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UNVEILING THE DARK SIDE OF CLINICAL TRIALS

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ABSTRACT

There is an old saying-"public health is public wealth". The evolution of drug discovery traverses a long and fascinating journey. The security of drugs is pivotal because no drug is absolutely safe for all people, in all places, at all times. In the last few decades, biomedical research has grown tremendously and the use of animals has also increased as a research model for clinical trials. Clinical trials are crucial for identifying novel disease treatments as well as innovative methods of disease detection, diagnosis, and risk reduction. Researchers can learn things about what works and doesn't work in humans through clinical trials that cannot be discovered through laboratory or animal testing. Biomedical research also assists medical professionals in determining whether a novel treatment's adverse effects are tolerable in comparison to its potential benefits. There should be strong reasons based on laboratory, animal, and human trials if greater doses are to be examined. But there would also be a higher chance of adverse outcomes. Management of Drug Disasters among the human population remains a major therapeutic challenge throughout the world.

INTRODUCTION

In the early 1960s, the use of Thalidomide in forty six countries by pregnant women or who subsequently became pregnant resulted in the "biggest man-made medical disaster ever," with more than 10,000 children born with a range of severe deformities(phocomelia), as well as thousands of miscarriages.(1)

The total number of people affected by the use of thalidomide during pregnancy is estimated at more than 10,000, of whom approximately 40 percent died at or shortly after the time of birth.(2)

Brain death is characterized by a generalized inflammatory response that results in multiorgan damage. This process is mainly mediated through cytokines, which amplify graft immunogenicity. (3)

Common side effects include constipation, hypothyroidism, ACTH stimulation, hypoglycemia, xerostomia, fever, mood changes,, peripheral neuropathy, somnolence, sedation, rash, and deep vein thrombosis (4)

Though the use of Thalidomide was banned in most countries at that time, it proved to be a useful treatment for leprosy and later, multiple myeloma. (5)

Thalidomide increases the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients receiving treatment for multiple myeloma. (6,7)

Early clinical symptoms included nausea, vomiting, and severe abdominal pain, which led many of the survivors to discontinue the medication. Later symptoms included manifestations of renal failure such as polyuria, anuria, flank pain, coma, and seizures.(8)

Some of the withdrawn drugs precipitated serious drug–drug interactions (e.g., Astemizole, Cisapride, mibefradil, terfenadine). Others were withdrawn because of the potential to cause hepatotoxicity (e.g., bromfenac, pemoline, troglitazone), valvular heart disease (e.g., fenfluramine, dexfenfluramine), rhabdomyolysis (e.g., cerivastatin), hemorrhagic stroke (e.g., phenylpropanolamine), and other adverse cardiac and neurological effects (e.g., rofecoxib, rosiglitazone).(9,10)

Management of therapeutic drugs with the potential for extreme adverse effects requires an interprofessional team, including clinicians,pharmacists, nurses, and social workers (11,12)

Drugs that enhance the activity of endocannabinoids such as cannabinoid receptor agonists, agents modifying cannabinoid transport or inhibiting their metabolism have the capacity to be used as analgesics, hypnotics, antiemetics, antihypertensive, antiasthmatics, antiepileptic neuroprotective, immunomodulatory, anti-inflammatory, alcohol withdrawal, and eating disorders (13,14)

The critical involvement of the endocannabinoid (eCB)

system in modulating immune functions, we investigated the potential role of the main elements of such a system, namely type-1 and type-2 cannabinoid receptors (CB_1 and CB_2), and fatty acid amide hydrolase (FAAH), in distinct immune cell populations of the peripheral blood of AD patients.(15)

Other clinical trials that are conducted on (fatty acid amide hydrolase) FAAH inhibitors are Merck's MK-4409, Pfizer's PF-04457845, and Vernalis'V158866.(16,17).

The primates can very well predict species-specific effects as observed by an increase in cytokines and interferon levels at higher doses used in cynomolgus macaques, in the preclinical part of the TGN1412 trial(18).

The endocannabinoid system has been implicated in a growing number of physiological functions, and its modulation holds therapeutic promise in a variety of disparate diseases and pathological conditions (19)

The enzyme fatty acid amide hydrolase (FAAH) is primarily responsible for hydrolyzing the endocannabinoid anandamide (AEA) and related signaling lipids (20)

History

In 1952, thalidomide was synthesized by Chemical Industry Basel (CIBA), but was found "to have no effect on animals" and was discarded on that basis. In 1957, it was acquired by Chemie Grünenthal in Germany where researchers found that it was an effective antiemetic that had an inhibitory effect on morning sickness (21).

