Review Article

Future Journal of Pharmaceuticals and Health Sciences

Published by Pharma Springs Publication Journal Home Page: https://pharmasprings.com/fjphs

Drug Induced Diseases and Teratogenicity

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Article History:

Received on: 20 Apr 2023
Revised on: 09 May 2023
Accepted on: 10 May 2023

Keywords:

Drug-Induced, Teratogenicity, Cortocosteriods, Disorders

Abstract

Drug-induced ailments, also referred to as iatrogenic diseases, are a common but little-researched phenomenon. Risk factors for drug-induced diseases include a variety of chronic ailments, various doctors, hospitalization, medical or surgical procedures, long-term medication use, advancing age, female sex, and a particular class of pharmaceuticals. Prescribers must therefore be aware of and keep up with rapidly evolving pharmacological facts in this era of personalised medicine. Teratogenicity is the occurrence of congenital malformations and their causes due to teratogenic agents such as some viral, spirochetal, and protozoal infections, physical agents such as ionising radiations and excessive heat, and pharmaceutical drugs such as thalidomide, excessive vitamin A, corticosteroids, antiepileptic, antimalarial, anti-leishmaniasis, as well as antihypertensive drugs. The prevalence of congenital birth defects ranges from 2 to 5% in the first year following delivery. In this review, we have collected the information from review and research articles related to the drug induced diseases. This review is intended to aid the understanding of some basic concepts regarding the drug induced diseases. This tends to provide information about the some commonly occurring drug-induced disorders, the drugs responsible for inducing disorders, their prevention and some of the treatments.

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eISSN: 2583-116X pISSN:

DOI: https://doi.org/10.26452/fjphs.v3i2.452

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INTRODUCTION

A medication-induced disease occurs when a drug has an unanticipated side effect that causes mortality or morbidity and has symptoms severe enough for a patient to get medical help as well as need hospitalisation [1]. Unexpected or anticipated pharmacological effects can lead to drug-induced disease. The late 19th century saw the first public and professional concern over drug-induced disorders [2]. An investigation into a jaundice linked to SALVARSAN, a natural arsenical used to treat syphilis, was conducted in 1922 [3]. 107 Americans perished in 1937 after ingesting a sulfanilamide elixir that also included the solvent diethylene glycol [4]. This resulted in the creation of the Food and Drug Administration (FDA), whose job it was to investigate the security of novel medications before approving their marketing [5]. The thalidomide tragedy was the most significant modern disaster that altered professional and popular perceptions of medications [6]. The thalidomide incident sparked

a public outcry, resulted in the establishment of drug regulatory agencies around the globe, led to the development of a significantly more sophisticated method for preclinical testing as well as clinical evaluation of drugs prior to marketing, and also significantly raised awareness of the negative effects of drugs but also techniques for identifying them. Due to negative reactions, certain medications have been taken off the market or had their labels modified.

Types

Drug-induced or drug-caused illnesses can either be predictable or unpredictable. Predictable: Predictable side effects are a continuation of the drug's typical pharmacological effects. As an illustration, a side effect of blood thinners (anticoagulant and antiplatelet medications) intended to prevent blood clotting is bleeding. Several medications for diabetes, including sulfonylureas as well as insulin, can lower blood sugar levels.

Unpredictable

Unpredictable side effects, on the other hand, have absolutely nothing to do with the drug's therapeutic benefit. For instance, the medication amiodarone, which is used to treat irregular heartbeats, might harm the lungs. Drug-induced disorders can be categorised as mild, moderate, severe, or lethal if they result in death, depending on how serious they are. Diseases brought on by drugs can impact the body's many organ systems. Following are some examples of drugs that have been outlawed due to their propensity to cause serious diseases, listed according to the organ system they affect.

