is important in the detoxification of free radicals and toxic oxygen radicals, thiol-disulfide exchange, and storage of transferred cysteine. It appears to be especially important in organs with exposure to exogenous toxins such as the liver, kidney, lung and intestines. Cellular mitochondrial glutathione is the main defense against physiologic oxidative stress generated by cellular respiration. It is noted that many drugs are detoxified by glutathione. An example of a therapeutic application with glutathione is the use of N-acetylcysteine, which is an antidote for acetaminophen toxicity. N-acetylcysteine has the ability to increase hepatic glutathione under depleted conditions, even though under normal conditions N-acetylcysteine will not increase total glutathione. There appears to be a feedback control system. The availability of glutathione in various tissues is determined by the liver and the kidney which synthesize and release glutathione and glutathione precursors into the plasma.

Acetaminophen and renal and bladder cancer.

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Epidemiology 1996 Jul;7(4):358-62

Acetaminophen is a metabolite of phenacetin, a drug that has been implicated as a causal agent in the development of renal and bladder cancer. We conducted matched case-control studies to estimate the risk of renal and bladder cancer among heavy users of acetaminophen, using data from Group Health Cooperative of Puget Sound. For the renal cancer study, we identified 222 incident cases diagnosed in the years 1980-1991 and 885 controls. For bladder cancer, we identified 504 cases and 2,009 controls. Exposure was defined according to the number of prescriptions for acetaminophen and acetaminophen-containing drugs filled at the Group Health Cooperative pharmacy. The relative risk estimate for renal cancer for subjects who filled 40 or more prescriptions was 2.6 [95% confidence limits (CL) = 1.1, 6.0], compared with the risk for subjects who did not fill any prescriptions for acetaminophen. We found only a small increased risk of bladder cancer among subjects with heavy acetaminophen exposure (odds ratio = 1.3; 95% CL = 0.6, 2.8).

Gastroprotective capability of exogenous phosphatidylcholine in experimentally induced chronic gastric ulcers in rats.

Dunjic BS, Axelson J, Ar'Rajab A, Larsson K, Bengmark S. Dept. of Surgery, Lund University, Sweden.

Phosphatidylcholine (PC) is a main component of the hydrophobic gastric mucosal barrier. Exogenously administered, it prevents acute lesions. We evaluated the gastroprotective capacity of exogenous PC in both acute (ethanol- and indomethacin-induced) and chronic (indomethacin-induced) lesions in rats. Polyunsaturated (PPC) or hydrogenated PC in different concentrations were given intragastrically, before or after the injury factor, in single or repeated doses. Mucosal lesions were significantly reduced by a single dose of PPC, given before or after the injury factor, in both acute models. In the chronic model a single dose of PPC or hydrogenated PC significantly reduced lesions evaluated 6 h after ulcer induction, whereas after 72 h no protective effect was noticed. Repeated doses of PC were ineffective. In conclusion, in acute models exogenous PC reduces lesions in a dose-dependent manner and contributes to the mucosal defense. In chronic models an incomplete and temporary protection might be due to complex pathogenesis that requires activation of all levels in the mucosal defense. Strengthening of only one level was insufficient to restrict injury.

Regular use of analgesics is a risk factor for renal cell carcinoma.

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Br J Cancer 1999 Oct;81(3):542-8

Phenacetin-based analgesics have been linked to the development of renal pelvis cancer and renal cell carcinoma (RCC). The relationship between non-phenacetin types of analgesics and kidney cancer is less clear, although laboratory evidence suggests that these drugs possess carcinogenic potential. A population-based case-control study involving 1204 non-Asian RCC patients aged 25-74 and an equal number of sex-, age- and race-matched neighbourhood controls was conducted in Los Angeles, California, to investigate the relationship between sustained use of analgesics and risk of RCC according to major formulation categories. Detailed information on medical and medication histories, and other lifestyle factors was collected through in-person interviews. Regular use of analgesics was a significant risk factor for RCC in both men and women (odds ratio (OR) = 1.6, 95% confidence interval (CI) = 1.4-1.9 for both sexes combined). Risks were elevated across all four major classes of analgesics (aspirin, non-steroidal anti-inflammatory agents other than aspirin, acetaminophen and phenacetin). Within each class of analgesics, there was statistically significant increasing risk with increasing level of exposure. Although there was some minor variability by major class of formulation, in general individuals in the highest exposure categories exhibited approximately 2.5-fold increase in risk relative to non- or irregular users of analgesics. Subjects who took one regular-strength (i.e. 325 mg) aspirin a day or less for cardiovascular disease prevention were not at an increased risk of RCC (OR = 0.9, 95% CI = 0.6-1.4).

