Introduction

In many hospitals acute poisoning is one of the most common reasons for acute admission to a medical ward.

In such cases poisoning is usually by self administration of prescribed and over the counter medicines or illicit drug.

Those involved are most often females under the age 35 years, who are in good physical health they take an overdose in circumstances where they are likely to be found or in the presence of others.

In those older than 55 years, of age, men predominate and usually taken in the course of depressive illness or because of poor physical health.

In the developing world pesticide poisoning is by far a commoner cause.

In addition, ingestion of heating fuels (e.g. petroleum distillates) anti malarial, anti tuberculous, and traditional medicine is reported frequently.[1]

Paraphenylendiamine (PPD) an aromatic diamine is a hair dye used as cosmetic in Africa, Middle East, and countries of Indian subcontinent where it is commonly mixed with henna and applied to color the palms of the hands and soles of the feet and to dye hair a dark red shade.[2]

Ingestion produce characteristic clinical sequences of events that's often fatal.

In Sudan and parts of upper Egypt it's a frequent cause of suicidal poisoning. Intensive supportive care may lead to recovery.[3]

Passing of chocolate brown urine and acute renal failure is a constant feature of PPD poisoning.[4]

Acute renal failure is due to rhabdomyolysis, haemolysis, hypoxia, and the metabolic products of PPD which are execrated through the kidney. Oxidation of these products produces quinine structure which is nephrotoxic.[5]

The major clinical symptoms of presentation was cervicofacial edema followed by upper airway tract edema, oliguria, acute renal failure and shock.[6]

Aim of the Work

This work aims to study the systemic effect of black hair dye “PPD” on kidney function, and to asses the incidence and prevalence of renal affection. Also this work aims to understand the type of renal damage that occur after ingestion of black hair dye and finally to known renal outcome and mortality rate.

Drugs and Kidney

Drug

- Derived from the French word (Drogue) which means (dry herb).
- It is any substance that alter the body or the mood function by interaction at the molecular level.
- Used for diagnosis, prevention and treatment of diseases.

A) Effect of the Kidney on Drug (Renal Handling of Drugs)

Removal of a drug from the body may occur via a number of routes, the most important being through the kidney into the urine. Other routes include the bile, intestine, lung, or milk in nursing mothers.

1) Glomerular filtration: Drugs enter the kidney through renal arteries, which divide to from a glomerular capillary plexus. Free drug flows through the capillary slits into Bowman's space as part of the glomerular filtrate.

2) Proximal tubular secretion: Drug that was not transferred into the glomerular filtrate leaves the glomeruli through efferent arterioles, which divide to from a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two

energy-requiring active transport systems, one for anions and one for cations.[7]

3) **Distal tubular reabsorption:** as a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen back into the systemic circulation. Manipulating the pH of the urine to increase the ionized from of the drug in the lumen may be used to minimize the amount of back-diffusion and, hence, increase the clearance of an undesirable drug. For example, a patient presenting with a Phenobarbital overdose can be given bicarbonate, which alkalinize the urine and keeps the drug ionized, thereby decreasing its reabsorption. If the drug is a week base, acidification of the urine with NH_4CL leads to protonation of the drug and an increase in its clearance. This process is called "ion trapping".[8]

4) **Role of drug metabolism:** Most drugs are lipid soluble and diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space. To minimize this reabsorption, drugs are modified by the body to be more polar using two types of reactions: Phase I reactions that involve either the addition of hydroxyl groups or the removal of blocking groups from hydroxyl, carboxyl, or amino groups, and Phase II reactions that use conjugation with sulfate, glycine, or

glucuronic acid to increase drug polarity. The conjugates are ionized, and the charged molecules cannot back-diffuse out of the kidney lumen.[9]

B) Effect of Drugs on Kidney (Drugs Nephrotoxicity)

Drugs can lead to renal damage in a number of different ways:

1) Alteration of in renal blood flow

- NSAID (non steroidal anti inflammatory drugs)
- ACE

2) Direct nephrotoxicity (acute tubular nerosis)

