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Xenobiotics in Health and Disease: The Two Sides of a Coin: A Clinician's Perspective

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Abstract

Xenobiotics are agents that are foreign to the body or a biological system. The potential effect of xenobiotics over humans by causing environmental pollution, drug induced organ toxicity and carcinogenesis are of clinical concern. The most common pathway of xenobiotic metabolism involves enzymatic metabolism. The cytochrome P450 enzymes are the predominant enzymes involved in xenobiotic metabolism. The cardiotoxic effects of anticancer drugs like doxorubicin, trastuzumab leading to heart failure are well known. Premature ageing in young cancer survivors due to chemoradiation therapy is reported. Anticancer drugs like bleomycin, busulfan are associated with clinically significant pulmonary toxicity. Instances of drug induced interstitial lung disease are common in clinical practice. Reports of drug induced liver injury warrant regular monitoring for liver toxicity. Nephrotoxicity is noted among ICU patients due to anticancer drugs like cisplatin. Administration of antibiotics like aminoglycosides and indiscriminate use of NSAIDS is also associated with nephrotoxicity. Commonly used drugs like digoxin and antiepileptics like phenytoin and carbamazepine are drugs that may present as xenobiotic toxicity. Endocrine disrupting chemicals that are ubiquitous may have serious health effects. Environmental xenobiotics like polychlorobiphenyls and perfluoro alkyl substances are global environmental contaminants. Sentinel health events like pulmonary tuberculosis, asthma and pulmonary fibrosis are occupational hazards among coal workers or workers exposed to asbestos. Nanomaterials are reported to be toxic environmental xenobiotics or can be used in vaccines or therapeutics. The role of gut microbiome in gastrointestinal homeostasis is immense. Gut dysbiosis may be caused by drugs, food additives, pollutants or agrochemicals. Gut dysbiosis is postulated as a cause for non-alcoholic liver disease. It is essential that ongoing research on xenobiotics should be translated to clinical practice for prevention, early detection and evidence-based management of xenobiotic toxicity. Also projects researching on the beneficial effects of xenobiotics are the need of the hour. Periodic workshops on clinical aspects of xenobiotics, community education on xenobiotics and strict implementation of regulatory guidelines on xenobiotics are of public health importance. This article covers the above aspects and suggests some remedial measures.

Keywords: Xenobiotics; Toxicity; Clinician

Introduction

"There's a very fine line between pleasure and pain. They are two sides of the same coin, one not existing without the other" - E L James

Ideally there exists nothing in nature which is exclusively beneficial to the biological system. Everything that the body encounters will have both beneficial as well as deleterious effects and xenobiotics are no exception to this general rule. The term "xenobiotic" refers to agents that are foreign to the body or a biological system [1]. Xenobiotics are defined as chemicals to which an organism is exposed that are extrinsic to the normal metabolism of that organism [2]. The word Xenobiotic was coined by Dr Howard Mason in the 1960s. While there has been extensive research, both earlier and ongoing in the field of xenobiotics, it is pertinent to review this field from the clinician's perspective. Translational research in the field of xenobiotics should enrich us with knowledge of prevention, detection and treatment of xenotoxicity. Xenobiotics affect the human body such as through inhalation (respiratory tract), ingestion (gastrointestinal tract), dermal contact (skin), and parenteral (circulation/muscles) as a result of intentional or accidental exposure [3]. The potential effect of xenobiotics over humans by causing environmental pollution, organ toxicity and carcinogenesis are matters of clinical concern. Although an extensive and comprehensive review on the topic of xenobiotics will certainly benefit every researcher immensely, the present article focusses on pertinent aspects

from a clinician's viewpoint. A xenobiotic is all pervasive and can originate from environment, air, water, food additive, a drug, dietary supplements. antioxidants or dyes, emulsifiers, cosmetics, soaps, perfumes, nanomaterials in earth's crust like silica, asbestos, industrial chemicals or pesticides.