Overdose of Extended-Release Acetaminophen

Graudins A, Aaron CK, Linden CH Andis Graudins, M.B., B.S., University of Massachusetts N Engl J Med 1995 Jul 20;333(3):196

This is a case report of a healthy 13-year-old female who was seen in a hospital 19 hours after ingesting 2 handfuls of Tylenol Extended Relief (McNeil Pharmaceuticals) which is a formulation containing 650 mg of acetaminophen per tablet in a time-release manner. The patient received an oral dose of 140 mg of acetylcysteine per kg of body weight followed by 6 doses of 70 mg per kg and 11 doses of 100 mg per kg. The alanine aminotransferase level that was over 7,000 and the international normalized ratio of 4.2 peaked 59 hours after the ingestion of acetaminophen. The patient remained clinically well and was sent home on day 4 with resolving liver function values. There was a linear decline in serial acetaminophen -measurements. Tylenol Extended Relief is designed to maintain the analgesic effects for up to 8 hours. There are no published data with its overdose. Animal studies show that the dose of acetylcysteine needed to prevent hepatotoxicity is proportional to the dose of acetaminophen ingested.

Disposition and hepatoprotection by phosphatidyl choline liposomes in mouse liver.

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Chem Biol Interact 1987;64(1-2):127-37

Small unilamellar liposomes with an average diameter of 80 nm were prepared from phosphatidyl choline of various sources using the dialysis method with cholate as a detergent. When ¹⁴C-labeled soybean liposomes were intravenously injected into male NMRI mice, up to 10% of the total label was found in the liver lipid. The uptake was dose-dependent and reached an apparent saturation 4 h after injection. The liver maintained a constant radioactivity corresponding to 1.9 +/- 0.13 mg phospholipid/g liver until ten hours after injection of 850 mg labeled phosphatidyl choline/kg body wt. Little radioactivity was taken up by the spleen. Analogous doses of liposomes prepared from egg yolk phosphatidyl choline led to a radioactivity corresponding to 1.3 +/- 0.4 mg lipid/g liver 4 h after injection. Liposomes with a similar size were prepared from hydrated, i.e., saturated phosphatidyl choline. After intravenous

administration of these liposomes, an amount of 5.3 +/- 0.5 mg labeled lipid was found per g liver after 4 h. In contrast to unsaturated liposomes, 5.8 +/- 0.8 mg lipid per gram spleen was trapped by the spleen. The pharmacodynamic effect of these different liposomes was studied in benzo[a]pyrene-pretreated mice intoxicated with 400 mg/kg paracetamol. Animals which received paracetamol exhibited serum alanine aminotransferase activities of 4220 +/- 1140 units/l after 4 h and exhaled 120 +/- 19 nmol ethane kg⁻¹ h⁻¹. When pretreated with 850 mg soybean phosphatidyl choline/kg body wt. (i.v.) 2 h prior to paracetamol, the increase in serum transaminase activity was reduced to 117 +/- 104 units/l and ethane exhalation amounted to 18 +/- 8 nmol kg⁻¹ h⁻¹. In contrast, similar pretreatment with egg yolk phosphatidyl choline or hydrated phosphatidyl choline failed to protect against paracetamol-induced hepatotoxicity. The different pharmacodynamic effects of the two phosphatidyl cholines of plant or animal origin cannot be explained on the basis of their different pharmacokinetics. In the case of soybean phosphatidyl choline liposomes, the amount of radioactive lipid found in the liver correlated with the hepatoprotective potency.

Mechanism of action and value of N-acetylcysteine in the treatment of early and late acetaminophen poisoning: a critical review.

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J Toxicol Clin Toxicol (United States) 1998, 36 (4) p277-85

INTRODUCTION: The mechanism of action of N-acetylcysteine in early acetaminophen poisoning is well understood, but much remains to be learned of the mechanism of its possible benefit in acetaminophen poisoning presenting beyond 15 hours.

METHODS: Selective review of medical literature. N-acetylcysteine should be used in all cases of early acetaminophen poisoning where the plasma acetaminophen concentration lies "above the line," which line is chosen depends on individual preference and whether enzyme induction is suspected. Particular care should be taken with the use of the nomogram for patients with chronic excess ingestion of acetaminophen or for those who have taken slow-release formulations.

CONCLUSIONS: While there is a trend suggesting a beneficial effect of N-acetylcysteine in some patients presenting beyond 15 hours, further research is necessary to establish just how effective N-acetylcysteine is, particularly in patients presenting with fulminant hepatic failure. Candidate mechanisms for a beneficial effect include improvement of liver blood flow, glutathione replenishment, modification of cytokine production, and free radical or oxygen scavenging. Hemodynamic and oxygen delivery and utilization parameters must be monitored carefully during delayed N-acetylcysteine treatment of patients with fulminant hepatic failure, as unwanted vasodilation may be deleterious to the maintenance of mean arterial blood pressure. (75 Refs.)

Acetaminophen and the risk of renal and bladder cancer in the general practice research database.