Cardiovascular system

Anticancer medications are not the only therapeutic drug classes that can cause unexpected cardiotoxicities. But because toxicity may not become apparent until after a prolonged accumulation of the drug or its metabolites, chronically administered drugs like neurologic/psychiatric agents and anticancer chemotherapeutic agents can cause cardiotoxicity. This is a significant issue. Drug-induced cardiotoxicity, which is frequently manifested as cardiac muscle malfunction that can lead to cardiac failure, is a serious side effect of some routinely used conventional antineoplastic drugs, such as anthracyclines, cyclophosphamide, 5 fluorouracil, taxanes, as well as newer agents such as biological monoclonal antibodies, e.g., trastuzumab, bevacizumab, and nivolumab; tyrosine kinase inhibitors, e.g., sunitinib and nilotinib; antiretroviral drugs, e.g., zidovudine; antidiabetics, e.g., rosiglitazone; as well as some illicit drugs such as alcohol, cocaine, methamphetamine, ecstasy, and synthetic cannabinoids. The majority of affected people had no history of the condition.

Drug-Induced Cardiovascular Diseases

Left Ventricular Systolic Dysfunction (LVSD) and Heart Failure (HF)

It's critical to comprehend how heart failure (HF) and left ventricular systolic dysfunction (LVSD) interact. The two conditions are not the same, although there is unquestionably a lot of overlap. However, it is important to note that up to 50% of patients with HF are not suffering from LVSD, as well as that 50% of people with LVSD are asymptomatic and therefore do not have HF. Drugs can either create de novo LVSD in a person who was previously healthy or they can accelerate the progression of HF symptoms in those who already have them.

Skin

Skin conditions brought on by drugs are frequently divided into acute and chronic categories. Erythematous eruptions, urticaria, angioedema, and anaphylaxis, fixed-drug eruptions, hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), warfarin-induced skin necrosis, vasculitis, serum sickness-like reaction, acute generalised exanthematous pustulosis (AGEP), and photosensitivity are examples of acute diseases. Drug-induced lupus, drug-induced acne, and pigmentary alterations are examples of chronic diseases.

Clinical Cutaneous Drug-Induced Manifestations

1. Contact dermatitis
2. Allergic eczematous contact dermatitis
3. Systemic eczematous "contact-type" dermatitis
4. Dermatitis medicamentosa
5. Pruritus
6. Utricaria and angjoedema
7. Exanthematic eruptions
8. Exfoliative dermatitis
9. Erythema multiforme-like eruptions
10. Stevens-Johnson syndrome
11. Erylhema nodosum-like eruptions
12. Fixed drug eruptions
13. Purpuric eruptions

14. Henoch-Schiinlein (anaphylactoid) purpura
15. Photosensitivity
16. Other drug-induced dermatoses (possibly allergic)
17. Eczematous eruptions
18. Vesiculobullous eruptions
19. Toxic epidermal necrolysis
20. Lichen planus-like eruptions
21. Vacculitis
22. Other drug-induced dermatoses (not allergic)
23. Acneiform eruptions
24. Tumors
25. Pigmentary changes
26. Alopecia

Gastrointestinal system

In clinical practise, Endoscopic pathology and gastrointestinal symptoms brought on by medicine prevalent. Irritable bowel syndrome and inflammatory bowel diseases are examples of GI disorders that can be caused by medication. Drug causes symptoms via modifying GI physiology (e.g., anticholinergic medication causes constipation, NSAIDs cause ulcers), influencing the intestinal microbiota (e.g., antibiotics cause Clostridium difficile infection), or by an unknown mechanism (e.g., metformin causes diabetes). Nausea and vomiting can be triggered by mechanisms that are not related to the gastrointestinal tract. Drug-induced gastrointestinal system-based disorders are discussed in Table 1.

Excretory system

Currently, the entire population is exposed to a variety of pharmacological drugs, the majority of which are harmful and prescribed without scientific backing.

Given that the kidney excretes the majority of the drug, it's logical to believe that the kidney could be a special target for their hazardous effects.

Immune-related toxic effects, analgesic neuropathy, drug-induced glomerular diseases, the direct toxic effects of the drugs, nephrogenic system fibrosis, selective toxic effects, renal hemodynamics related renal failure, and crystalline neuropathy will be presented according to their pathophysiologic mechanisms. Table 2 shows the effects of drugs on the excretory system.

