

Iatrogenic Disorders

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Iatrogenic disease is the result of diagnostic and therapeutic procedures undertaken on a patient. With the multitude of drugs prescribed to a single patient adverse drug reactions are bound to occur. The Physician should take suitable steps to detect and manage them.

Iatrogenic (of a disease or symptoms) induced in a patient by the treatment or comments of a physician.

Chambers English Dictionary

One of the basic principles in treatment stated by Hippocrates is “First do no harm”. Stories of medical remedies causing more harm than good have been recorded from time immemorial. An iatrogenic disorder occurs when the deleterious effects of the therapeutic or diagnostic regimen causes pathology independent of the condition for which the regimen is advised. It would be impossible to provide the benefits of modern medicine if reasonable steps in diagnosis and treatment were withheld because of possible risks [1]. Diagnostic procedures (mechanical and radiological), therapeutic regimen (drugs, surgery, other invasive procedures), hospitalization and treating doctor himself can bring about iatrogenic disorders.

Adverse effects of diagnostic procedures

Mechanical procedures

Diagnostic aspiration of fluids may lead to hemorrhage, secondary infection, etc. Rapid pleural or peritoneal fluid aspiration and needle biopsies may lead to shock and even death. Endoscopic procedure may cause perforation of hollow viscus.

Diagnostic radiology

Reactions to contrast media injected intravenously or intra-arterially may be mild, moderate or severe, and some are potentially fatal. Intravascular contrast media may have a nephrotoxic reaction. Cerebral angiography may cause transient or permanent neurological deficits.

Radioisotopes are safe except in pregnant mothers or in newborn [2].

Adverse effects of therapeutic regimen

Adverse drug reactions (ADR)

ADR is defined by World Health Organization as any response for a drug which is noxious, unintended and which occurs at doses normally used for prophylaxis, diagnosis and therapy of disease [3]. ADR can be classified as predictable (side effects, toxicity, super infection, drug interactions) and unpredictable (intolerance, idiosyncrasy, allergy or pseudo allergy) [4].

When fewer than 6 different drugs are given in hospitalized patients, the probability of an adverse reaction is about 5%, but if more than 15 drugs are given, the probability is more than 20%. Of the patients admitted to a General hospital, 2 to 5% are due to ADR and fatality in patients with ADR varies from 2-12%. ADR occurs in the elderly more frequently [5].

To overcome the inadequacies in the WHO definition, new definition for adverse drug reaction is “an appreciably harmful or unpleasant reaction, resulting from an interaction related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment or alteration of the dosage regimen or withdrawal of the product”. They are classified into six types (with mnemonics), dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure) [6].

Anaphylaxis

Penicillin and other Beta-lactum antibiotics and various types of vaccines and sera, and human insulin, are the most common agents that cause anaphylaxis. Aspirin and other nonsteroidal anti-inflammatory agents (NSAIDs) cause non-IgE mediated anaphylactoid reactions [7].

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Drug induced cutaneous manifestations

Some of the cutaneous manifestations are [8]:

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| 1. Alopecia | Cytotoxic agents |
| 2. Erythema multiforme | Chlorpropamide,
Sulphonamides |
| 3. Exanthematous eruptions | Allopurinol, Anti
convulsants |
| 4. Exfoliative dermatitis | Gold, streptomycin |
| 5. Fixed drug eruptions | Barbiturates,
Tetracyclines |
| 6. Photosensitivity | Griseofulvin,
Indomethacin |
| 7. Toxic epidermal necrolysis | Barbiturates,
Sulphonamides |

Drug induced haematological disorders**Megaloblastic Anaemia (MA)**

Oral contraceptives, phenytoin, phenobarbitone and primidone cause MA due to folic acid deficiency, colchicines, neomycin, paramino salicylic acid (PAS) due to vitamin B₁₂ deficiency and 6-mercaptopurine, 5 fluoro-uracil, hydroxy-urea, acyclovir and zidovudine by interfering with DNA metabolism [9].