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Epidemiology 2001 Nov;12(6):690-4

We conducted a nested, matched case-control study in the General Practice Research Database (GPRD) to assess whether acetaminophen use is associated with renal or bladder cancer. We matched 109 cases of renal cancer and 189 cases of bladder cancer with up to 4 controls each by age, sex, general practice, duration of drug history in the GPRD, and index date. We found that use of acetaminophen from 1 to 5 years before the index date was associated with an increased risk of renal cancer, with a direct relation between risk and number of prescriptions and an adjusted odds ratio of 2.3 (95% CI 1.0-5.3) for subjects with 20 or more prescriptions. There was no evidence for an increase in risk of bladder cancer with acetaminophen use. We found no association between use of non-steroidal anti-inflammatory drugs and either renal or bladder cancer. These results support previous findings from our group and are consistent with a slight increase in the risk of renal cancer, but not bladder cancer, with heavy acetaminophen use.

Clinical-toxicological case (1). Dosage of N-acetylcysteine in acute paracetamol poisoning

Kind B; Krahenbuhl S; Wyss PA; Meier-Abt PJ Schweizerisches Toxikologisches Informationszentrum (STIZ), Departement Innere Medizin, Universitatsspital Zurich.

Schweiz Rundsch Med Prax (Switzerland) Aug 2 1996, 85 (31-32) p935-8

There are currently three protocols used for the administration of N-acetylcysteine in the treatment of acute paracetamol poisoning. In the USA only the oral protocol is approved, while in Europe an intravenous protocol is used. If treatment is started within 10 h. after paracetamol ingestion, all three protocols appear to be equally effective. If treatment is started 10 to 24 h. after the ingestion, the oral protocol and the Smilkstein protocol appear to be superior to the Prescott protocol. N-acetylcysteine is effective also when

started more than 15 h after the ingestion. Patients who present with liver failure after paracetamol poisoning should be treated with a prolonged course of N-acetylcysteine.

Role of oxidative stress and antioxidant therapy in alcoholic and nonalcoholic liver diseases.

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Adv Pharmacol (United States) 1997, 38 p601-28

The main pathway for the hepatic oxidation of ethanol to acetaldehyde proceeds via ADH and is associated with the reduction of NAD to NADH; the latter produces a striking redox change with various associated metabolic disorders. NADH also inhibits xanthine dehydrogenase activity, resulting in a shift of purine oxidation to xanthine oxidase, thereby promoting the generation of oxygen-free radical species. NADH also supports microsomal oxidations, including that of ethanol, in part via transhydrogenation to NADPH. In addition to the classic alcohol dehydrogenase pathway, ethanol can also be reduced by an accessory but inducible microsomal ethanoloxidizing system. This induction is associated with proliferation of the endoplasmic reticulum, both in experimental animals and in humans, and is accompanied by increased oxidation of NADPH with resulting H₂O₂ generation. There is also a concomitant 4- to 10-fold induction of cytochrome P4502E1 (2E1) both in rats and in humans, with hepatic perivenular preponderance. This 2E1 induction contributes to the well-known lipid peroxidation associated with alcoholic liver injury, as demonstrated by increased rates of superoxide radical production and lipid peroxidation correlating with the amount of 2E1 in liver microsomal preparations and the inhibition of lipid peroxidation in liver microsomes by antibodies against 2E1 in control and ethanol-fed rats. Indeed, 2E1 is rather "leaky" and its operation results in a significant release of free radicals. In addition, induction of this microsomal system results in enhanced acetaldehyde production, which in turn impairs defense systems against oxidative stress. For instance, it decreases GSH by various mechanisms, including binding to cysteine or by provoking its leakage out of the mitochondria and of the cell. Hepatic GSH depletion after chronic alcohol consumption was shown both in experimental animals and in humans. Alcohol-induced increased GSH turnover was demonstrated indirectly by a rise in alpha-amino-n-butyric acid in rats and baboons and in volunteers given alcohol. The ultimate precursor of cysteine (one of the three amino acids of GSH) is methionine. Methionine, however, must be first activated to S-adenosylmethionine by an enzyme which is depressed by alcoholic liver disease. This block can be bypassed by SAME administration which restores hepatic SAME levels and attenuates parameters of ethanol-induced liver injury significantly such as the increase in circulating transaminases, mitochondrial lesions, and leakage of mitochondrial enzymes (e.g., glutamic dehydrogenase) into the bloodstream. SAME also contributes to the methylation of phosphatidylethanolamine to phosphatidylcholine. The methyltransferase involved is strikingly depressed by alcohol consumption, but this can be corrected, and hepatic phosphatidylcholine levels restored, by the administration of a mixture of polyunsaturated phospholipids (polyenylphosphatidylcholine). In addition, PPC provided total protection against alcohol-induced septal fibrosis and cirrhosis in the baboon and it abolished an associated twofold rise in hepatic F₂-isoprostanes, a product of lipid peroxidation. A similar effect was observed in rats given CCl₄. Thus, PPC prevented CCl₄- and alcohol-induced lipid peroxidation in rats and baboons, respectively, while it attenuated the associated liver injury. Similar studies are ongoing in humans. (188 Refs.)