- Antibiotics
- Heavy metal

3) Acute interstibial nephritis

- Antibiotics (penicillin – sulphonamides)
- NSAIDs

4) Chromic tubule interstitial nephritis

- Analgesic nephropathy

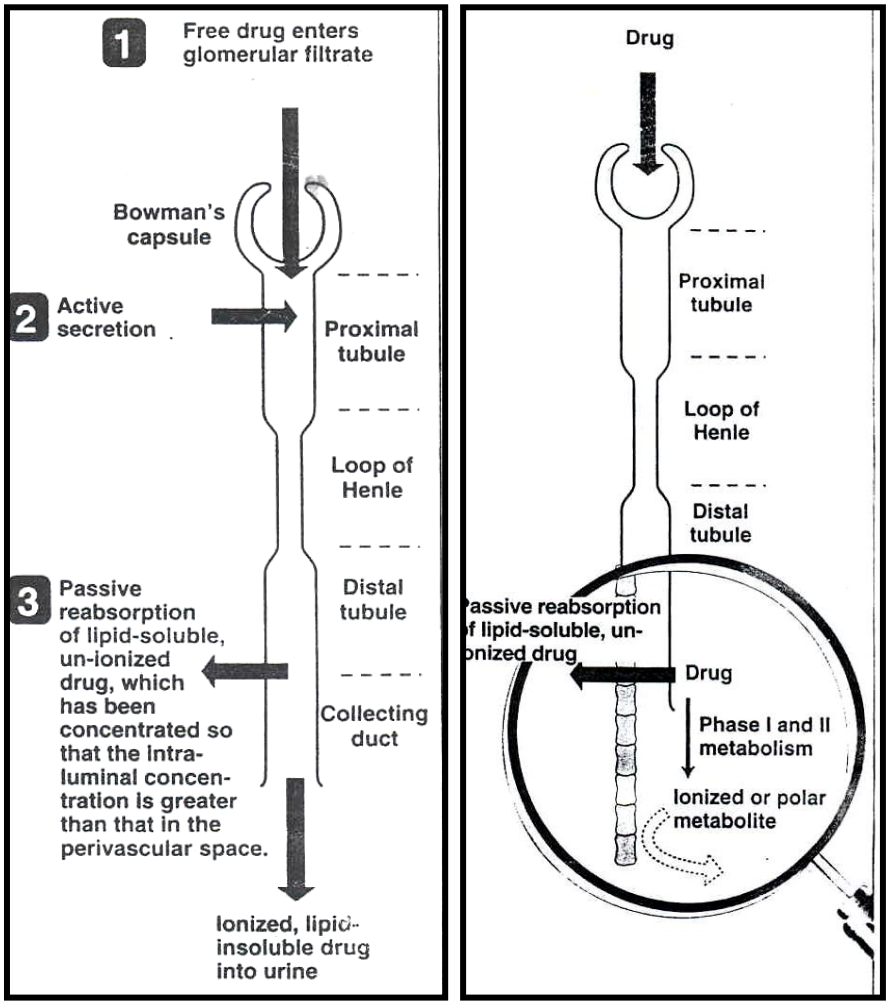

Figure (1): Renal handling of drugs.

Para-Phenylenediamine

(PPD)

Para-phenylenediamine (PPD), an aromatic diamine, is a hair dye used as a cosmetic in Africa, the Middle East, and the countries of the Indian subcontinents where it's commonly mixed with henna and applied to color the palms of the hands and soles of the feet and to dye hair a dark re shade.[10] Ingestion produces a characteristic clinical sequences of events that's often fatal. In Sudan it's a frequent cause of suicidal poisoning. Intensive supportive care may lead to recovery.[11]

Structural formula

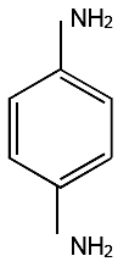

Figure (2): Structure of Para-phenylenediamine.

Physical properties of PPD

Para-phenylenediamine (1,4-diaminobenzene) is an aromatic diamine. Its molecular weight is 108.2. PPD occurs as a white to slightly red solids or crystals that darken on exposure

to air. The odour threshold for PPD has not been established. The vapor pressure for PPD is less than 1 mm Hg at 21^{o} and its log octanol/water partition coefficient (log kow) is -0.25. The Chemical Abstract Service Registry Number (CAS) is 106-50-3. The melting point is 145c the boiling point is 267c, its soluble in 100 parts cold water, soluble in alcohol, chloroform and ether.[12]

Uses of PPD

PPD has been used for over 70 years in permanent hair dyes. The dyeing action of PPD depends on its oxidation by the addition of hydrogen peroxide. It is also used for dyeing furs, as well as a photographic developing agent. PPD is used as a vulcanization accelerator and as an antioxidant in rubber compounds.[13]

Sources and preparation

PPD is a synthetic chemical and it is sold in local markets as a powder or as small stony dark lumps. PPD is a derivative of paranitroaniline.[14]

PPD is manufactured commercially by the reduction of p-nitro aniline. The process is divided into: reduction of the p-nitro aniline to PPD, filtration of reduction batch to remove iron oxide sludge, dehydration of filtered liquor and vacuum distillation of crude PPD.[15]

Toxic dose

An oral dose of about 7 gm of PPD may be followed by serious side effects. The lethal dose in man is estimated to be 10 g.[16]

Incompatibilities of PPD

PPD is a strong reducing agent and reacts violently with strong oxidizers, strong acids, acid chlorides, acid anhydrides, chloroformates and strong bases. PPD is incompatible with organic anhydrides, isocyanates, aldehydes. Heat and light contribute to its instability.[17]

Metabolism and excretion of PPD

PPD is a good hydrogen donor and is metabolized by one electron oxidation to a cation free radical by cytochrome P450 peroxidase to form a reactive benzoquinoredimine. This further oxidized to a trimmer known as Bandrowski's base, a compound reported to cause anaphylaxis as well as being strongly mutagenic. The metabolic products of PPD are excreted through the kidney.[18]

