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Great Ormond Street Hospital for Children



NHS Trust

Pharmacology and Drug Toxicity

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Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations.

They will not be repeated here.

- Kinetic concepts: first order & zero order kinetics of drug metabolism, effect of loading doses, changes in serum drug levels as a function of time and drug elimination, half life concept
- Dynamics of drug-receptor interaction: agonists, antagonists, partial agonists, inverse agonists, concentration-effect relationships: hysteresis
- Patterns of absorption & routes of administration: relationship of bioavailability and route of administration, protein binding.
- Mechanisms of drug interactions: inhibition and promotion of drug uptake; competitive protein binding; receptor inter-actions
- Patterns of drug distribution: volume of distribution, role of fat solubility, effect of protein binding, factors effecting protein binding, role of perfusion, drug molecular size and formulation on disposition
- Patterns of drug metabolism: phase I and II (conjugation) mechanisms
- Patterns of drug excretion and elimination: concepts of drug clearance, applied to whole body and individual organs; simple 1 and 2 compartmental models; concepts of wash-in and wash-out curves; hepatic and renal excretion, alterations with organ failure, alterations with clearance with extracorporeal support
- Pharmacogenetics: familial variation in drug response

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum

Pharmacology:

- Factors influencing cutaneous, enteral and intramuscular drug absorption
- Aerosolised/nebulised drug delivery
- Drug distribution in CNS and intrathecal drug administration
- Kinetics of intraosseous drug administration
- Organ-toxic side effects of drugs
- Effects of acute organ failure on drug levels and elimination; therapeutic drug monitoring
- Drug interactions

Intoxication:

General principles of drug intoxication management:

- indications & contraindications to gastric emptying, alimentary binding agents
- Forced renal excretion including the role of dialysis/haemofiltration
- Plasma protein binding
- Role of local poison information service.

Curriculum Notes for Year 1:

FACTORS INFLUENCING CUTANEOUS, INTRAMUSCULAR AND ENTERAL DRUG ABSORPTION

1. Cutaneous Drug Absorption

- Drugs must be lipid soluble to be absorbed via this route.
- Topical administration is usually used for a local effect. Cutaneous absorption is generally poor through unbroken skin as the lipid solubility of most drugs is too low.
- Drugs used on PICU where cutaneous administration is used for systemic effect include hyoscine patches, fentanyl patches
- Intranasal cutaneous absorption is important for drugs such as desmopressin (DDAVP).

2. Subcutaneous and Intramuscular Drug Absorption

- The mechanism of absorption is diffusion through the tissue.
- Rate of absorption depends on
 - site of injection
 - local blood flow
- Hyaluronidase breaks down the intracellular matrix therefore increasing diffusion
- Absorption will be decreased in cardiovascular or septic shock.

3. Enteral Drug Absorption

- Predominant mechanism for drug absorption is passive transfer, determined by ionization and lipid solubility of the drug. Drugs with very low lipophilicity and strong acids or bases will generally be poorly absorbed. Other mechanisms include carrier-mediated transport (eg iron and calcium).
- The main factors which determine rate and extent of absorption are
 - GI motility
 - GI pH
 - Splanchnic blood flow
 - Drug molecular size
 - Drug formulation
 - Drug physicochemical factors
- In general, approximately 75% of a drug will be absorbed within 1-3 hours of enteral administration.
- Remember that different enteral formulations of the same drug may have different bioavailability eg phenytoin, nifedipine.
- It is important to consider site of absorption of drug with respect to whether patient has an NG or NJ tube in situ. Drugs which are primarily absorbed higher up in the GIT will be unsuitable for NJ administration, eg aciclovir, phenytoin, sodium ferredetate (Sytron), alimemazine (Vallergan).
- For advice on whether a drug is suitable for NJ administration contact the PICU pharmacist or Medicines Information.

AEROSOLISED/NEBULISED DRUG DELIVERY

- Drugs may be given via inhalation for two purposes, either for local action with preferably minimal systemic absorption, or for systemic drug delivery where the large surface area of the lung and blood flow allows rapid alterations in plasma concentrations, eg for anaesthetics.
- Chemical modification of a drug may be used to target local delivery to the lungs while minimizing systemic absorption and thus decreasing systemic adverse effects, eg ipratropium is a quaternary ammonium ion analogue of atropine with poor systemic absorption.
- Drug delivery to the lungs will depend upon:
 - particle size distribution
 - inertial impaction
 - sedimentation (settling)
 - diffusion (Brownian motion)
 - electrostatic precipitation
 - delivery device (neb v inhaler)
 - type of ventilation

- For a summary of the pharmacological and pharmaceutical aspects of aerosolised drug delivery and for useful articles discussing issues relevant to aerosolised drug delivery in ventilated patients, see the references listed at the end of this document.