Kidney

Drug-related acute kidney injury (AKI) may occur up to 60% of the time, while drug-induced nephrotoxicity is a common issue in clinical medicine. Drugs including ACEI, angiotensin-converting enzyme blockers [ARBs], NSAID, cyclosporine, as well as tacrolimus can affect intraglomerular hemodynamics as well as lower GFR. Crystal nephropathy is linked to a number of medications, including ampicillin, ciprofloxacin, sulfonamides, acyclovir, ganciclovir, methotrexate, and triamterene. Alcohol and statins can have a deleterious effect on myocyte activity, which can lead to rhabdomyolysis. Drugs such as aminoglycosides, amphotericin B, cisplatin, beta-lactams, quinolones, rifampin, sulfonamides, vancomycin, acyclovir, and contrast agents have been linked to tubular cell toxicity and acute interstitial nephropathy. Acetaminophen, aspirin, diuretics, and lithium use over an extended period of time are linked to chronic interstitial nephritis, which causes fibrosis as well as kidney scarring.

Blood

Depending on the illness and the medication used to treat it, different drugs and illnesses might cause idiosyncratic hematologic abnormalities. The actual frequency of these adverse responses has only been studied in a small number of epidemiologic studies, yet they seem to be uncommon. Drugs including chloramphenicol, sulfonamides, and carbamazepine can decrease the bone marrow's ability to create red blood cells, whereas primaquine, penicillin, and sulfonamides can cause hemolysis, which results in the destruction of newly formed red blood cells. Patients with a glucose-6-phosphatase enzyme deficiency experience hemolysis more frequently. Some medications lower white blood cell counts and raise the risk of contracting infections. These consist of clozapine, phenylbutazone, and methimazole. Heparin has been linked to thrombocytopenia, a disorder that reduces blood platelet counts and ups the likelihood of bleeding.

Bone

Drugs have the potential to hasten bone loss and alter serum calcium levels. Use of glucocorticoids for an extended period of time can weaken bones, resulting in osteoporosis and raising the risk of fractures. Ethambutol and pyrazinamide, two antitubercular medications, can raise uric acid levels in the blood, resulting in a condition similar to gout.

Diagnosis of DIDs

Drug-induced illnesses are typically identified based on the patient's or the family member's history of drug use. After taking the drug, the symp-

Table 1: Drug-induced gastrointestinal system-based diseases

Disease	Drug Causing	Mechanism
Oesophagitis	Tetracycline, bisphosphonate, Potassium chloride, NSAIDs, Iron	Due to mucosal injury
Gastroesophageal Reflux	Nitrates, Calcium channel antagonists Dopaminergic agents, anticholinergic drugs Progesterone, Methylxanthine	Alter lower oesophageal sphincter pressure
Dysphagia	Anti-psychotic drugs, Alcohol Anticholinergic drugs, Calcium channel blocker, Theophylline	Inhibit striated muscle function Inhibit smooth muscle function
Nausea and vomiting	Potassium chloride, NSAIDs, Iron Digoxin, Dopaminergic agent, Opiates, Chemotherapeutic agent	Cause tissue damage Act via chemoreceptor in central nervous system
Constipation	Nifedipine	Inhibition of colonic motor activity

Table 2: Drug-Induced Excretory System Based Diseases

Disease	Drug Causing	Mechanism
Suppression of TSH	Hydrocortisone Prednisolone	The glucocorticoid receptor is activated. TRH synthesis/secretion inhibition
	Dopamine agonists	On thyrotropes, dopamine receptors (D2) are activated. TSH pulse amplitude is reduced.
	Somatostatin analogs	Somatostatin receptors in thyrotropes are activated. TSH secretion is inhibited. Thyroid hormone metabolism may have been changed
Hyperprolactinemia mia	verapamil, methyldopa, tramadol, buprenorphine, methadone	The concentration of PRL in the blood is moderately elevated.
Thyroiditis	pembrolizumab	circulating CD56, CD16 and NK cells
Grave's disease	cancer immunotherapy, alemtuzumab	Not Known
Obesity	Long acting insulin, sulfonylurea, maglinitide	Increased subcutaneous fat and fluid retention

toms should start to manifest within an acceptable amount of time. To avoid missing a drug-induced disease, doctors should automatically ask any patient who visits the clinic with a problem about any medications they have been taking. The symptoms could return if the medication is taken again. This is known as re-challenging. Re-challenging is usually not done for ethical grounds even when it proves a drug-induced sickness.