ALCOHOL: its metabolism and interaction with nutrients.

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Annu Rev Nutr 2000;20:395-430

In the past, alcoholic liver disease was attributed exclusively to dietary deficiencies, but experimental and judicious clinical studies have now established alcohol's hepatotoxicity. Despite an adequate diet, it can contribute to the entire spectrum of liver diseases, mainly by generating oxidative stress through its microsomal metabolism via cytochrome P4502E1 (CYP2E1). It also interferes with nutrient activation, resulting in changes in nutritional requirements. This is exemplified by methionine, one of the essential amino acids for humans, which needs to be activated to S-adenosylmethionine (SAME), a process impaired by liver disease. Thus, SAME rather than methionine is the compound that must be supplemented in the presence of significant liver disease. In baboons, SAME attenuated mitochondrial lesions and replenished glutathione; it also significantly reduced mortality in patients with Child A or B cirrhosis. Similarly, decreased phosphatidylethanolamine methyltransferase activity is associated with alcoholic liver disease, resulting in phosphatidylcholine depletion and serious consequences for the integrity of membranes. This can be offset by polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines comprising dilinoleoylphosphatidylcholine (DLPC), which has high bioavailability. PPC (and DLPC) opposes major toxic effects of alcohol, with down-regulation of CYP2E1 and reduction of oxidative stress, deactivation of hepatic stellate cells, and increased collagenase activity, which in baboons, results in prevention of ethanol-induced septal fibrosis and cirrhosis. Corresponding clinical trials are ongoing.

Relation of analgesic use to renal cancer: population-based findings.

McLaughlin JK; Blot WJ; Mehl ES; Fraumeni JF Jr

A population-based case-control study of renal cancer (495 cases of renal cell cancer, 74 cases of renal pelvis cancer, and 697 controls) was conducted in the Minneapolis-St. Paul 7-county metropolitan area. Information was obtained on a large number of variables, including the use of analgesic drugs. Long-term use (greater than 36 mo) of phenacetin-containing products was associated in both sexes with a twofold increased risk for renal cell cancer. Long-term use of phenacetin- and acetaminophen-containing products was associated with elevated risks of nearly threefold to eightfold for cancer of the renal pelvis. The separate effects of these analgesics could not be adequately assessed because most long-term users took both products.

Over-the-Counter Drug is Treatment for Alzheimer's.

Mitchell, T., Needham, A.

Life Extension 2000 Nov; 7(10): 50-55. http://www.lef.org/magazine/mag2000/nov2000_report_otc.html

Fatal acetaminophen poisoning with evidence of subendocardial necrosis of the heart.

Price LM; Poklis A; Johnson DE Department of Pathology, Medical College of Virginia, Richmond.

J Forensic Sci 1991 May;36(3):930-5

The authors describe a case of fatal acetaminophen overdose which occurred in a 16-year-old female. Her serum acetaminophen concentration 11.5 h postingestion was 154 mg/L. Antidotal therapy was unsuccessful, and after 9 days she died. Autopsy findings included centrilobular zonal liver necrosis, acute proximal renal tubular necrosis, and diffuse alveolar pulmonary damage. Her heart was transplanted into a young woman with congenital heart disease. The recipient expired 14 days after the transplant as a result of sepsis complicating bowel ischemia. The transplanted heart showed extensive subendocardial myocyte necrosis related to acetaminophen toxicity and not rejection.

Acetaminophen-induced depletion of glutathione and cysteine in the aging mouse kidney.

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Biochem Pharmacol 1992 Jul 7;44(1):129-35

Glutathione (GSH) plays an essential role in the detoxification of acetaminophen (APAP) and the prevention of APAP-induced toxicity in the kidney. Our previous results demonstrated that a GSH deficiency is a general property of aging tissues, including the kidney, suggesting a hypothesis that senescent organisms are at greater risk to APAP-induced renal damage. To test this, C57BL/6NIA mice of different ages through the life span were injected with various doses of APAP, and the extent of GSH and cysteine (Cys) depletion and recovery were determined. At time intervals up to 24 hr, kidney cortex samples were obtained, processed and analyzed for glutathione status, namely GSH, glutathione disulfide (GSSG), Cys and cystine, using an HPLC method with dual electrochemical detection. In the uninjected controls, GSH and Cys concentrations decreased about 30% in the aging mouse, but the GSSG and cystine levels were unchanged during the life span.

Cholestyramine as an antidote against paracetamol-induced hepato- and nephrotoxicity in the rat.