DRUG DISTRIBUTION IN CNS AND INTRATHECAL DRUG ADMINISTRATION

- Drug penetration of the blood-brain barrier depends on the following drug properties:
 - lipid solubility
 - ionic dissociation at blood pH
 - protein binding
 - molecular size
 - serum drug concentration
- The degree of meningeal inflammation and integrity of the blood-brain barrier will also determine whether drugs will penetrate. Meningitis results in inflammation which disrupts the integrity of the blood brain barrier, allowing drugs which otherwise would not normally permeate the bbb to cross into the brain – eg penicillins, rifampicin.
- Where drugs have poor penetration across the blood-brain barrier and it is necessary to achieve high levels in the CSF, intrathecal drug administration may be necessary, eg aminoglycosides and vancomycin for shunt infections.
- It is essential that a preservative-free product is used for all intrathecally administered drugs, and that for all IT therapy, the policies for intrathecal drug administration are strictly adhered to (located on the GOS web).

KINETICS OF INTRAOSSEOUS DRUG ADMINISTRATION

- The marrow of long bones has a rich network of vessels that drain into a central venous canal, and ultimately into the systemic venous circulation. Medications and fluids that are infused via the intraosseous route gain entry to the central circulation within seconds.

ORGAN-TOXIC SIDE EFFECTS OF DRUGS

1. Type A Adverse Drug Reactions:

- Pharmacologically predictable
- Dose dependent
- High incidence
- Morbidity high but mortality low
- Dose adjustment may be sufficient for management

2. Type B Adverse Drug Reactions:

- Unrelated to the drug's pharmacology therefore unpredictable
- Dose independent
- Low incidence
- Low morbidity but high mortality
- Management is to immediately stop the causative drug
- May be caused by immunological mechanisms eg anaphylaxis, blood dyscrasias
- Examples of severe Type B adverse drug reactions that have been seen on the unit in the last few years include acute severe hepatotoxicity with phenytoin, azithromycin and erythromycin.

NB: Remember that a yellow ADR card (found at the back of the BNF-C) should be completed for all suspected reactions to new drugs, and any serious suspected reactions to established medicines (even if well recognised or a causal relationship is uncertain).

EFFECTS OF ACUTE ORGAN FAILURE ON DRUG LEVELS AND ELIMINATION; THERAPEUTIC DRUG MONITORING

1. Hepatic impairment

- Drug dosing is generally empirical as, unlike in renal impairment, there is no accurate measure of the degree of hepatic impairment.
- Reduction in drug metabolism may occur due to either
 - a reduction in enzyme metabolizing capacity
 - decreased hepatic blood flow or intra/extra hepatic shunting.

- Dosage adjustment may be required for drugs that are extensively hepatically metabolised, especially those with a high extraction ratio.
- The extraction ratio of a drug is the extent to which a drug is cleared on a single pass through the liver; clearance of drugs with a high extraction ratio is limited by blood flow. Clearance of drugs with a low extraction ratio is limited by metabolizing capacity.
- Drugs with a high extraction ratio will have increased bioavailability in hepatic impairment due to a reduction in first-pass metabolism.
- Drugs with a low extraction ratio will not have an elevated peak concentration but the half-life will be prolonged and dosage interval may need to be extended.
- A significant reduction in drug metabolism is usually only seen in severe hepatic impairment. As a general rule, dosage reduction is by 50% for hepatically metabolised drugs with a high extraction ratio, and by 25% for drugs only affected by enzyme metabolizing capacity.
- For advice on dosage adjustments in hepatic impairment, contact the PICU pharmacist or Medicines Information.

