IATROGENIC DISEASES AND DRUG INJURY

ZURIEL DANIEL

UON

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Iatrogenic Disease

Doctor - Created Illness

- 1999 - National Academy of Sciences - “hospital errors kill up to anywhere from 44,000 to 98,000 patients a year.”
- 2002 – Annual Review of Public Health - 1983 to 1998, U.S. deaths from acknowledged prescription errors increased by 243 percent.
- 2003 Null et al. – 783,936 in 2002!

Iatrogenic Disease

Center For Disease Control 2002

- "Top Five" causes of death in the U.S
  - Heart Disease (709,000)
  - Cancer (551,000)
  - Stroke (166,000)
  - Lower Respiratory (123,000)
  - Accidents (93,000)

Iatrogenic Disease (283,936)

- Where does Iatrogenic disease fit in???
- Medicine has become a major cause of death

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 disease means disease produced by a physician
Derived from the Greek word
"Iatros" for physician "Genic" to produce

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

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.

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

A-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

B-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.

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.***

ADR can be classified as **predictable** (*side effects*, *toxicity, super infection*, *drug interactions*) *and* ***unpredictable*** *(intolerance, idiosyncrasy, allergy or pseudo allergy*).

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.

- 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:

- Dose-related (Augmented)
- Non-dose-related (Bizarre)
- Dose-related and time-related (Chronic)
- ime-related (Delayed)
- Withdrawal (End of use)
- Failure of therapy (Failure).

Anaphylaxis

Penicillin and other Beta-lactam antibiotics and various types of vaccines and sera, and human insulin, are the most common agents that cause anaphylaxis.

Aspirin and other non steroidal anti-inflammatory agents (NSAIDs) cause non-IgE mediated anaphylactoid reactions.

Drug induced cutaneous manifestations

Some of the cutaneous manifestations are:

1Alopaecia; 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 flurouracil, hydroxy-urea, acyclovir and zidovudine by interfering with DNA metabolism.

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).

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, NSAIDSs, analgin, thiouracil, anticonvulsants, anti diabetics, cimetidine, tranquilizers

Drugs producing Neutropenia:

Analgesics and NSAIDs :Indomethcin, Phenacetin,

Acetaminophen, Phenyl-Butazone and Aminopyrine

Anticonvulsants :Phenytoin, Carbamazepine

Antithyroid drugs :Thiouracil, Methimazole

Phenothiazines :Chlorpromazine

Antiarrhythmic :Quinidine

Drugs that cause thrombocytopaenia:

Alpha-methyldopa, carbimazole, chloramphenicol, cyclosporins, phenylbutazone, quinine, quinidine, rifampicin, sulphonamides etc

Hazards of blood transfusion:

Complications occur ***in 2 percent*** of blood transfusions.

a.Immunological reaction : Allergic-anaphylaxis, fever, haemolysis, non cardiac pulmonary oedema.

b. 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;

Oral lesions

1. Lichen planus like lesions : methyldopa, chloroquine and propranolol.
2. 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, methyldopa) 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 methyldopa account for 20-50% of cases.

Respiratory disorders due to drugs :

Type of reaction and Example of drug

1. Airway obstruction- Beta-Blockers, Adenosine, (Bronchospasm) 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*
7. Pleural disease *Hydralazine, Methysergide*
8. Pulmonary thromboembolism - *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 *-(donorubicin, emetine and lithium),*
- hypo or hypertension- *(glucocorticoids and sympathomimetics),*
- pericardial disease - *(emetine, procainamide and minoxidil), and sparfloxacin).*

Renal disorders caused by drugs.

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 and Drugs

1. Pre-renal failure/functional RF- *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.*

- 4. Thrombotic- *Mitomycin-C, Cyclosporine, Quinine,* microangiopathy/hemolytic uremic syndrome -*Cocaine, Clopidogrel.*

5. Isolated proteinuria with *Gold, heroin, Captopril,* nephritic syndrome- *NSAIDs, IFN-alpha, D-penicillamine.*

6. Chronic tubulointerstitial disease -*NSAIDs, Thiazides, Lithium, Chinese herb-Germanium.*

7. Retroperitoneal fibrosis- *Methysergide,*

Neurological manifestations

1Aseptic 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

Drug induced psychiatric syndromes :

1Delirium or Confusional state – *Anticholinergics, Glucocorticoids, Phenothiazines*

2. Depression - *Beta blockers, Glucocorticoids, Nifedipine*

3. Drowsiness - *Antihistamines*

4. Hallucination -*Beta blockers, Levodopa, Narcotics*

5. Hypomania, Mania - *Glucocorticoids, Sympathomimetics*

6. Paranoid states - *Amphetamines*

Drug induced musculoskeletal/rheumatic disorders

1Arthralgia - Fluorides, growth hormone, Penicillin, Quinolones (in children), Sulphonamides

2. Hyper-uricaemia and Gout _*Cytotoxic drugs, Cyclosporine, Salicylates,Ethambutol, Levodopa, Nicotinic acid, Phenytoin, Diuretics.*

3. Mylagia/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, disorder Penicillamine, Silicon Breast implants.*

Adverse reactions due to sudden stoppage of drug

A 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 methyldopa* 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:

1Leukemia 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

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, b-lactum antibiotics etc*).

A history of allergy, skin rash or eosinophilia is often absent in cases of drug fever

Adverse reactions following immunization :

1. Inherent vaccine (a) Mild and common induced - local reaction, fever

(b) Moderately severe and uncommon –suppurative lymphadenitis (*BCG vaccination)*

(c) Severe and rare hypersensitive reactions -Encephalopathy and (*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

Ophthalmological complications

1. Cataract - Busulphan

2. Corneal opacities - *Chloroquine*

3. Colour vision alteration - *Digitalis*

4. Glaucoma - *Sympathomimetics*

5. Optic neuritis - *Quinine*

6. Retinopathy - *Chloroquine*

Radiation hazards

1. Acute and chronic progressive radiation injuries

2. Pneumonitis

3. Glomerulosclerosis and chronic interstitial nephropathy

4. Enteritis and cystitis

5. Venoocclusive 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

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.

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.

NB- Home work

Drugs affecting the fetus or breastfed babies are not discussed.

THE PHYSICIAN AS A CAUSE OF IATROGENIC INJURY

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- Ignorance of the possibility of a reaction is a clear evidence of negligence
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