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Toxicol Lett 1989 May;47(2):179-84

Besides hepatotoxicity, paracetamol may exert nephrotoxic effects in experimental animals and man. The present study in rats shows that cholestyramine given 4 and 24 h after paracetamol provided protection against both hepato- and nephrotoxicity; this was evidenced by reduced increments in plasma enzyme activities (SDH, GPT), indicating liver damage, and diminished retention of plasma and creatinine, indicating renal failure. The recovery of paracetamol and its conjugates in urine was markedly reduced by cholestyramine at 24-48 h after treatment. The protective effects of cholestyramine are explained by adsorption of paracetamol and conjugates in the intestine undergoing biliary excretion and enterohepatic circulation.

Glutathione enhancement in various mouse organs and protection by glutathione isopropyl ester against liver injury.

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Intraperitoneal administration of glutathione isopropyl ester to fasted, male NMRI mice dose dependently increased the glutathione concentration in various organs. Administration of 1 g/kg glutathione isopropyl ester led to the following increases: liver 166%; lung 164%; heart 121% after 4 hr; and brain 133% after 6 hr. Spleen, kidney, muscle, serum and blood cell glutathione were not affected by the treatment. Pretreatment with glutathione isopropyl ester was found to protect against paracetamol (acetaminophen) or allyl alcohol-induced liver damage. Following treatment with the ester a significant correlation between protection against liver damage and enhancement of liver glutathione content was obtained. The dose dependence of this protection was studied.

Hepatic uptake and antihepatotoxic properties of vitamin E and liposomes in the mouse.

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Chem Biol Interact 1990;75(1):83-92

Intravenous administration of soybean phosphatidylcholine liposomes containing different amounts of tocopherol acetate leads to a dose and time dependent increase of mouse liver tocopherol content, which was not observed when the preparation was given orally. When benzo[a]pyrene pretreated mice intoxicated with 400 mg/kg AAP were pretreated 2 h before with 1 g/kg phosphatidylcholine liposomes containing 4 mg/kg vitamin E acetate, these animals were protected against liver damage. Vitamin E alone or liposomes lacking vitamin E showed no protection. In an inflammatory liver disease model, i.e. fulminant hepatitis induced by intraperitoneal administration of 700 mg/kg galactosamine and 1 microgram/kg lipopolysaccharide phosphatidylcholine liposomes protected at a dose of 1 g/kg i.v. In this case, however, the protection was not due to the presence of vitamin E. These findings demonstrate the usefulness of phosphatidylcholine for liver protection and show that the protective spectrum is improved when they contain vitamin E. The data suggest that phosphatidylcholine is an excellent carrier for delivery of vitamin E to the liver.

Tissue distribution of silibinin, the major active constituent of silymarin, in mice and its association with enhancement of phase II enzymes: implications in cancer chemoprevention.

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Carcinogenesis 1999 Nov;20(11):2101-8

Polyphenolic antioxidants are being identified as cancer preventive agents. Recent studies in our laboratory have identified and defined the cancer preventive and anticarcinogenic potential of a polyphenolic flavonoid antioxidant, silymarin (isolated from milk thistle). More recent studies by us found that these effects of silymarin are due to the major active constituent, silibinin, present therein. Here, studies are done in mice to determine the distribution and conjugate formation of systemically administered silibinin in liver, lung, stomach, skin, prostate and pancreas. Additional studies were then performed to assess the effect of orally administered silibinin on phase II enzyme activity in liver, lung, stomach, skin and small bowel. For tissue distribution studies, SENCAR mice were starved for 24 h, orally fed with silibinin (50 mg/kg dose) and killed after 0.5, 1, 2, 3, 4 and 8 h. The desired tissues were collected, homogenized and parts of the homogenates were extracted with butanol:methanol followed by HPLC analysis. The column eluates were detected by UV followed by electrochemical detection. The remaining homogenates were digested with sulfatase and beta-glucuronidase followed by analysis and quantification. Peak levels of free silibinin were observed at 0.5 h after administration in liver, lung, stomach and pancreas, accounting for 8.8 +/- 1.6, 4.3 +/- 0.8, 123 +/- 21 and 5.8 +/- 1.1 (mean +/- SD) microg silibinin/g tissue, respectively. In the case of skin and prostate, the peak levels of silibinin were 1.4 +/- 0.5 and 2.5 +/- 0.4, respectively, and were achieved 1 h after administration. With regard to sulfate and beta-glucuronidate conjugates of silibinin, other than lung and stomach showing peak levels at 0.5 h, all other tissues showed peak levels at 1 h after silibinin administration. The levels of both free and conjugated silibinin declined after 0.5 or 1 h in an exponential fashion with an elimination half-life ($t_{1/2}$) of 57-127 min for free and 45-94 min for conjugated silibinin in different tissues. In the studies examining the effect of silibinin on phase II enzymes, oral feeding of silibinin at doses of 100 and 200 mg/kg/day showed a moderate to highly significant ($P < 0.1-0.001$, Student's t-test) increase in both glutathione S-transferase and quinone reductase activities in liver, lung, stomach, skin and small bowel in a dose- and time-dependent manner. Taken together, the results of the present study clearly demonstrate the bioavailability of and phase II enzyme induction by systemically administered silibinin in different tissues, including skin, where silymarin has been shown to be a strong cancer chemopreventive agent, and suggest further studies to assess the cancer preventive and anticarcinogenic effects of silibinin in different cancer models.