The presence of 6-aminobenzothiazole in urine was interpreted as being a metabolic reaction since the compound was not present as an impurity in the ingested PPD powder.[19]

Topical application of PPD leads to its conversion in human skin and/or human keratinocytes to its corresponding

acetylated metabolite. Acetylation of PPD is considered to be a detoxification pathway. It has shown that, of the absorbed fraction of topically applied PPD, more than 80% is excreted by man in the urine as its N, N-diacety1 derivative.[20]

Toxicity of PPD

PPD's potential for systemic toxicity is well recognized in Africa, Middle East and some Asian countries where availability makes it an attractive poisoning agent. In 1924 Nott described the first case of systemic toxicity with PPD in the proprietor of a hairdressing salon where toxicity occurred intermittently from handling dye. Since then there have been sporadic reports of systemic poisoning with PPD.[21]

Routes of PPD poisoning may be ingestion, inhalation, skin and/or eye contact. PPD affect the respiratory system, skin, liver, kidneys, blood, muscles and eyes.[22]

Today, the low concentration of PPD in standard hair dye formulation (max 2% PPD in 100 ml dye solution) makes the possibility of accidental poisoning negligible.[23]

Skin effects (allergy)

Skin contact with PPD can severely irritates and burns the skin. Repeated or prolonged contact may cause skin sensitization and allergy. The allergic potential of PPD and its derivatives remains an important cause of occupational allergy, particularly in cosmeticians and hairdressers. PPD was the fifth most frequent contact allergen after nickel, fragrance mixture, balsam of Peru and thimerosal.[24]

The relative prevalence of contact allergy to PPD appears to have decreased in recent years despite the increasing use of hair dyes in the industrialized world.[25]

Hsu et al. (2001) in USA reported 8 Arabic men with beard dermatitis associated with dye use between 1994 and 1999. These men commonly grow beards and dye them with PPD-containing dye. The lesions were described as pruritic, erythematous, popular eruptions. The symptoms subside after the patients discontinued use of the PPD dye and received treatment with topical corticosteroids. To avoid allergic reactions to PPD hair dyes, skin sensitivity test is recommended 48 hours before the hair coloring procedure. The skin test can be considered as an effective method for detection and prevention of hair dye allergy.[26]

An 18-year-old dental technician in Spain presented with dry hyperkeratotic lesions on his left palm that were limited to an area that was in contact with a rubber a container in which he had prepared the molds for a dental prosthesis. Thin layer chromatography of a piece of the rubber container detected the presence of PPD. The lesions resolved when the patient stooped using the container. The patient was diagnosed as occupational allergic contact dermatitis.[27]

Toxicity of PPD ingestion

Through, uncommon in the west, both accidental and intentional (suicidal or homicidal) ingestion of PPD is frequently reported from Africa, Middle East and India.[28]

A report from Sudan described that in the year 1982-1983, PPD ingestion was the most cause of suicidal poisoning in Omdurman. In another series from Khartoum, poisoning with PPD ingestion was diagnosed in 31 Sudanese children between the years 1984 and 1989.[29] There are two phase of serious toxic effects following PPD ingestion.[30]

The first phase

The first phase usually appears within 4 to 6 hours after PPD ingestion. Initially local irritation of the mucus membranes and skin results in numbness and burning of mouth, throat, epigastric pain and gastritis with persistent vomiting which may lead to dehydration. Intense progressive oedema of pharynx, larynx, head and neck is the most prominent feature in this phase. Hard swollen, protruding wooden tongue may results. The clinical picture may resemble a Ludwig's angina. Upper respiratory tract obstruction may result from the oedema and endotrachial intubations may be difficult. Death occurs usually in this phase and is due to acute respiratory distress.[31]

The second phase

This phase occurs later within 12 hours in a minority of the victims, in the form of rhabdomyolysis indicated by pain, weakness, tenderness and contracture, initially developed in the lower extremities and subsequently extending to allover the skeletal muscles with fever, malaise, tachycardia, nausea and vomiting. Acute renal failure with oliguria or anuria occurs in this phase. The urine is chocolate brown in colour.[32]

Skeletal muscles showed scattered coagulation necrosis and partially infiltrated with inflammatory cells on microscopic examination while renal collecting tubules and distal tubules were occluded by dark brownish myoglobin casts and its epithelium massively necrotized. Acute renal failure is due to rhabdomyolysis, haemolysis, hypoxia and metabolic products of PPD which are excreted through the kidneys. Oxidation of these products produce quinine structure which is nephrotoxic.[33]

Cardiovascular effects

Hypotensive shock (due to muscle oedema) is recognized in some cases presented with acute PPD poisoning and seems to be associated with poor prognosis.[34]

Also, lethal cardiogenic shock secondary to myocardial rhabdomyolysis, ECG changes in the form of arrhythmia and myocarditis may occur due to poisoning with this substance.[35]