Hemolytic anemia

Drugs causing haemolysis by direct action are phenacetin, PAS, sulphonamides: by immune mechanism are aminopyrine, chlorpromazine, quinine and tetracycline: and in G-6 PD deficient patients, antimalarials (primaquine) and antibiotics (nitrofurantoin) [10].

Aplastic anaemia

Drugs that regularly produce bone marrow depression: busulphan, cyclophosphamide, chlorambucil, vinblastine, and 6 mercaptopurine. Drugs which rarely produce bone marrow depression: chloramphenicol, penicillamine, sulphonamides, isoniazid, NSAIDs, analgin, thiouracil, anticonvulsants, anti diabetics, cimetidine, tranquilizers etc [11].

Drugs producing Neutropenia [12]:

Analgesics and NSAIDs	:Indomethcin, Phenacetin, Acetaminophen, Phenyl- Butazone and Aminopyrine
Anticonvulsants	:Phenytoin, Carbamazepine
Antithyroid drugs	:Thiouracil, Methimazole
Phenothiazines	:Chlorpromazine
Antiarrhythmic	:Quinidine

Drugs that cause thrombocytopenia [12]:

Alpha-methyl dopa, carbimazole, chloramphenicol,

cyclosporins, phenylbutazone, quinine, quinidine, rifampicin, sulphonamides etc.

Hazards of blood transfusion[13]:

Complications occur in 2 percent of blood transfusions.

- Immunological reaction : Allergic-anaphylaxis, fever, haemolysis, non cardiac pulmonary oedema.
- Non immunological : Circulatory overload, thrombophlebitis and embolism, bacterial contamination, transmission of diseases like malaria, hepatitis, syphilis and AIDS and transfusion siderosis in multiple transfusion.

Drug induced gastro-intestinal diseases [5,7]**Oral lesions**

- Lichen planus like lesions : methyl dopa, chloroquine and propranolol.
- Lupus erythematosus like lesions : hydralazine, gold.
Acid peptic disease : acetyl salicylic acid, NSAIDs, corticosteroids etc.
Pancreatitis : azathioprine, glucocorticoids and oral contraceptives.
Malabsorption : broad-spectrum antibiotics, cholestyramine and neomycin.

Hepatic damage

Drug induced liver injury is a potential complication of nearly every medication because liver metabolizes virtually all drugs. Acute (acetaminophen, halothane) and chronic (nitrofurantoin, methyl dopa) hepatocellular injury, veno occlusive disease (cyclophosphamide) and hepatocellular carcinoma (sex and anabolic hormones) can all occur. There are many new drugs like glyburide, ketoconazole, lisinopril, lovastatin, ticlopidine etc. which were also associated with hepatotoxic reactions. Among causes of fulminant hepatic failure certain drugs like halothane, acetaminophen, phenytoin and alpha methyl dopa account for 20-50% of cases [14].

Respiratory disorders due to drugs [5,15]:

Type of reaction	Example of drug
1. Airway obstruction (Bronchospasm)	Beta-Blockers, Adenosine, NSAIDs
2. Cough	ACE inhibitors
3. Nasal congestion	Oral contraceptives, Reserpine, Guanithidine
4. Pulmonary oedema	Contrast media, Methadone, Interleukin 2
5. Pulmonary hypertension	Fenfluramine
6. Pulmonary infiltration	Anticancer agents, Acyclovir, Amiodarone

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| 7. Pleural disease | Hydralazine, Methysergide |
| 8. Pulmonary thrombo-embolism | Oral contraceptives |

Drug induced cardiovascular diseases

Drug reactions may lead to exacerbation of angina (alpha blockers), arrhythmias (digitals, beta-adrenergic agents, tricyclic anti-depressants and quinine), cardiomyopathy (daunorubicin, emetine and lithium), hypo or hypertension (glucocorticoids and sympathomimetics), pericardial disease (emetine, procainamide and minoxidil), and Torsades de pointes (sparfloxacin) [5].

Renal disorders caused by drugs [16].

The kidney is the main excretory organ of the body and hence affected by most drugs.

