Though delayed, I am sure, this issue will be a source of fresh breeze in your overburdened and compacted daily routine. Some knowledge tit-bits, current opinions and concerns in the field of poisoning and environmental health and a new food for thought may make you a little wiser. At the same time, you can catch up with the activities going on in the Poison Control Centre. Needless to mention, it gives us a great opportunity to keep in touch with you as well.

Contents:
- Scientific Articles / Reviews
  - N-Acetylcysteine in the treatment of Paracetamol poisoning
- Current Concerns
  - Cardiac care for poisoning cases differs from protocols.
- Regulatory Issues
  - Intellectual impairment in children with blood lead concentration below 10µg/deciliter.
  - Updated warning for Lindane use.
- Poison Control Centre News
  - WHO workshop to strengthen analytical toxicology and clinical services in Oman, 2-4 Nov. 2002
- Regular Feature
  - Brain teasers: Answers of the previous issue and new food for thought.
- Conferences / Training Courses

**N-Acetylcysteine in the Treatment of Paracetamol Poisoning**

Paracetamol is the most common drug amongst the pharmaceutical-induced poisoning in Oman. The data of central registry of poisoning cases and the results of hospital-based studies indicate high incidence of paracetamol poisoning both in adults as well as in children. Its widespread use as an antipyretic of choice, unsafe storage at home and nonavailability of child-resistant packs, all contribute towards easy accessibility of the drug to children. The accidental exposures in children are usually to subtoxic doses (<150mg/kg), while self-poisoning in adults involves high doses (>15 tablets of 500 mg each) often resulting in severe toxicity.

In acute overdose, it mainly causes liver toxicity; however, 1-10% of patients may develop acute renal failure in conjunction with severe hepatic failure. In therapeutic doses, after achieving the peak plasma levels within 4 hours, the drug is metabolized in liver by glucuronidation (60%) and sulfation (30%). A minor metabolic pathway via hepatic cytochrome P-450 mixed function oxidase system (CYP 2E1, 1A2, 3A4 subtypes) produces an intermediate toxic metabolite N-acetyl-p-benzoquinon- eimine (NAPQI), which is normally quickly detoxified by reduced glutathione and excreted in urine. However, after an overdose, the glutathione gets depleted, and more than 70% depletion of glutathione leads to accumulation and binding of this toxic metabolite to hepatic proteins and enzymes, causing hepatocellular centriloculare necrosis. The degree of liver injury depends on the (i) dose ingested (ii) the blood concentration of Paracetamol (iii) activity of cytochrome oxidase enzymes and (iv) rate of regeneration of hepatic glutathione. The risk of hepatotoxicity is higher in patients with liver disease, HIV infection and in patients being treated with hepatic enzyme inducer drugs (anticonvulsants,isoniazid).

**Mechanism of action**

NAC protects against liver damage in early stage (within 8 hours of ingestion) by (i) preventing NAPQI binding to liver cells (ii) acting as a precursor for glutathione (iii) replenishing reduced glutathione stores (iv) acting as a precursor for sulfite to conjugate NAPQI and by (v) reducing reconversion of NAPQI back to paracetamol. When administered within 8-24 hours after ingestion of paracetamol, the efficacy of NAC diminishes, however it is still effective and is used if toxic blood levels or overt hepatic toxicity is present. At this stage, it is suggested to act as an antioxidant, decrease neutrophil accumulation and improve microcirculation possibly by repleting sulfhydryl groups, necessary for the production of endothelium derived relaxing factor, thereby improving tissue oxygen exchange.
Use of NAC within 8 hours of ingestion

The early phase of poisoning begins after half an hour of ingestion and may last for 12-24 hours. Patient usually has anorexia, nausea, vomiting, diaphoresis, malaise and pallor. Some patients may even remain asymptomatic. Blood sample for paracetamol level should always be drawn at or after 4 hours of overdose to allow time for complete absorption. If the time of ingestion is unknown, but less than 4 hours, then immediately a blood sample should be drawn and a repeat sampling should be done after 2-4 hours to ensure peak levels. Blood for routine investigations and liver and renal function tests should also be drawn. These tests need to be repeated at 24 hours intervals.

The measured paracetamol levels are plotted on the Rumack-Matthew nomogram (Fig.1). At 4 hours of ingestion, if the blood level is equal to or above 200 µg/ml (200mg/L) it is considered toxic and requires NAC treatment. In USA, 4-hour level above 150 µg/ml is considered toxic (to allow possible errors in assay and time since ingestion). For alcoholics, AIDS patients, malnourished and those on enzyme inducers (high risk), the peak level of 100 µg/ml is considered for antidote therapy.