Xenobiotic Metabolism

A xenobiotic may course through different paths-either it could be (a) eliminated unchanged-hydrophilic compounds in urine and lipophilic through faeces (b) retained in the body unchanged-e.g. lead and cadmium. (c) may undergo spontaneous transformation or (d) may be metabolized enzymatically, the last one being the most common pathway [4]. A xenobiotic can be a parent compound, intermediate or product of a metabolic pathway. Xenobiotics are metabolized by the Xenobiotic- Metabolising Enzymes (XMEs). XMEs can be either Phase I enzymes, (activation), Phase II (conjugation) or Phase III (Transporter enzymes). Xenobiotic metabolism, particularly biotransformation can be affected by various physiological and pathological states. Extra-hepatic metabolism of the toxic xenobiotic may lead to target organ toxicity. Chemical modification of xenobiotics in the human body, including therapeutic agents aids their elimination [5]. The cytochrome P450 (P450) monooxygenase enzymes are the predominant enzyme system involved in human drug metabolism, accounting for about 75% of the total reactions for drug metabolism in the human liver, intestine, and kidney. The rate at which drugs and xenobiotics are metabolized by P450s affects the pharmacokinetics of the compound and, consequently, may also affect the pharmacodynamic response [6]. Every organ in the body can be a target of xenotoxicity due to exposure to them. The adverse health consequences from xenobiotics range from allergic skin reactions to major life-threatening consequences involving cardiovascular, neurological, renal, reproductive systems, causation of cancer and may affect from the foetal stage to the elderly. Gender and age-related differences in metabolism impact the effect of a xenobiotic.

Cardiotoxicity

Drug-induced cardiotoxicity is due to mitochondrial dysfunction [7]. Anticancer drugs like anthracyclines (doxorubicin/adriamycin), cisplatin, trastuzumab (Herceptin,mitoxantrone, imatinib, bevacizumab, antiviral compound azidothymidine and several oral antidiabetics e.g. rosiglitazone, illicitdrugs such as alcohol, cocaine, methamphetamine, ecstasy, and synthetic cannabinoids may lead to mitochondria-related cardiotoxicity. Cardiotoxic drugs like doxorubicin may produce cardiovascular adverse effects in a predictable, dose and time dependant manner. These xenobiotics may present as heart failure as in toxicity due to doxorubicin, Trastuzumab, alcoholic cardiomyopathy as in alcohol and arrhythmias due to cocaine abuse [8]. Chemo-radiation therapy leads to accelerated premature aging in young cancer survivors and also in older patients with pre-existing cardiovascular disease and may lead to adverse outcomes [9]. It is interesting to note that this knowledge has led to the evolution of a new branch of medicine, now known as cardio-oncology. The hemodynamic and physiological changes during pregnancy significantly affect the pharmacokinetics of cardiovascular medication [10]. The placenta as a link between the mother and foetus is involved in exchange of nutrients and waste products between mother and foetus. Pregnant women are exposed to several xenobiotics in the form of diet, smoking and drugs. The physiological changes in pregnancy will influence the toxicodynamics and toxicokinetics. Changes in the absorption, distribution, metabolism, transfer between maternal and fetal compartments, and elimination of many xenobiotics occur during pregnancy [11]. Hence it is imperative for the obstetrician to be extremely judicious in administering cardiac drugs during pregnancy taking into both maternal and fetal safety considerations. Drugs for treatment of arrhythmias, heart failure, anti-hypertensives, anticoagulants need to be decided based on their safety profile. Certain anticancer drugs can lead to pulmonary toxicity due to *per se* cytotoxicity. Bleomycin, mitomycin C, and busulfan, are associated with clinically significant pulmonary toxicity [12-13]. Antiarrhythmic drugs like amiodarone lead to interstitial pneumonitis. A large number of drugs are also implicated in development of drug-induced interstitial lung disease [14]. Xenoestrogens or Endocrine Disruptors (EDC) (e.g. phthalate or polychlorinated biphenyls (DDT, Dioxin)) cause sterility and decreased sperm count in men [15]. The oncogenic potential of xenoestrogens is of particular concern.