2. Renal Impairment

- Dose adjustment may be required either if a drug is renally cleared, or if a drug is renally toxic.
- Dosage adjustments for renally cleared drugs should be made on the basis of the degree of renal impairment, ie whether impairment is mild, moderate or severe. The degree of impairment may be approximated by the patient's creatinine clearance:

- mild impairment:	CRCL = 20-50 ml/min
- moderate impairment:	CRCL = 10-20 ml/min
- severe impairment:	CRCL < 10ml/min

- Where it is not practical to take a 24 hour urine collection to determine creatinine clearance, the following equation may be used to estimate CRCL in children aged 1-18 years:

$$\text{Estimated CRCL} = \frac{40 \times \text{Height}}{S_{CR}} \text{ (ml/min/1.73m}^2\text{)}$$

Where S_{CR} = Serum creatinine in micromol/L

- For infants below 1 year of age, creatinine clearance equations are not generally reliable however the following equation may be helpful when deciding dosage adjustments:

$$\text{Estimated CRCL} = \frac{30 \times \text{Height}}{S_{CR}} \text{ (ml/min/1.73m}^2\text{)}$$

Where S_{CR} = Serum creatinine in micromol/L

- Remember that drug dosing recommendations in renal impairment are guidelines only and the clinical status of the child must be taken into account – in septic children where the risk of subtherapeutic dosing of antibiotics is greater than the potential risk of accumulation and drug toxicity, it may be the decision of the clinician to decrease the drug dose empirically by a smaller degree than usual to avoid underdosing the patient.
- Drugs which may require dose adjustment in renal failure because of their inherent nephrotoxicity include ciclosporin, which is an example of a hepatically metabolised but potentially highly nephrotoxic drug.
- For information on drug dosage adjustments in renal impairment, or in patients undergoing renal replacement therapies, contact the PICU pharmacist or call Medicines Information.

3. Therapeutic Drug Monitoring (TDM)

- Drugs with a narrow therapeutic index and for which there is a close correlation between plasma drug concentration and effect may require therapeutic drug monitoring.
- Drugs for which TDM should be undertaken include:

- aminoglycosides
 - vancomycin
 - digoxin
 - phenytoin
 - phenobarbital
 - carbamazepine
 - thiopentone
 - theophylline/aminophylline
- For such drugs, any adjustment of dosage regimes for organ impairment should be based on serum levels. An empirical dose adjustment may be necessary for the initial dose, eg with aminoglycosides, as per dosing recommendations in the GOS Antibiotic Policy. For subsequent dose adjustments once serum levels have been taken, discuss with the PICU pharmacist or Medicines Information.

DRUG INTERACTIONS AND USEFUL EXAMPLES

Drug interactions may be classified into pharmacodynamic or pharmacokinetic interactions. For a drug interaction to be clinically significant, the drug usually has to have a narrow therapeutic index, and for pharmacokinetic interactions, also exhibit a steep dose-response curve.

Pharmacodynamic interactions are where the pharmacological effect of the drug is altered while the plasma concentration remains the same. These may be due to drug synergy or antagonism at the receptor site, or to indirect receptor effects eg insulin and beta blockers. Pharmacodynamic interactions are usually more predictable than pharmacokinetic interactions.

Pharmacokinetic interactions are where the plasma concentration of a drug is altered before it reaches the site of action.

Pharmacokinetic interactions may occur during any of the four stages of absorption, distribution, metabolism and elimination of the drug. Pharmacokinetic interactions are influenced by interpatient variability and as such are unpredictable, but may be anticipated by looking at the kinetic properties of the drug. The majority of clinically significant pharmacokinetic drug interactions result from hepatic metabolism interactions.

1. Absorption:

- Several mechanisms may be involved eg
 - drug binding (chelation)
 - alterations in gut motility
 - alterations in pH
 - alterations in microbial flora
 - alterations in drug metabolism within gut wall
- Drug binding: Physicochemical properties of the drugs may result in chelation of two drugs and therefore decreased absorption. The main culprits are iron, calcium, antacids and sucralfate, which chelate drugs such as tetracyclines and ciprofloxacin. This also occurs with anionic exchange resins eg cholestyramine, which binds drugs such as digoxin, warfarin, ciclosporin and thyroxine.
- It is important to remember that chelation may also occur with enteral feeds – eg a clinically significant interaction exists between enteral feeds and enteral phenytoin. Enteral feeds must be stopped for at least 30 minutes before and after phenytoin administration. Sucralfate may also chelate with enteral feeds causing bezoar formation.
- Alterations in gut motility: this generally affects absorption rate of drugs rather than the extent of absorption. A useful interaction is metoclopramide and paracetamol.
- Alterations in pH: Gastric pH can affect the solubility, ionization and release characteristics of specialised formulations. An example of a useful absorption interaction is that ranitidine is given with pancreatic enzymes – the increased pH causes an increase in the absorption of the enzymes thus allowing a lower dose of pancreatic enzymes to be used.
- Alterations in gut microbial flora and drug metabolism within the gut wall: In approximately 10% of patients, a substantial proportion of digoxin is metabolised and

inactivated by gut bacteria. Broad spectrum antibiotics such as erythromycin may increase digoxin concentrations by as much as 100% in these patients.