To summarize, the indications for NAC are (i) plasma paracetamol concentration in the toxic range on the toxicity nomogram, (ii) estimated ingestion of paracetamol more than 150 mg/kg within 8 hours (iii) elevated liver function tests and history of paracetamol overdose (iv) liver failure due to paracetamol.

Though the nomogram is very useful to decide for NAC treatment, its value is limited in patients who have ingested sustained-release preparations of paracetamol or have co-ingested paracetamol and a drug, which reduces gastric motility. Also the nomogram is not useful in treating chronic paracetamol overdose.

Administration of NAC

NAC can be administered intravenously as well as orally. There have been much a discussion on the pros and cons of iv versus oral administration; however, no controlled study has compared the two routes of administration. In Oman, intravenous route is used like in Europe, while in US oral treatment is common.

Intravenous preparation (Par-volex) is available as ampoule containing 2 g of NAC (20% w/v) in 10 ml of solution. The ampoule is diluted in 5% dextrose or 0.9% Sodium chloride. The initial loading dose in adults is 150 mg/kg, given as 200 ml infusion over 15 minutes, then followed by 50mg/kg in 500 ml fluid over next 4 hours then 100 mg/kg in 1000 ml infusion fluid over the next 16 hours, i.e. a total dose of 300mg/kg or 21 g for 70 kg in 20 hours. Children should be treated with the same dose but the quantity of the iv fluids needs to be monitored according to the age and weight of the patient.

Oral preparation of NAC is mucomyst, supplied as 10% or 20% solution. Loading dose of 140mg/kg followed by maintenance doses of 70mg/kg every 4 hours for 17 doses are administered through nasogastric or duodenal tube. To control vomiting, metoclopramide or ondansetron should be administered before NAC. Administration of activated charcoal does not interfere with the orally administered NAC.

Adverse Effects

After intravenous infusion, hypersensitivity reactions (anaphylactoid) may occur manifesting as nausea, vomiting, flushing, urticaria, pruritus angioedema, bronchospasm, hypotension, tachycardia and respiratory distress. These effects usually occur during first hour of infusion in 5% of patients. Asthmatics are at special risk. To prevent and treat anaphylactoid reaction, (i) administer NAC very slowly, (ii) stop infusion for sometime, and restart after antihistaminic treatment.

Rarely severe reactions as status epilepticus, cortical blindness, ECG abnormalities, fainting, and even death have been reported. However, these were mostly caused by wrong dose or too rapid infusion of the drug.

Oral therapy has less side effects except for severe nausea and vomiting due to its foul taste and smell, no serious adverse reactions have been reported. Antiemetic therapy is given to prevent these effects.

Conclusion

NAC is an effective antidote for acute paracetamol poisoning when administered within first 8 hours after ingestion, i.e. before hepatotoxicity develops. However, it will also provide some benefit in patients, who present after 8 hours with abnormal LFT or with fulminant hepatic failure. When used in proper dose schedule, it is reported to be safe. All patients with intentional exposure to paracetamol, more than 150mg/kg must be started on NAC treatment within 8 hours of ingestion. Pregnancy is no contraindication to NAC. Patients with history of ingestion of over the counter available analgesic/antipyretic/cold remedies must be investigated for plasma paracetamol levels.
Current Concerns

Cardiac Care for Poisoning Cases Differs from Protocols

Treatment of a cardiac dysrhythmia depends on its etiology. Because conventional advanced cardiac life support (ACLS) protocols were not designed with poisoning in mind, use of these guidelines may have inappropriate or dangerous effects. For example, a patient with tricyclic antidepressant intoxication may have wide-complex tachycardia resulting from severe depression of sodium-dependent channels in the myocardial cell membrane. However, use of the ACLS protocols for wide-complex tachycardia or possible ventricular tachycardia may lead the treating physician to administer procainamide, a class IA antiarrhythmic agent with cardiodepressant effects that could be additive to the effects of the tricyclic antidepressants. A patient with multiple premature ventricular contractions or runs of ventricular tachycardia after intoxication with chloral hydrate or inhalation of a chlorinated solvent would respond more readily to a beta blocker than to lidocaine, the drug recommended by the ACLS protocols. Finally, cardiac dysrrhythmias from digitalis intoxication are most appropriately treated with digoxin specific antibodies.

From WebMD Scientific American Medicine 01/02/2003.

Regulatory Issues

Intellectual Impairment in Children with Blood Lead Concentrations below 10\(\mu\)g per deciliter.

Despite dramatic declines in children’s blood lead concentrations and a lowering of the Centers for Disease Control and Prevention’s level of concern to 10\(\mu\)g per deciliter (0.483\(\mu\)mol per liter), little is known about children’s neurobehavioral functioning at lead concentrations below this level.