Treatment of DIDs

The initial phase in treating diseases brought on by drugs is to inform the doctor about any side effects. He or she will then decide whether to cease prescribing the prescription altogether or occasionally cut the dosage while substituting a suitable substitute. This straightforward action frequently helps the sufferer feel better. Depending on the adverse event, those who do not recover require extra treatments.

Prevention of DIDs Steps that could help to prevent a drug-induced disease include the following

Before receiving a prescription for medication, always let your doctor know if you are currently taking any other medications, including dietary supplements, or if you have a medical condition. If you have ever experienced an adverse reaction to a medicine or any other item, such as a food ingredient, let your doctor know. Only take the medication as directed

Table 3: Drug-induced teratogenicity

Drug	Mechanism of action/ Effects
Asprin	Delay in the onset of labour, premature closure of the ductus arteriosus, jaundice, and foetal brain damage
Topiramate	Hypospadias and oral clefts in neonates are connected
Tetracycline	Increased susceptibility to cavities in the body, slowed bone growth, and persistent yellowing of the teeth
Warfarin	Vitamin K antagonists impede -carboxylation of glutamyl residues, lowering protein-calcium binding capacity. The skeletal anomalies could be explained by this suppression throughout foetal development.
Kanamycin	Damage to the fetus's ear causes deafness (risk of ototoxicity)
Vitamin a	Pregnant rats given high dosages of vitamin A developed neural tube defects like exencephaly, spina bifida with meningocele, hydrocephalus, malformed eyes, as well as cleft palate.
Carbamazepine	damages DNA and is associated with IQ problems, growth retardation, and malformations of the cranium.
Phenobarbital	While macroscopically, this creates free radicals and DNA base transversion, it also causes poor growth, motor development, and foetal death.
Maternal smoking	Birth weight is reduced. Heart, brain, and face birth abnormalities are also more likely in smokers' children.

by your doctor. Follow the dosage, treatment schedule, and any recommendations, such as consuming it soon after meals.

Teratogenicity

Teratogens are substances that, when exposed to a pregnant woman, may result in physical or functional abnormalities in the human embryo or foetus. Such substances include, for example, alcohol and cocaine. The length of the exposure, the quantity of the teratogen, and the stage of development the embryo or foetus is in at the time of the exposure all have an impact on the foetus or embryo. Teratogens can have a variety of effects on the embryo or foetus, including physical deformities, issues with the child's behavioural or emotional growth, and a lower IQ. Teratogens can also have an impact on pregnancies and result in issues including premature labour, spontaneous abortions, or miscarriages. Physical agents, metabolic circumstances, infections, and finally, medications and chemicals, are the four categories into which teratogens are divided.

At a conference on congenital malformations in 1959, James G. Wilson introduced the basic concepts of teratology. He later developed these concepts at the University of Florida Medical School in Gainesville, Florida, in 1977. Verbatim from Wilson's six teratology guiding principles:

1. Sensitivity to teratogen-induced malformation depends on the genotype (species) of the conceptus.
2. There are key times of sensitivity to agents and organ systems at the time of exposure, and teratogen-induced malformation sensitivity varies during various developmental stages.
3. Teratogens cause a series of altered developmental processes by acting through a particular mechanism on growing cells and tissues.
4. The nature of the teratogen, including its chemical properties, the route of exposure, the bioactivation of the mother and foetus, placental transit, etc., determines the teratogenic consequences.
5. Teratogens consistently cause development to deviate from normal. Death, deformity, growth retardation, or a functioning impairment are all examples of deviations.
6. Teratogen-induced abnormalities range in severity from complete mortality to no detectable deformities, and they are dose-dependent.