1. Directly toxic to the tubular cells: paracetamol, amphotericin B, cisplatin, sulphonamides etc.
2. Function as an antigen or as a hapten and the resulting antigen antibody reaction damages renal interstitium and leads to acute interstitial nephritis : penicillins, cephalosporins, NSAIDs, anticoagulants, gold salts, captopril etc.
3. Renal failure by reducing renal blood flow: noradrenaline and dopamine in high doses. NSAIDs indirectly affect renal blood flow by inhibiting production of prostaglandins.

Analgesic nephropathy – heavy and prolonged consumption of compound analgesic preparations particularly those containing phenacetin can cause chronic renal failure. This analgesic nephropathy is part of a broader analgesic syndrome, which includes hypertension, peptic ulcer, anaemia and recurrent headache.

Syndrome of drug-induced kidney disease

Common risk factors which precipitate adverse effects include old age, volume-depleted state, pre-existing renal dysfunction and co-existing use of other nephrotoxins.

- | Syndrome | Drugs |
|---|---|
| 1. Pre-renal failure/functional renal failure | NSAIDs, ACE-inhibitors, Diuretics, Interleukin-2, Amphotericin-B. |
| 2. Acute tubular necrosis | Aminoglycosides, Rifampicin, NSAIDs, Cyclosporine, Cisplatin |
| 3. Acute Interstitial nephritis | Penicillins, NSAIDs, Allopurinol, Thiazides, Sulfonamides. |

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| 4. Thrombotic microangiopathy/hemolytic uremic syndrome | Mitomycin-C, Cyclosporine, Quinine, Cocaine, Clopidogrel. |
| 5. Isolated proteinuria with nephritic syndrome | Gold, heroin, Captopril, NSAIDs, IFN-alpha, D-penicillamine. |
| 6. Chronic tubulointerstitial disease | NSAIDs, Thiazides, Lithium, Chinese herb nephropathy, Germanium. |
| 7. Retroperitoneal fibrosis | Methysergide, Hydralazine, Methyl dopa. |

Neurological manifestations[17]

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| 1. Aseptic meningitis | Intravenous immunoglobulin |
| 2. Extra pyramidal lesions | Haloperidol, Methyl dopa, Phenothiazine |
| 3. Peripheral neuropathy | Isoniazid, Metronidazole, Gold salts, Nitrofurantoin, Amiodarone, Vaccines. |
| 4. Pseudomotor Cerebri or intracranial hypertension | Amiodarone, Glucocorticoids, Oral contraceptives |
| 5. Convulsions | Amphetamine, Analeptics, Lithium, Phenothiazine |
| 6. Stroke | Oral contraceptives |
| 7. Encephalitis and Guillain-Barre syndrome | Anti-rabies vaccination (purified chick embryo cell) |
| 8. Myopathy | Statins |

Neuroleptic malignant syndrome – Rigidity, hyperthermia, altered mental status resembling catatonia, labile blood pressure and autonomic dysfunction characterize one of the serious complications of neuroleptic agents like Haloperidol [18].

Drug induced psychiatric syndromes [5]:

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| 1. Delirium or Confusional state | Anticholinergics, Glucocorticoids, Phenothiazines |
| 2. Depression | Beta blockers, Glucocorticoids, Nifedipine |
| 3. Drowsiness | Antihistamines |
| 4. Hallucination | Beta blockers, Levodopa, Narcotics |

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| 5. Hypomania, Mania | Glucocorticoids,
Sympathomimetics |
| 6. Paranoid states | Amphetamines |

Drug induced musculoskeletal/rheumatic disorders[19]

Disorder	Drug
1. Arthralgia	Fluorides, growth hormone, Penicillin, Quinolones (in children), Sulphonamides
2. Hyper-uricaemia and Gout	Cytotoxic drugs, Cyclosporine, Salicylates Ethambutol, Levodopa, Nicotinic acid, Phenytoin, Diuretics.
3. Myalgia/Myositis	Amphotericin B, Chloroquine, Cimetidine, Clofibrate, Colchicines, Cyclosporines, Gemfibrozil, Lovastatin, Levodopa, Penicillamine, Phenytoin, Rifampicin, Vincristine, Zidovudine.
4. Osteoporosis	Anticonvulsants, Corticosteroids, Heparin, Methotrexate.
5. Scleroderma like disorder	Bleomycin, INH, Penicillamine, Silicon Breast implants.