Authors measured blood lead concentrations in 172 children at 6, 12, 18, 24, 36, 48, and 60 months of age and administered the Stanford-Binet Intelligence Scale at the ages of 3 and 5 years. The relation between IQ and blood lead concentration was estimated with the use of linear and nonlinear mixed models, with adjustment for maternal IQ, quality of the home environment, and other potential confounders. The blood lead concentration was inversely and significantly associated with IQ. In the linear model, each increase of 10\(\mu\)g per deciliter in the lifetime average blood lead concentration was associated with a 4.6-point decrease in IQ (P=0.004), whereas for the sub sample of 101 children whose maximal lead concentrations remained below 10\(\mu\)g per deciliter, the change in IQ associated with a given change in lead concentration was greater. When estimated in a nonlinear model with the full sample, IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10\(\mu\)g per deciliter. It was concluded that blood lead concentrations, even those below 10\(\mu\)g per deciliter, are inversely associated with children’s IQ scores at three and five years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations.


Updated Warnings of Lindane Use

Gamma-hexachlorocyclohexane (Lindane) is approved as second-line topical treatment for pediculosis and scabies. Lindane has been marketed since 1951, but was labeled as second-line therapy in 1995 since safer alternative treatments were available. The Food and Drug Administration has issued additional warnings since toxicity (often secondary to misuse) continues to be reported. Neurotoxicity and deaths have been reported with excessive use, oral ingestion, or enhanced topical absorption (especially in children). Populations that are most vulnerable to neurotoxicity are children, small adults (ie <50kg), and elderly adults. New labeling includes the following:
Boxed-warning emphasizing second-line treatment.

Limit quantity dispensed to 1-2 ounces to avoid excessive application or reapplication.

Medication guide for patient use that must be dispensed by the pharmacist with each new prescription.

First-line treatments for scabies includes permethrin 5% cream (Elimite, Nix), crotamiton cream (Eurax), or malathion lotion 0.5% (Ovide). Preferably treat lice with pyrethrum 0.33% with piperonyl butoxide shampoo and permethrin cream rinse 1% (Nix, Rid).

From FDA MedWatch, 28.3.24-06-2003

Poison Control Centre News

WHO Workshop to Strengthen Analytical Toxicology and Clinical Services in Oman held from 02-04 November 2002.

The workshop was inaugurated by H.E. Saif Bin Ahmed Al-Ravahy, Undersecretary of Administration and Finance Affairs, Ministry of Health. In his inaugural speech, he emphasized that analytical toxicology is an integral part of the Poison Control Programme and is concerned with the early diagnosis and appropriate treatment of acute poisoning and chronic toxic exposures. Strengthening of such services is important to reduce the morbidity and the health care cost due to poisoning, which is a significant health problem in the country. Dr. Abdel Rahim, WHO Representative, Oman also graced the occasion. Fifty participants included laboratory personnel nominated from the clinical laboratories of all regional hospitals, Forensic laboratory, Ibn Sina Hospital, Institute of health Science and laboratories of SQU and Royal Hospital. The emergency medical experts from referral hospitals in Muscat and Emirate administrators also attended the workshop. Dr. Robert J. Falangan, Consultant Clinical Scientist at Medical Toxicology Unit, Guy’s and St. Thomas Hospital Trust, London, was the WHO Consultant for conducting the Workshop. The three day workshop mainly focused on (i) existing laboratory facilities and expertise (ii) role of analytical toxicology services in managing poisoning and (iii) practical aspects of such services related to laboratory organization and good laboratory practices. Some important analytical procedures and role of simple tests in diagnosis that can be established at primary health care level, were also discussed.

Regular Features

Brain Teasers : Answers of the previous issue.

- Ventilatory failure in some snake bites is due to paralysis of ventilatory muscles.
- Tricyclic depressants produce anticholinergic effects.
- A combination of elevated anion and osmolar gaps suggests poisoning due to methanol.
- Treatment with lithium can lead to hyperkalemia

New food for thought

- Vitamin K1 or K3 is effective antidote for super warfarin rodenticide poisoning?
- Folinic acid (leucovorin) and not folic acid should be used to treat methotrexate overdose. True / False.
- QRS and OT interval prolongation in ECG, is a typical finding of tricyclic antidepressant and carbamazepine poisoning. True / False.
- Treatment of methemoglobinemia with methylene blue is ineffective in cases with G6PD deficiency. True / False.

Forthcoming Conferences / Training Courses / Symposia During 2003 in Muscat

Symposium on Poison Control, Expert Group Meeting, May/June 2003
National Training Course on Lead Poisoning with Special Emphasis on Women and Children's health - September 2003.