Teratogenicity is the capacity to bring about birth abnormalities in an unborn child. Many medications, including thalidomide, may cause it as a

side effect. According to numerous experts, giving women lithium during the first trimester of pregnancy might result in congenital problems, particularly in the cardiovascular system like Ebstein's abnormality (a rare heart defect). Due to this assertion, a "Register of Lithium Babies" was established in Risskov, Denmark, while a later "American Registry of Lithium Babies" was established in San Francisco [Table 3].

Nitrous Oxide

Chronic Toxicity (or Exposure)

Animal

Studies on rats, rabbits, cats, and hamsters that were exposed to nitrous oxide revealed teratogenicity. In a nitrous oxide carcinogen bioassay, mice exposed for 4 hours per day, five days per week, for 78 weeks, showed neither neoplastic or non-neoplastic lesions that were thought to be associated to nitrous gas.

Human

Psychological damage has been linked to occupational exposure, however, these effects are not seen at trace doses. Recent studies appear to suggest a link between nitrous oxide anaesthesia and hyperhomocysteinemia, an independent risk factor for coronary artery disease. However, a recent review of the available data concluded that exposure to trace amounts of nitrous oxide is not associated with impaired fertility or an increased risk of developing cancer. Megaloblastic bone-marrow depression and neurological symptoms could result from prolonged exposure to high levels of nitrous oxide. Humans treated for tetanus with high amounts of nitrous oxide for four days showed signs of bone-marrow depression. The common inhalant medication nitrous oxide has been linked to severe myeloneuropathy as a side effect. The American Conference of Governmental Industrial Hygienists (ACGIH) classifies nitrous oxide as A4 (not classifiable as a human carcinogen).

Loxapine

Reproductive Toxicity

In trials of loxapine in pregnant rats, dogs, or rabbits, no teratogenicity was seen. Renal papillary abnormalities were observed in the offspring of rats treated with 0.6 and 1.8 mg kg1 beginning in the middle of pregnancy. If loxapine is given to a foetus during the third trimester, extrapyramidal symptoms and possibly withdrawal symptoms may result. In neonates exposed to loxapine in utero, symptoms included agitation, hyper- and hypotonia, tremors, somnolence, respiratory issues, and poor feeding. It has been demonstrated that loxapine is absorbed into nursing dogs' milk. If it is excreted in human milk is unknown. If at all possible, avoid using Loxapine during nursing.

Phenylphenol

Genotoxicity

In teratogenicity research, groups of 25–27 female rats were produced, and on days 6–15 of gestation, daily dosages of 100, 300, or 700 mg OPP kg–1 bw by gavage were administered. The administration of the two lower dose levels did not result in any signs of toxicity in either the mother or the foetus. The high dose was mildly toxic to the dams but had no embryotoxic or teratogenic effects as shown by the reduced body weight gain and food intake during the treatment period.

Imidacloprid

Developmental Toxicity

In the rat and rabbit, the potential for imidacloprid to cause developmental harm, including teratogenicity, was investigated. The maternal NOEL was 10 mg kg-1 day-1 and the foetal NOEL was 30 mg kg-1 day-1 in the rat, while foetal abnormalities were not observed at any dose. The foetal NOEL was 24 mg kg1 day1 while the maternal NOEL was 8 mg kg1 day1. In the rabbit, foetal abnormalities were not obvious at any dose, and embryotoxicity was only detectable at a maternally toxic level. Imidacloprid is not teratogenic and is not a main embryotoxicant, according to the findings in these species.

Amitraz

Reproductive Toxicity

In developmental tests on rats and rabbits, doses that produced maternal toxicity (clinical signs, decreased weight gain) also caused teratogenicity (foetal visceral and skeletal abnormalities) and embryotoxicity (increased foetal death, decreased size). Reduced litter size and pup survival were observed in all three generations of rat multigenerational research. While mice did not exhibit prolonged estrus cycling, special reproductive studies on rats did show changes in hormone levels and the ratio of proestrus to diestrus in mice. Negative effects on fertility and the reproductive systems of mice were indicated by decreased male fertility, higher resorptions, and changes in the weights of the reproductive organs.