2. Distribution

- Drug interactions involving distribution are seldom clinically important and protein binding displacement is frequently overestimated as a cause of potential interactions.
- Those that are of clinical significance usually involve drugs with a narrow therapeutic index, low Vd or with saturable kinetics eg phenytoin.
- Acidic drugs are more frequently involved in displacing other drugs from albumin binding sites than basic drugs.
- Displacement of drugs from plasma protein binding sites transiently increases the concentration of free unbound drug, but this is followed by an increase in drug elimination. This results in a decrease in total plasma drug concentration while the free (active) concentration returns to similar levels as initially. An example of this interaction is chloral hydrate or triclofos with warfarin. The major metabolite of chloral hydrate and triclofos is trichloroacetic acid, which is highly protein bound and transiently displaces warfarin from plasma proteins, resulting in a temporary rise in INR, which may then return to the previous level with continued therapy.
- Another drug to be aware of is phenytoin. If a drug is introduced which displaces phenytoin from protein binding sites, the total drug concentration will be reduced due to increased elimination, but there will be no loss of efficacy as the free (active) drug concentration will remain the same. This needs to be taken into account when interpreting phenytoin levels, which reflect the total drug concentration, both bound and unbound. If it is not recognised that the therapeutic range has been reduced then this could result in an inappropriate dose increase and potential toxicity.

3. Metabolism

- The liver is the principal organ for drug metabolism but metabolism also occurs in the gut, lung, skin, kidney, blood and platelets.
- Phase I metabolism generally involves the hepatic cytochrome P450 mixed function oxidase system, and it is this enzyme system which is implicated in most clinically significant drug interactions.
- It is important to consider the isoenzyme by which the drug is metabolised, as drugs may be metabolised by, inhibit or induce different isoenzymes.
- **Enzyme inhibition** is the most commonly reported mechanism responsible for drug interactions. The mechanism involved is usually competitive. The inhibiting drug may or may not be metabolised itself by the enzyme it inhibits.
- Enzyme inhibition usually reaches a maximum within 24 hours unless the inhibitor has a very long half life. When the half-life of an inhibitor is less than that of the object drug, the offset of an interaction will be quicker than its onset.
- Examples of **enzyme inhibitors** include:-
 - allopurinol
 - amiodarone
 - chloramphenicol
 - cimetidine
 - ciprofloxacin
 - diltiazem
 - enoxacin
 - erythromycin
 - alcohol (acute)
 - oral contraceptives
 - isoniazid
 - MAOI's
 - metronidazole
 - omeprazole
 - quinine
 - verapamil
 - fluconazole
 - itraconazole
 - sodium valproate
- **Enzyme induction** appears to be dose related and it is difficult to predict the degree of enzyme induction in any given patient. Enzyme inducers usually have high lipid solubility and primarily affect phase 1 metabolism, although some phase 2 reactions may also be affected.
- Enzyme induction interactions usually exhibit a delayed onset, generally anywhere from 4-14 days after initiation of the enzyme inducing drug.
- Some drugs may induce their own metabolism (autoinducers), eg carbamazepine

- Examples of **enzyme inducers** include:-
 - rifampicin
 - carbamazepine
 - phenobarbitone
 - phenytoin
 - St John's wort
 - primidone
 - alcohol (chronic)
 - griseofulvin
 - tobacco smoke

