Acute Versus Chronic Poisoning

Christopher S.G. Murray
A.A.S. (Pharm), R.Ph, B.Pharm (Hons)
MPhil Student, Section of Pharmacology
University of the West Indies, Mona

Poisoning

- This refers to exposure to any agent which is capable of producing a deleterious response in a biological system, seriously injuring function or producing death

- Poisoning occurs as a result of exposures.

General Pathway of Toxicants

Delivery

Interaction With Target Molecule

Cellular Dysfunction, Injury

Dysrepair

Attributes of Target Molecules

- All are potential targets
- Must possess appropriate reactivity
- If a target molecule is responsible for toxicity, the ultimate toxicant must:
  - React with the target and adversely affect its function
  - Reach an effective concentration at the target site
  - Alter the target in a way that is mechanistically related to the observed toxicity.

Processes That Increase or Decrease Concentration at Target Sites

- Increase
  - Absorption
  - Distribution to the Site of Action
  - Reabsorption
  - Toxication
- Decrease
  - Presystemic elimination
  - Distribution away from the Site of Action
  - Excretion
  - Detoxication

Categories of Exposure

- Toxicologists usually divide exposure into four categories:
  - Acute - exposure for less than 24 hours
  - Sub-acute - exposure for one month or less
  - Sub-chronic - exposure for 1-3 months
  - Chronic - more than 3 months

Features of Acute Poisoning

- Characterized by sudden and severe exposure
- Rapid absorption of the toxicant
- Usually involves single, large exposures
- Often reversible

Features of Chronic Poisoning

- Prolonged or repeated exposures lasting over many days, months or years
- Symptoms may not be immediately apparent
- Often irreversible
- May have far-reaching and deleterious effects

Factors Influencing Acute versus Chronic Toxicity

- Differences in disposition of chemicals (ADME)
- High absorption rates cause higher concentrations of toxicant at site of action
- Toxicant may be distributed to a site other than the target organ, decreasing toxicity
- Biotransformation may result in more/less toxic metabolites
- Rapid elimination rates reduce toxicity in target tissues.

Toxicity Testing in Animals

- The basis for toxicity testing in animals is
  - To establish safety in humans
  - To provide regulatory bodies with information
  - To provide guidelines to users

Acute Toxicity Testing

- First toxicity test to be performed on a chemical
- Male and female animals are used
- Number of animals to die in a 14-day period after a single dose is tabulated.

Acute Toxicity Testing (cont'd)

- This gives a quantitative estimate of acute toxicity (LD50) for comparison with other substances
- Identifies target organs and other clinical manifestations of acute toxicity
- Establishes the reversibility of the toxic response
- Provides dose-ranging guidance for other studies
- 24-hr dermal exposure/4-hr inhalation studies may also be done

Sub-acute toxicity testing

- Obtains information on toxicity of a chemical after repeated administration
- 3-4 different dosages are given to different groups of animals, usually rats (10/sex/dose)
- 14-day exposure
- Clinical chemistry, histopathology performed 14 days after exposure

Sub-chronic toxicity testing

- 90-day duration
- Goal is to establish a NOAEL, as well as to identify and characterize organs affected after repeated administration
- LOAEL may also be obtained for species tested
- Results have regulatory implications, e.g. EPA uses NOAEL to calculate reference doses.

Sub-Chronic Toxicity Testing (cont'd)

- Conducted in two species, by routes of intended exposure
- 3 doses employed; high (90%), intermediate and low
- All animals killed after 90 days and clinical chemistry and pathology done

Chronic Exposure Studies

- Similar to sub-chronic studies, except that period of exposure is greater than 90 days.
- In rodents, duration is 6 months-2 years.
- Length of exposure usually dependent on intended length of exposure in humans, e.g. short-course agents for 6mths long-term for 2 years.

Carcinogenicity

- These studies are performed in rats and mice, concurrent with chronic studies
- Maximum tolerated doses are given daily
- Benign and malignant tumours are statistically represented.

The Human Correlation

- Animal testing results provide information for safety of agents
- The likelihood of acute versus chronic poisoning, or both, can be elucidated
- The reversibility or mode of supportive treatment for episodes of toxicity can be ascertained

Toxicity with Individual Agents

- An agent may exhibit acute or chronic toxicity, or both
- Where both occur, this may manifest in different ways
- Modes of treatment for acute versus chronic may differ
- Prognostic outcomes may differ

Toxic Agents-Pharmaceutical Drugs

- Aspirin- Single ingestion of more than 200mg/kg will produce significant acute intoxication; chronic with >100mg/kg/day
- Paracetamol- Doses greater than 140 mg/kg will cause acute toxicity within first 24h
- Tricyclic antidepressants cause severe acute intoxication, 30-60 minutes after overdose; chronically they may cause arrhythmias