Adverse reactions due to sudden stoppage of drug

Sudden stoppage of drugs can cause[20]:

- a “rebound phenomenon” : relapse with or without exacerbation of the basic disease
- b. a “withdrawal phenomenon” : a new clinical syndrome unrelated to the original disease

Antihypertensive drugs: Sudden stoppage of clonidine and alpha methyl dopa cause syndrome resembling pheochromocytoma.

Beta-blockers: Sudden stopping of the drug in coronary artery disease may cause infarction, aggravation of angina or rhythm disorders.

Corticosteroids: Withdrawal accidents are seen after prolonged treatment, unrelated to the dose and duration of treatment and relapse of basic disease even in an aggravated form.

Barbiturates: Sudden stoppage in epileptic patients can induce status epilepticus. When used to induce sleep, sudden stoppage can cause acute insomnia, confusion, agitation, hallucinations and convulsions.

Drugs producing malignant diseases[21]:

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| 1. Leukemia
(esp. acute myeloid leukemia) | - Anti cancer agent, Radiotherapy, rarely Chloramphenicol and Phenyl-butazone |
| 2. Cancer of breast and endometrium | - Estrogens, Tamoxifen |
| 3. Cancer of vagina | - Diethyl stilbesterol |
| 4. Liver cancer | - Anabolic steroids, Oral contraceptives |

Drug nutrient interaction

Drugs may decrease nutrient absorption, increase urinary excretion, directly compete with or antagonize the nutrient from a carrier protein and interfere with the synthesis of an enzyme or coenzyme essential for the metabolism of the nutrient[22].

Drug induced fever

Drug fever constitutes one percent of all fevers of unknown origin. Any drug can cause fever (antihistamines, barbiturates, iodides, penicillins, phenytoin, propylthiouracil, β -lactum antibiotics etc). A history of allergy, skin rash or eosinophilia is often absent in cases of drug fever [23].

Adverse reactions following immunization [24]:

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| 1. Inherent vaccine induced | (a) Mild and common
- local reaction, fever
(b) Moderately severe and uncommon –suppurative lymphadenitis (BCG vaccination)
(c) Severe and rare- Encephalopathy and hypersensitive reactions (paralytic polio following oral polio vaccine). |
| 2. Programmatic errors | Septic – toxic shock syndrome and abscess. |

Interaction between indigenous and prescription drugs:

Use of indigenous drugs is neither inquired in the drug history nor are the patients advised to avoid such an indiscriminate concurrent use of drugs. Sometimes these factors lead to either a therapeutic failure or a drug interaction or an accentuation of the unknown toxicities of the chemical prescription drugs [25].

Ophthalmological complications [5]

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| 1. Cataract | Busulphan |
| 2. Corneal opacities | Chloroquine |

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| 3. Colour vision alteration | Digitalis |
| 4. Glaucoma | Sympathomimetics |
| 5. Optic neuritis | Quinine |
| 6. Retinopathy | Chloroquine |

Radiation hazards [5]

1. Acute and chronic progressive radiation injuries
2. Pneumonitis
3. Glomerulosclerosis and chronic interstitial nephropathy
4. Enteritis and cystitis
5. Venocclusive disease of liver
6. Bone marrow depression
7. Malignancy

Hazards of hospitalization

The prevalence of hospital-acquired infections is around 10%. Urinary tract infections and respiratory infections are the commonest. There is increased chance of infections associated with diagnostic and therapeutic procedures and with antibiotic resistant bacterial flora [26].

Physician as the cause of the disease

The harm that a physician can do is not limited to the imprudent use of medicine or procedure, but may include unjustified remarks and misinterpretation of investigational data. The physician should be aware of the properties of drugs that he prescribes and their potential dangers. Ignorance of the possibility of a reaction is a clear evidence of negligence. The physician should warn the patient of the likely side effects [1,27].

The list of drugs given in this article is in no way complete and only examples are given. Readers should look up the references to have more details. Drugs affecting the fetus or breastfed babies are not discussed.

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