4. Elimination/Excretion

- The main mechanisms by which one drug may affect the excretion of another are by:
 - altering protein binding and therefore degree of filtration
 - inhibiting tubular secretion of the drug
 - altering urine flow and/or urine pH
- The mechanism by which tubular secretion of a drug is inhibited is by direct competition for the transport protein. Examples of clinically significant interactions of this type are that probenecid inhibits the tubular secretion of penicillins and cephalosporins, and probenecid and aspirin inhibit the tubular secretion of methotrexate.
- Diuretics tend to increase the urinary excretion of other drugs but this is seldom of clinical significance.
- Drugs that undergo passive tubular reabsorption may be affected by changes in urinary pH. This is because diffusion is governed by the concentration and lipid solubility of the non-ionic form of the drug on either side of the membrane. Ionisation of the drug will depend on urinary pH and drug's pKa. Weak acids (pKa 3-7) and weak bases (pKa 7-11) tend to be susceptible to urine pH changes.
 - In acidic urine, weak acids tend to be reabsorbed.
 - In alkaline urine, weak bases tend to be reabsorbed.
- A useful example of this type of interaction is that urinary alkalisation is used to promote methotrexate excretion.

Physical incompatibilities may also be classified as a type of drug interaction. These are where the physicochemical properties of the two drugs result in complexation when the drugs are mixed together in a syringe or at a Y-site, thus potentially causing precipitation. This should always be considered when advising two or more infusions to be given concurrently via the same lumen of an intravenous line, ie Y-sited. For information on physical compatibility and advice regarding administration of combinations of drugs, contact the PICU pharmacist or Medicines Information.

REFERENCES, WEBSITES AND OTHER SOURCES OF INFORMATION:

1. Drug Interactions:

<http://medicine.iupui.edu/flockhart/>

<http://www.drugdigest.org/DD/Interaction/ChooseDrugs/1,4109,.00.html>

- Stockley IH. Drug Interactions Electronic Version CD Rom 2003. Pharmaceutical Press, London, UK 2003
- Hansten PD, Horn JT. Drug Interactions - Analysis and Management. Wolters Kluwer Health, Missouri, USA 2005

2. Adverse Effects:

- Dukes MNG, Aronson JK. Meyler's Side Effects of Drugs, 14th edn. Elsevier Science BV, Amsterdam, 2000
- Davies DM, Ferner RE, de Glanville H. Davies's Textbook of Adverse Drug Reactions, 5th edn. Chapman & Hall Medical, London, UK 1998

3. Pharmacology:

- Walker R, Edwards C. Clinical Pharmacy and Therapeutics, 3rd edn. Churchill Livingstone, Edinburgh, UK 2003. Chapters 1, 2, 3
- www.merck.com/mrkshared/mmanual/section22/sec22.jsp
- Rang HP, Dale MM, Ritter JM. Pharmacology, 5th edn. Churchill Livingstone, Edinburgh, UK, 2004.
- Hardman JG, Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edn. McGraw-Hill, USA 1996
- Winter ME. Basic Clinical Pharmacokinetics. 4th edn. Lippincott Williams & Wilkins, 2003
- Audus KL, Chickale PJ, Miller DW, Thompson SE, Borchardt RT. Brain uptake of drugs: chemical and biological factors. Adv Drug Res 1992; 23:1-64

4. Aerosolised Drug Delivery

- Fink JB. Aerosol delivery to ventilated infant and pediatric patients. Respir Care June 2004; 49(6): 653-65. Review.
- Bauer TT, Torres A. Aerosolized beta2-agonists in the intensive care unit: just do it. Intensive Care Med Jan 2001; 27(1): 3-5
- O'Doherty MJ, Thomas SHL. Nebuliser therapy in the intensive care unit. Thorax 1997; 52(S2): S56-S59
- Aulton ME. Pharmaceutics, 2nd edn. Churchill Livingstone, Edinburgh, UK 2001.

INTOXICATION

GENERAL PRINCIPLES OF DRUG INTOXICATION MANAGEMENT:

Indications & contraindications to gastric emptying, alimentary binding agents:

Gastric decontamination is unlikely to benefit most patients with toxic ingestion.

Syrup of Ipecac to induce emesis is no longer recommended for use in toxic ingestion in children. In order to be effective, emesis has to be induced within minutes of ingestion, and there is no clinical evidence that even when given relatively early, patient outcomes are improved.

The evidence for clinical benefit in **gastric lavage** is equally poor! Very early (within 1hr of ingestion) gastric lavage in severe ingestion with full airway protection cannot be ruled out as clinically useful, especially in those agents not adsorbed by activated charcoal (iron salts, fluorides, potassium salts, lithium preparations, methanol, ethylene glycol). Gastric lavage is contraindicated after ingestion of strong alkalis (e.g. sodium hydroxide), strong acids (sulphuric and hydrochloric acid) and hydrocarbons.