SUGGESTED READING

Refining the level for anticipated hepatotoxicity in acetaminophen poisoning

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Treatment of an acetaminophen overdose with N-acetyl cysteine usually is based on the position of the 4-h acetaminophen (APAP) level on the Rumack- Matthew nomogram; however, there is disagreement on the level at which clinically relevant hepatotoxicity occurs. A retrospective review of all acute adult formulation APAP exposures reported to our poison center between 1986 and 1993 was performed and cases corresponding to the 'possible risk or toxicity' range on the nomogram were identified. Our current poison center protocol for APAP poisoning does not recommend treatment with N- acetylcysteine (NAC) in low-risk patients if the 4-h serum APAP level or the extrapolated equivalent falls within the possible toxicity range on the nomogram. Seventeen cases met the inclusion criteria for the study and received no NAC; six additional patients met inclusion criteria but received one or two doses of NAC before therapy was discontinued. No patients in either group demonstrated clinical evidence of hepatotoxicity. This pilot study suggests that patients with no risk factors and APAP levels in the 'possible risk' range may not require NAC therapy.

Cysteine isopropylester protects against paracetamol-induced toxicity.

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Biochem Pharmacol 1992 Feb 4;43(3):483-8

Cysteine isopropylester (CIPE), a novel ester of cysteine, has been synthesized in order to evaluate its potential as a chemoprotectant. The increased lipophilicity of the ester relative to cysteine should facilitate its entry into cells where, following hydrolysis, it should act as an intracellular source of cysteine or be utilized for the synthesis of glutathione so protecting the cell against various types of chemical insult. In this study, we evaluate the ability of CIPE to protect against paracetamol-induced hepatotoxicity in mice. When administered to mice, CIPE produced a rapid but transient elevation of levels of non-protein sulphhydryls (NPSH) in liver, lung, kidney and spleen. The greatest increase in NPSH was seen in the lung, but after 60 min all NPSH values had returned to control levels, demonstrating the capacity of the mouse to rapidly metabolize both CIPE and cysteine. In mice pretreated with benzo(a)pyrene, CIPE protected against paracetamol-induced toxicity.

Factors responsible for continuing morbidity after paracetamol poisoning in Chinese patients in Hong Kong.

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Singapore Med J (Singapore) Jun 1996, 37 (3) p275-7

To determine those factors responsible for continuing prevalence of liver damage after paracetamol poisoning, 222 Chinese patients presenting to the Prince of Wales Hospital, Hong Kong from 1988 to 1993 were studied. Of the 27 patients with plasma paracetamol concentrations above the recommended "treatment line", 13 developed liver damage. Time elapsed between ingestion and treatment with intravenous N-acetylcysteine (NAC) was the most important prognostic factor. Failure to give NAC appropriately (50%) and late presentation (23%) were the main reasons for the continuing morbidity. Liver damage in some of the remaining patients (30%) could have been prevented if NAC was started in the Emergency Department within 8-15 hours of ingestion. Liver damage after paracetamol poisoning remains common (5.9%) in Hong Kong because of the failure to give NAC appropriately or late presentation. We hope to improve patient management by repeatedly emphasising the importance of adherence to the standard protocols and having the toxic plasma level results phoned directly to the duty registrars.

Outpatient N-acetylcysteine treatment for acetaminophen poisoning: An ethical dilemma or a new financial mandate?

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Veterinary and Human Toxicology (USA), 1996, 38/3 (222-224)

The mainstay of treatment for acetaminophen-induced hepatotoxicity, produced by the accumulation of the toxic metabolite N-acetylbenzoquinoneimine, is an enteral 18-dose course of N-acetylcysteine (NAC). However, absence of characteristic symptomatology is a frequent reason for premature cessation of NAC and early discharge of the toxic acetaminophen poisoned patient. We report a series of confirmed acetaminophen poisonings who were discharged early with NAC and instructions to self-administer. All cases of acute acetaminophen poisoning without concomitant drugs, reported to a certified Regional Poison Information Center for a 3-mo period of time, were reviewed. Inclusion criteria included patients who were discharged with orders to complete the course of NAC outside of a hospital, despite toxic serum acetaminophen concentrations. Data parameters evaluated included age, amount taken, symptoms, laboratory results, treatment, and medical outcome. 131 cases of confirmed toxic acetaminophen poisoning yielded 6 patients who received 4 to 6 doses of NAC during hospitalization, but were discharged to home

with the remaining 11-13 doses. Patients' ages ranged from 16-28 y (mean 20.0 y). Serum acetaminophen concentrations measured at 4 h post-ingestion ranged from 171-198 mcg/ml (mean 182 mcg/ml). Follow-up by the certified Regional Poison Information Center at 1-3 w post-discharge determined dosing compliance to be 83%. All 6 patients remained asymptomatic with normal liver function testing. Since health care reform encourages practitioners to reconsider established approaches to the delivery of health care, perhaps home delivery of NAC would not only be clinically preferred to premature cessation of the antidote, but also offer cost savings. Self-administration of NAC in the home setting may be representative of a new era in America's health care delivery system.