Hepatotoxicity

Hepatotoxicity is caused by prescription drugs and over the counter drugs. About 10% of the drugs in clinical practice are associated with Drug-Induced Liver Injury (DILI). DILI may be caused due to toxic effects of reactive metabolites, reactive oxygen species, induction of inflammation, mitochondrial dysfunction, and imbalances between cellular damage and protective mechanisms [16]. Hepatic drug metabolism involving an imbalance between the generation of toxic metabolites and detoxification processes, can influence the degree of hepatotoxicity. Acetaminophen and antibiotics like amoxycillin-clavulanate are the common causes of Drug Induced Liver Injury (DILI). Drug induced liver injury may present as hepatocellular, cholestatic or mixed injury. The mechanism of hepatotoxicity may be predictable as in acetaminophen, unpredictable, or idiosyncratic. The primary treatment of DILI is withdrawal of the offending drug.

Renal Toxicity

The kidney being the recipient of the 25% of cardiac output is a major clearance organ is involved in clearance of drugs and metabolites. Around 32 % of the drugs undergo renal elimination .Around 20%-30% of intensive care unit patients and 5% of hospitalized patients develop acute kidney toxicity, and nearly 20% of these toxicities are attributed to nephrotoxic drugs [17]. Nephrotoxicity can be produced by anticancer drugs like cisplatin,

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amphotericin, aminoglycosides and NSAIDS [18]. **A**ccumulation of cadmium and lead in kidney results in nephrotoxicity [19]. It is well known that commonly used drugs like cardiac glycosides lead to drug-induced toxicity [20]. Drugs like Phenobarbital, phenytoin, and carbamazepine also have xenobiotic toxicity [21].

Endocrine-Disrupting Chemicals (EDC):

EDCs are exogenous agents that disrupt normal endocrine physiology by interfering with hormone synthesis, metabolism, and/or cellular actions [22]. While EDCs exist naturally in soy, legumes, and other plant-based products, their major source is most likely from industrial processes. EDCs are found in air, water, and soil, as well as in numerous household products and medical devices, and have thus become ubiquitous in our environment. As with other environmental contaminants, EDCs can cross the placenta and and are now implicated in the developmental origin of diseases such as obesity and diabetes. Epidemiologic data suggest that the rise in diabetes, cancer, and infertility in the past two to three decades could be attributable, at least in part, to *in utero* exposure to these toxic chemicals. These EDCs may be Plant-derived (phytoestrogens, Industrial chemicals (pesticides, flame retardants (per- and polyfluoroalkyl substances, combustion products (polycyclic aromatic hydrocarbons **(**dioxins), lubricants (polychlorinated biphenyls). Household, personal care, and consumable items like-Cosmetics, sun-screens, toys, food and beverage packaging materials, contaminated food, contaminated groundwater, tobacco products**,** tea tree and lavender oils, benzophenone-3 and oxybenzone, bisphenol A (BPA), phthalates, perchlorate and dioxins are xenobiotics [23].

Endocrine-Disrupting Chemicals (EDCs) can stimulate or inhibit the production and metabolism of endogenous hormones or disrupt peripheral transport of hormones to their target tissues. Endocrine-Disrupting Chemical (EDC) exposure can occur through ingestion of food, dust, and water; inhalation of gases and particles in the air; skin contact; biological transfer across the placenta; or from mother's milk. These EDCS affect the neuroendocrine system by directly acting over the hypothalamic pituitary axis. Exposure to EDCs may lead to precocious puberty in children, affect reproductive development and ovarian function and fertility in women. EDCS are postulated to be a causation for PCOS, endometriosis and uterine fibroids. In men, they are likely to lead to reproductive developmental abnormalities.

Organotin Compounds and Renal Toxicity

Commercially used Organotin compounds (OTs) as Endocrine -Disrupting Chemicals are synthetic persistent organometallic xenobiotics and exert harmful effects in brain, liver, adipose tissue, and reproductive organs and kidney [24].

Air Pollution and Xenobiotics

Both indoor and outdoor environs are affected by xenobiotics. Various indoor activities like cooking, smoking, cleaning affect the indoor air quality. Indoor environment reaction products might be more toxic and harmful for occupants of indoor areas. Periodic monitoring of air pollutants and effective ventilation systems are needed [25].