Activated charcoal presents a very large surface area for adsorption of many agents. It should be given early for greatest benefit – within one hour of ingestion being recommended. However, later administration is often used, as are multiple doses. Airway protection must be maintained.

Whole bowel irrigation (WBI) with PEG (polyethylene glycol) may be useful in illegal drug packet elimination, heavy metals, sustained release or enteric coated preparations.

References, websites etc

Clinical Toxicology 1997;35:695-792 – Position statements on ipecac syrup, gastric lavage, single-dose activated charcoal, cathartics, and WBI

Clinical Toxicology 2004;42:133-143, 243-253, 843-854, 933-943 – revised statements on ipecac syrup, gastric lavage, cathartics, and WBI

Clinical Toxicology 2005;43:61-87 - revised statement on single-dose activated charcoal

Clinical Toxicology 1999;37:731-751 – revised statement on WBI

Forced renal excretion, dialysis and haemofiltration

Urinary alkalisation may be used for instance in aspirin overdose – maintain urinary pH 7.5-8.5. 'Forced' diuresis is not recommended.

Haemodialysis is recommended for use in toxic ingestions of several agents, especially where other supportive measures have failed, or where there is significant renal impairment. It may be used electively in methanol poisoning. Haemodialysis/filtration/perfusion may have benefits in different agents depending on the physical properties and protein binding of the ingested toxin.

Role of local poison information service.

Advice is always available via The National Poisons Information Service (NPIS 0870 2432241 or <http://www.medtox.org/info/>). They should be contacted early for expert and up to date advice on the management of significant overdose.

Other resources:

<http://www.spib.axl.co.uk/> or <http://www.toxbasebackup.org/>

<http://www.npis.org/NPIS/uk%20npis.htm>

Information for Year 2 ITU Training (advanced):

Year 2 ITU curriculum

Specific management of the following drug intoxications can be found in the BMJ articles appended - (Poisoning in children – parts 1-5)

– references in brackets refer to the relevant part.

- Salicylate: (2)
- Acetaminophen: (2)
- Tricyclic antidepressants: (3)
- Digoxin: (5)
- Clonidine
- Beta Blockers: (5)
- Anticonvulsants:
- Narcotics: (2)
- Cyanide: (5)
- Amphetamines: (5)
- Petroleum distillates: (4)
- Corrosive agents: (4)
- Organophosphates: (5)
- Heavy metals: (3)
- Carbon monoxide:
- Glycol and methanol: (5)
- Alcohol: (4)
- Illicit “recreational drugs”: (5)

Curriculum Notes for Year 2:

ITU Management of Intoxication and Overdose:

The BMJ articles, plus the one from *Pediatric Annals* 2005 (Diagnosis and management of the poisoned child) contain lots of useful information. The National Poisons Information Service should be used to support and guide specific therapy (NPIS 0870 2432241 or <http://www.medtox.org/info/>).

The *Pediatric Emergency Care* article on antidotes has some interesting updates as well as information on nerve agents.

References, websites etc

- M Riordan, G Rylance and K Berry *Arch. Dis. Child.* 2002;87;392-396. Poisoning in Children 1: General management
- M Riordan, G Rylance and K Berry *Arch. Dis. Child.* 2002;87;397-399. Poisoning in Children 2: Painkillers
- M Riordan, G Rylance and K Berry *Arch. Dis. Child.* 2002;87;400-402. Poisoning in Children 3: Common medicines
- M Riordan, G Rylance and K Berry *Arch. Dis. Child.* 2002;87;403-406. Poisoning in Children 4: Household products, plants and mushrooms
- M Riordan, G Rylance and K Berry *Arch. Dis. Child.* 2002;87;397-399. Poisoning in Children 5: Rare and dangerous poisons
- J Dave Barry *Pediatric Annals Dec* 2005; 34, 12; 937-946. Diagnosis and Management of the Poisoned Child
- Marjorie Lee White, Erica L. Liebelt *Ped. Emerg. Care.* Nov 2006; 22, 11; 740-747. Update on Antidotes for Pediatric Poisoning
- <http://www.spib.axl.co.uk/> or <http://www.toxbasebackup.org/>
- <http://www.npis.org/NPIS/uk%20npis.htm>