A comparison of the protective effects of N-acetyl-cysteine and S-carboxymethylcysteine against paracetamol (acetaminophen)-induced hepatotoxicity.

Ioannides C; Hall DE; Mulder DE; Steele CM; Spickett J; Delaforge M; Parke DV

Toxicology. 1983 Nov;28(4):313-21.

The protective effect of the sulphur-containing amino acids N-acetyl-cysteine and S-carboxymethylcysteine against paracetamol-induced hepatotoxicity was evaluated in the hamster by biochemical and histological methods. Of the animals receiving paracetamol alone 25% died within 24 h following administration. All surviving animals showed acute hepatocellular injury and marked loss of cytochrome P-450 and hepatic mixed-function oxidase activities. Simultaneous administration of N-acetylcysteine decreased the mortality rate, partly prevented the paracetamol-induced liver damage and partly restored enzyme activities. Simultaneous administration of S-carboxymethylcysteine with paracetamol afforded no protection. Kidneys from all animals were histologically normal. Human liver microsomes and liver microsomes from 3-methylcholanthrene-pretreated hamsters metabolised paracetamol to intermediate(s) that bind covalently to microsomal proteins. The rate of covalent binding was inhibited markedly by N-acetylcysteine and to a lesser extent by S-carboxymethylcysteine.

Pearls, pitfalls, and updates in toxicology

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Emergency Medicine Clinics of North America (USA), 1997, 15/2 (427-450)

Pearls, pitfalls, and updates in toxicology provide practical information for the clinical practice of emergency medicine. Clinical pearls in toxicology include using diagnostic tests to detect end-organ toxicity, applying physiologic principles to the management of hemodynamically unstable poisoned patients, and dealing with psychologic injuries from hazardous materials incidents. Recognizing serious complications from poisoning and adverse drug effects, including the serotonin syndrome, are offered as pitfalls. New therapies for clinical toxicology and pharmaceuticals with new toxicologic challenges are rapidly developing. Therefore, updates on the evolving role of N-acetylcysteine as an antidote for acetaminophen poisoning, new psychotropic medications, and new antidotes are included.

Management of acetaminophen toxicity

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American Family Physician (USA), 1996, 53/1 (185-190)

Acetaminophen poisoning is a significant medical problem in the United States and is frequently managed by family physicians. The primary clinical effect of acetaminophen poisoning is hepatotoxicity that occurs after ingestion of large single doses of acetaminophen or after ingestion of smaller doses in patients with hepatic metabolism that is altered by drugs or concurrent medical conditions. Hepatocellular damage is probably caused by accumulation of the toxic intermediate metabolite N-acetyl-p-benzoquinoneimine when hepatic glutathione stores are depleted. Treatment of acetaminophen poisoning consists of preventing gastrointestinal absorption of the drug, use of the antidote N-acetylcysteine and supportive care.

Inducers of cytochrome P450 2E1 enhance methotrexate-induced hepatocytotoxicity.

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Clin Biochem 1999 Oct;32(7):519-36

OBJECTIVES: To study the effect of cytochrome P450 2E1-inducers on methotrexate (MTX)-induced cytotoxicity in human hepatocytes, and investigate the role of silymarin in preventing this toxicity.

DESIGN AND METHODS: Cells were exposed to MTX in the presence of either ethanol (EtOH) or acetaminophen (APAP), or either combined with silymarin (S). Apoptosis and necrosis were measured by analyzing 6000 cells/sample using transmission electron microscopy, while cytokine release and apoptosis were quantitated by ELISA. Cytokine expression was measured by RT-PCR. Glutathione (GSH) content was determined in cytosolic (c) and mitochondrial (m) fractions.

RESULTS: MTX+EtOH and MTX+APAP increased MTX cytotoxicity 2.9-fold and 1.9-fold, respectively. S abolished this toxicity. MTX + EtOH increased the release of IL 6, IL 8 and TNF alpha by 1.0, 1.2, and 1.1 times, respectively. Cytokine expression was upregulated versus control for IL 6 (22%), IL 8 (38%), and TNF alpha (29%). Addition of 0.5 mmol/L S downregulated TNF alpha expression and reduced cytokine release. TNF alpha increased cytotoxicity by 22%, while anti-TNFalpha antibody eradicated it. MTX+EtOH depleted 45% mGSH ($0 < 0.001$) while S replenished it to 87% ($p < 0.001$), when both were compared to control levels.