Environmental Xenobiotics

Polychlorinated biphenyls, (PCBs) and Perfluoroalkyl and polyfluoroalkyl substances PFASs are global environmental contaminants and enter the environment as accidental releases, leaks, allowable discharges, and as breakdown products. Air pollution is a significant contributor to illness and increased mortality rates and can be measured by the Air Quality Index (AQI). The AQI quantifies five air pollutants, including:

a. Ground level ozone,

b. Particulate matter (PM of aerodynamic diameters 10 microns or less and very fine particles with aerodynamic diameter of 2.5 microns or less)

c. Carbon monoxide

d. Sulfur dioxide

e. Nitrogen dioxide

Air pollutants are associated with dermatitis, cardiovascular, respiratory, hepatitis and cancers [26].

In addition, exposure to nanomaterials in the industrial workplace leads to respiratory problems. Diagnosis of a Sentinel Health Event like pulmonary tuberculosis, asthma, contact dermatitis, bladder cancer, peripheral neuropathy, or pulmonary fibrosis should prompt the clinician to consider occupational history [27] and help in management of conditions like pneumoconiosis as in a coal worker or a worker exposed to asbestos. Lead toxicity among those exposed to lead at the workplace and arsenic toxicity due to drinking water contamination are other examples of environmental pollutants leading to clinical illness. Bioremediation is a waste management technique involving remediation or treatment that uses naturally occurring organisms to break down hazardous substances into less toxic or nontoxic substances or remove or neutralize pollutants from a contaminated site [28]. We need to address the environmental concerns affecting human health which include atmospheric pollutants from power plants, industries, transport, fuel combustion of military missiles and aircrafts, weapons of mass destruction such as chemical, nuclear and biological weapons, spacecrafts, electromagnetic fields and irradiation from nuclear weapons, nuclear power plants and modern technology radiation. A proper assessment of exposure, dose-response relationship, toxicogenomics (response of genome to toxic substances) among those exposed to xenobiotics is essential in risk management which includes risk analysis and risk assessment. Food additives impact human health. They are flavouring agents, enzyme preparations or those used for preservation, colouring or as sweeteners. Only those food additives certified by The Joint FAO/

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WHO Expert Committee on Food Additives (JECFA) are permitted for safe use. [29]. Apart from producing allergies, food additives are responsible for acquired metabolic diseases.

Xenobiotics and Environmental Toxicity

Immunotoxicology or environmental immunology is the study of how xenobiotics influence the immune system [30]. Nanomaterials as xenobiotics may have an immunomodulatory property which may be immunostimulatory or immunosuppressive [31]. While a desirable interaction between nanomaterial and the immune system may lead to beneficial outcomes such as vaccines or therapeutics for inflammatory and autoimmune disorders, an undesirable interaction may result in adverse outcomes such as hypersensitivity reactions and inflammation, or lowered response to infection and cancerous cells. Nanomaterials as xenobiotics also may result in host toxicity and/or reduced therapeutic efficacy of conventional pharmaceuticals.

Alcohol as a Xenobiotic

Alcohol and xenobiotics share the same oxidative microsomal pathway, which involves enzymes that belong to the family of cytochrome P450. This explains the pharmacokinetic or toxic interactions between alcohol and xenobiotics. Cytochrome P450 is inducible by chronic ethanol consumption and its activity is increased by three to five-fold in liver of alcoholics [32]. Chronic ethanol consumption leading to liver disease and metabolic problems and CVD is well known. Individual susceptibility to the toxic or carcinogenic effects of xenobiotics is increased by CYP2E1 induction due to heavy consumption of alcohol.

Organophosphorus (OP) Toxicity

The health effects of OP compounds as occupational exposure and OP poisoning is a well identified hazard in India. It is known that glyphosate, malathion, and diazinon, tetrachlorvinphos and parathion are possibly carcinogenic to humans [33]. In addition, this calls for a need to replace them with other pesticides.