Diagnosis

Drug-induced diseases are typically identified based on a patient's or family member's history of drug use. After taking the drug, the symptoms should develop within an acceptable amount of time. To avoid missing a drug-induced disease, clinicians

should ask about drug intake to any patient who comes to the clinic with a problem. Symptoms may recur if the medicine is re-administered. Re-challenge is the term for this. Re-challenge establishes the presence of a drug-induced disease; however, it is rarely done for ethical reasons.

Treatment

The first step in treating drug-induced diseases is to notify a physician, who may decide to cease taking the medicine or, in some cases, gradually reduce the dose and replace it with a suitable alternative. This easy step can often alleviate the patient's problems. Those who do not recover may need extra therapy, depending on the severity of the adverse event. In July 2010, the Central Drugs Standard Control Organization (CDSCO), New Delhi, Government of India, launched a national pharmacovigilance programme of India (PvPI) in recognition of its relevance. In the PvPI database, there are 84,470 Individual Case Safety Reports (ICSR). ADRs are considered to be the fourth to sixth major cause of death in the United States, accounting for more than one lakh deaths each year. We do not have DID numbers in our country, but the total ADRs in the PvPI database for the last few years is fewer than one lakh. This illustrates our country's underreporting of ADRs in comparison to the United States of America.

CONCLUSION

Iatrogenic illness, often known as drug-induced disease (DID), is a persistent issue for patients, medical staff, and managers of healthcare. Despite being a significant issue in clinical practise, DID has not received the proper attention. One of the reasons for this might be that DID makes medical professionals uneasy, which makes them uncomfortable and unwilling to participate in studies designed to lessen DID. A thorough investigation on this issue has not yet been published, despite multiple individual case reports about a certain iatrogenic condition being published in India. It is unknown how common DID actually is in our nation. 8.5 million ADR reports were submitted to the WHO-UMC (Uppsala Monitoring Centre) Global Drug Safety database in 2013. India's contribution to this amounts to just about 0.7% of the global data base. Nearly 90 drugs were either prohibited or removed from manufacture and sale in India over the past 30 years by CDSCO (Central Drugs Standard Control Organisation). In order to implement safety judgements and policy at the regulatory levels in the interest of patient safety, this foresees the urgent need to increase the nation's PvPI efforts. Promotion of population-based surveillance of DIDs by PvPI in collaboration with CDSCO can help reach policy decisions regarding patient safety and medication mistakes. In order to keep healthcare workers informed about DIDs and the steps being taken to avoid them, additional continuing medical education programmes and training must be provided. All healthcare personnel should be taught the value of reporting adverse medication reactions on their own, and this behaviour should be encouraged beginning in the undergraduate years. In order to encourage more reporting, care should be made to safeguard the confidentiality of the patients as well as the reporting individuals. The importance of considering DID as one of the causes of the disease must be emphasised both during the diagnosis and when teaching medical students and graduates. Researchers in basic science and epidemiology who are interested in evidence-based medicine and personalised medicine may be inspired to contribute to the identification, quantification, and mitigation of DIDs associated with commercially available medications. Additionally, conducting systematic reviews and meta-analyses to gather evidence of the occurrence of DID can add crucial data to the toolbox of pharmacovigilance.

ACKNOWLEDGEMENT

Thank to Dr Vijay Bhalla, Dean of Pharmacy, Department of Pharmaceutics, SGT College of Pharmacy, SGT University Gurugram122505, Haryana, India. He is guiding and supporting me in completing this review work.

Conflict of interest

The author declares no conflict of interest.

Funding support

The author declares that they have no budget for the study.

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Cite this article: Ankit Sharma, Vijay Sharma, Vijay Bhalla. Drug Induced Diseases and Teratogenicity. Future J. Pharm. Health. Sci. 2023; 3(2): 212-219.