CONCLUSIONS: Cytochrome P450 2E1-inducers contribute to increase oxidative stress in MTX-exposed cells by increasing TNF alpha and depleting both cGSH and mGSH. This enhances MTX-cytotoxicity and promotes apoptosis.

Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: Results of an open-label, clinical trial

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Journal of Pediatrics (United States), 1998, 132/1 (149-152)

We compared the clinical course of pediatric patients ($n = 25$) with acetaminophen poisoning treated with an investigational intravenous preparation of N-acetylcysteine (IV-NAC) with that of historical control subjects ($n = 29$) treated with conventional oral NAC (O-NAC) therapy. Patients received IV-NAC for 52 hours; historical control subjects received O-NAC (72 hours). There were no significant intergroup differences between treatment groups in age (15.5 vs 15.9 years), gender (88% vs 90% female) or distribution of risk categories (probable risk, 12 vs 15; high risk; 13 vs 14). The peak prothrombin time was significantly higher in the IV-NAC group (14.2 vs 13.6 seconds; $p = 0.048$). Mean treatment delay was significantly longer in the IV-NAC group (14.4 vs 10.4 hours; $p = 0.001$). Hepatotoxicity was noted in two (8.0%) patients in the IV-NAC treatment group and two (6.9%) patients in the O-NAC group. All patients recovered. Our results indicate that 52 hours of intravenous NAC is as effective as 72 hours of oral NAC.

Acetaminophen hepatotoxicity. An alternative mechanism.

Rosen GM; Singletary WV Jr; Rauckman EJ; Killenberg PG

Biochem Pharmacol (England) Jul 1 1983, 32 (13) p2053-9

Alcohol-fed hamsters were used to study the mechanism by which acetaminophen initiates hepatotoxicity. Animals maintained on an ethanol-containing diet (Group B) exhibited an increased mortality rate after administration of acetaminophen (400 mg/kg) as compared to control hamsters (Group A). However, in those animals in which the ethanol-containing diet had been replaced by the control diet 24 hr before receiving acetaminophen (Group C), significant protection against acetaminophen toxicity was observed as compared to control animals (Group A). This observation correlates well with the finding that Group C hamsters had higher levels of glutathione and catalase than was found in either Group A or Group B animals. It was also demonstrated that acetaminophen was oxidized by cytochrome P-450, producing acetaminophen free radical and hydrogen peroxide. The free radical in the presence of oxygen was found to generate superoxide and presumably N-acetyl-p-benzoquinone imine.

Protective effect of oral acetylcysteine against the hepatorenal toxicity of carbon tetrachloride potentiated by ethyl alcohol.

Simko V; Michael S; Katz J; Oberstein E; Popescu A Brooklyn VA Medical Center, NY 11209.

Alcohol Clin Exp Res 1992 Aug;16(4):795-9

Considering the well-documented protection of acetylcysteine (AC) in hepatotoxicity related to acetaminophen, we studied the preventive potential of AC against mild hepatotoxicity of CCl₄, potentiated with ethyl alcohol (ETH) and the role of tissue glutathione. Rats fed a liquid diet with 30% of energy from ETH, had-intraperitoneal CCl₄ administered in three injections, at 7-day intervals. AC was ingested at the level for acetaminophen overdose. ETH markedly potentiated the injury induced by CCl₄, as evidenced by higher values of serum alanine aminotransferase (ALT), urinary bile acids (BA), serum creatinine, histological score of liver cell necrosis, mortality and by lower body weights and lower liver glutathione, when compared with CCl₄ alone. Protective effect of AC consisted of a lesser hepatocytic necrosis, better body weights and higher liver glutathione. We conclude, that AC favorably modifies liver damage induced by CCl₄ and potentiated with ETH.

Intrinsic susceptibility of the kidney to acetaminophen toxicity in middle-aged rats.

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Toxicol Lett 1990 Jun;52(1):101-10

Acetaminophen (APAP)-induced nephrotoxicity is age-dependent in male Sprague-Dawley (SD) rats: middle-aged (9-12 months old) rats exhibit nephrotoxicity at lower dosages of APAP than do young adults (2-3 months old). The present study was designed to test the hypothesis that the intrinsic susceptibility of renal tissue to APAP toxicity is increased in middle-aged rats. APAP toxicity was evaluated in renal slices from naive 3- and 12-month-old male SD rats incubated with 0-50 mM APAP for 2-8 h. Renal slice glutathione (GSH) and APAP concentrations were determined; renal function was assessed by organic anion (para-aminohippurate, PAH) and cation (tetraethylammonium, TEA) accumulation; and cell viability was assessed by lactate dehydrogenase (LDH) leakage. At each concentration of APAP tested, accumulation of APAP by renal slices was similar in 3- and 12-month-olds. APAP toxicity in renal slices from both 3- and 12-month-old rats was characterized by concentration-dependent increases in LDH leakage.

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