In the wake of increasing need for organ transplantation, we need to explore ways to detect early organ rejection and prevent it. Global changes taking place in the biological system in response to exposure to xenobiotics can be detected by a systems toxicology approach involving omics technologies which include, genomics (study of the genome or DNA), transcriptomics (study of the transcriptome or mRNA), proteomics (study of the proteome or proteins), lipidomics (study of the lipidome or lipids), metabolomics or metabonomics (study of the metabolome or metabolites or small molecules), adductomics (study of DNA adducts due to xenobiotic exposure), and epigenomics (study of the epigenome).

Xenobiotics affect global gene expression either by genetic or epidenetic mechanisms. Global gene expression profiling using techniques of transcriptomics-microarray and next generation sequencing helps in identification of biomarkers for early detection of hepatic and pulmonary toxicity. Transcriptomics helps in and detecting toxicity at an early and preventable stage [34].

Genotoxicity

Genotoxicity is the property of chemical agents that damages the genetic information within a cell causing mutations which may lead to cancer [35]. The xenotoxic substances induce damage to the genetic material through interactions with the DNA sequence and structure e.g. pyrrolizidine, alkaloids. The genotoxic nature of a substance tested by either in-vitro or in-vivo or comet assays to evaluate the ability of a substance to induce genetic damage. Genotoxic chemotherapy is the utility of genotoxic drugs like alkylating agents, intercalating agents and enzyme inhibitors in cancer chemotherapy.

Human Gut Microbiota

The gut microbiome, a group of microorganisms in the human GIT, is involved in the biotransformation of xenobiotics [36]. The gut microbiota acts in concert with the host cells to maintain intestinal homeostasis, co-metabolize drugs and xenobiotics, and alter the expression levels of drug-metabolizing enzymes and transporters.Gut microbiota has an impact on the drug-metabolizing enzymes, there by affecting the pharmacokinetics of orally taken drugs and their bioavailability. The gut microbiota plays a critical role in the immune system by controlling the development and functionality, of Gut-Associated Lymphoid Tissues (GALT). Gut microbiota provides the branched-chain amino acids leucine, isoleucine and valine, and particularly glycine, which is required for the synthesis of glutathione-the main intracellular antioxidant and detoxifying agent necessary for many biological functions of the host. Curcumin, a naturally occurring phenolic with medicinal properties has anti-inflammatory and antioxidant activities. The pharmacologic activity of curcumin is thought to be due to the formation of its metabolite tetrahydro curcumin by the gut microbiota. Gut dysbiosis alters the microbiome metabolism in the host and affects inflammatory responses, adaptive immunity and also leads to metabolic disorders [37]. The use of innovative pharmaceutical and nutraceutical products to manage microbial colonization and development of a healthy gut microbial community at early childhood and adult life may prevent the occurrence of common inflammatory and metabolic pathologies. Finally, the discovery and development of drugs that target enzymes of metabolic pathways, and also drive pro- and anti-inflammatory responses of immune cells, will provide the next frontier medicine for metabolic therapies in near future Environmental chemicals affect the gut microbiota. Dietary plant substances in the form of traditional medicines and herbal supplements contain phytochemicals (phenolics and flavonoids which are converted into bioactive molecules.

A disruption in the composition of normal microbiota is known as Gut dysbiosis which may affect body metabolism. Dysbiosis

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may contribute to non-alcoholic fatty liver disease in which artificial sweeteners are proven to have a role. Food additives, pollutants, drugs, agrochemicals are harmful and influence metabolic processes or gut flora. The human microbiome plays a prominent role in the regulation of steroid hormone metabolism since endogenous oestrogens are the most important risk factor in breast cancer development especially in postmenopausal women.

Conclusions

Conducting periodic workshops on drug toxicity, educating patients about drug induced organ toxicity and strict implementation of rules by the drug regulatory authorities are of prime importance. There needs to be better regulation of environmental pollution, regulation of disposal of industrial wastes into lakes and ponds, monitoring of food additives. There needs be testing of agricultural and fruit produce before release into the market and implementation of stricter regulations. Extensive research on xenobiotics through translational research contributing to clinical application in toxicology and strict implementation of international regulatory guidelines leads to betterment of not only individual health but also public health.

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