Toxic agents-Pharmaceutical Drugs

- Narcotics may cause acute toxicity in high doses, manifested as respiratory arrest and coma; chronic toxicity may cause cardiac arrhythmias and myoglobinuria

- Digitalis glycosides- these may be acutely toxic in large doses, but chronic toxicity can occur from constant overmedication

Toxic Agents-Household Cleaning Agents

- Alkalies e.g. drain cleaners, ammonia – acute toxicity; penetrating liquefaction necrosis
- Concentrated acids, e.g. toilet bowl cleaners –acute toxicity; coagulation necrosis
- Weaker cleaning agents, e.g. household ammonia, household bleach- acute toxicity; superficial burns and irritation

Toxic Agents- Pesticides

- Organochlorines - exposure causes acute toxicity with neurological severity; chronic exposure results in much milder neurological symptoms
- Organophosphate anticholinesterases Acute toxicants when absorbed in sufficient doses; effects of one poisoning may be chronic.

Toxic Agents-Metals

- Arsenic – Ingestion of 70-80 mg of arsenic may be fatal due to cardiovascular failure. Anemia and granulocytopenia may also occur after acute exposure. Chronic exposure may cause neurotoxicity, liver damage and cancer

Toxic Agents-Metals (cont'd)

- Cadmium- Acute toxicity occurs with very high doses and may produce pneumonitis and edema; chronic exposure may cause COPD, nephrotoxicity, hypertension, and possibly cancer
- Mercury- Not much acute toxicity; chronic exposure results in neurological damage

Toxic Agents-Metals (cont'd)

- Nickel- Acute contact exposure causes dermatitis; chronic occupational exposure causes a five-fold increase of lung cancer and a 150-fold increase in nasal cancers
- Iron- Severe acute toxicity occurs after ingestion of more than 2.5g of ferrous sulphate; renal failure or hepatic cirrhosis may also occur. Chronic exposure to high levels of iron causes altered liver function, DM and other endocrine disorders

Toxic Agents-Metals (cont'd)

- Lead – Principal route of exposure in the general population is food, but water and air are also responsible
- Lead causes chronic poisoning; is neurotoxic, hematotoxic and nephrotoxic. It may also affect blood pressure and the reproductive system

Toxic Agents-Solvents and Vapors

- **Benzene – Acute exposure to high concentrations may depress the CNS, leading to unconsciousness and death, or cause fatal cardiac arrythmias.**

  Chronic exposure in the workplace leads to bone marrow damage, which may manifest as anemia, leucopenia or thrombocytopenia

Toxic Agents-Solvents and Vapors (cont'd)

- Chloroform – Exposure to very high levels can cause liver and kidney damage as well as cardiac arrhythmias by catecholamine sensitization

  Repeated exposure to lower, sub-narcotic levels can also cause kidney and liver toxicity

Toxic Agents-Solvents and Vapors (cont'd)

- Ethyl Alcohol –Acute effects on the CNS, dose-dependent CNS depression; serum levels >300mg/dL may cause coma

  Chronic effect is liver damage and cirrhosis

- Ethylene Glycol- Acute ingestion of doses of 1.4ml/kg is lethal in humans; causes a profound acidosis; chronic exposure may cause renal damage.

Toxic Agents-Solvents and Vapors (cont'd)

- Gasoline and Kerosene – Extremely high level exposures of vapor may result in dizziness, coma, collapse and death. Non-lethal exposures may result in brain damage.

  Chronic exposure may cause renal toxicity

Toxic Agents- Animal Toxins

- Snakes – Venom causes acute toxicity due to enzymatic activity which may be neurotoxic or cytolytic; antivenin needed to save patient
- Marine Toxins- usually acutely neurotoxic or anaphylactic
  - Ciguatera
  - Scombroid
  - Paralytic Shellfish Poisoning
  - Puffer Fish

Toxic Agents- Animal Toxins (cont'd)

- Spiders- Venom causes acute toxicity due to interaction with neurotransmitters ; progressive local necrosis, rarely hemolytic anemia
- Ants/bees/wasps/hornets- Acute toxicity due to venoms; usually allergic

Toxic Agents-Plants

- Plants may have acute or chronic effects.
  - Mushroom poisoning- amatoxin causes massive necrosis of the liver, kidneys and skeletal muscles
  - Ackee- young fruit can cause acute toxicity by presence of hypoglycin A

Regulatory Bodies

- FDA- enacted in 1938 and covers food for humans and animals, human and veterinary drugs, medical devices and cosmetics
- EPA- created in 1970, responsible for industrial chemical and pesticide regulation, regulation of drinking water supplies, hazardous waste control, and regulation of toxic pollutants of water and air

Regulatory Bodies (cont'd)

- OSHA- (1970) responsible for prescribing mandatory occupational safety and health standards; e.g. PEL, TWA, STEL
- CPSC- (1972) has authority to regulate products that pose an unreasonable risk of injury or illness to consumers

References

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