In 1937, S. E. Massengill Companya pharmaceutical manufacturer, created a liquid oral formulation of sulfanilamide using diethylene glycol(DEG) as the solvent and called the preparation "Elixir Sulfanilamide".(22).

It was also proclaimed a "wonder drug" for insomnia, coughs, colds, and headaches (23).

Way back then medications were not thoroughly tested for teratogenecity to elucidate potential harm to the fetus. The company launched Thalidomide in October 1957 and began marketing it under the trade name Contergan (24).

Only later the world was awakened to the infamous 'Thalidomide disaster' in 1960s.

This new formulation was not tested for toxicity. DEG is an antifreeze and a deadly poison. The improperly prepared sulfonamide caused mass poisoning in the United States in 1937. Victims were mostly children treated for streptococcal sore throat infections. They suffered kidney failure and other symptoms like severe abdominal pain, nausea, vomiting, stupor, and convulsions. No antidote was known for diethylene glycol poisoning then.

Biomedical Research

A new chemical entity, also called investigational new drug (IND) requires thorough evaluation in animals. Toxicological studies are performed in animals to elucidate acute and chronic toxicity, mutagenicity, effects on fertility, perinatal effects, teratogenicity, and carcinogenicity. Biomedical research in animals or preclinical studies is done to find out the efficacy or the desired biological effect and above all the safety of the drug. These studies are essential and form a backbone on which clinical trials are initiated thereafter. The initial pharmacokinetic and pharmacodynamic data of an IND are obtained after animal studies. The data includes an understanding of how the drug is absorbed, distributed through body compartments, metabolized, and excreted. It also gives an idea about the receptors or the different biomolecules which interact with the drug and brings about a therapeutic outcome. The dose selection of any chemical entity/ drug starts with animals. The calculated human dose is obtained after dosing in animals. Regulatory authorities throughout the world require preclinical data to assess the efficacy and potential adverse effects associated with any IND.

Research on Drug Safety

Drug safety and regulatory studies play a great role in ensuring the safety and efficacy of pharmaceutical products. These studies are monitored by regulatory authorities and are conducted by pharmaceutical industries, research organizations, and academic institutions as well. Specific regulations and practices vary from one country to another. In the United States, drug safety regulatory studies are primarily conducted by the Food and Drug Administration (USFDA). The FDA evaluates the safety and effectiveness of drugs through preclinical and clinical trials before granting approval. It also monitors post-marketing safety through its Adverse Event Reporting System (FAERS) and collaborates with other organizations for active surveillance.

The European medicine agency (EMA) is responsible for the safety and efficacy of drugs in the European Union (EU). They have a centralized procedure and operate the European Database of Suspected Adverse Drug Reaction Reports (Eudravigilance) to collect, analyze and recommend adverse drug events after marketing. Health Canada is the regulatory authority to overlook drug safety in Canada, similar to USFDA and EMA. The Therapeutic Goods Administration (TGA) is the regulatory body in Australia. The TGA conducts pre-market assessment of drugs and monitors post-market safety through the Australian Adverse Drug Reactions.

Research on Drug regulatory protocols in India

The drug regulatory protocols, in India, are governed by the Central Drugs Standard Control Organization (CDSCO) which functions under the aegis of the Ministry of Health and Family Welfare, Government of India. The CDSCO is responsible for the regulation of drugs, cosmetics, and medical devices in India. The regulatory process followed in India is the new drug (IND) approval process, clinical trial approval, implementation of good clinical practices (GCP) guidelines, and post-marketing surveillance. All these steps are initiated only after the completion of preclinical animal studies. The process for obtaining approval for a new drug in India starts with the submission of a document called a Investigational new drug (IND) application to the CDSCO. It has data from preclinical studies and all phases of clinical trials as per guidelines. The CDSCO reviews the documents and when found satisfactory grants approval for marketing of new drugs in India. Prior to conducting clinical trials in India, sponsors, and investigators must obtain approval from CDSCO's Drug Controller General of India (DCGI). Detailed information on drugs, study protocol, and ethical considerations will be reviewed. The CDSCO ensures compliance with Good Clinical Practices (GCP) guidelines and New Drugs and Clinical Trial Rules (NDCT) 2019.

High-Risk Therapeutic Products.

" STALINON ": A therapeutic disaster

A French pharmacist invented an oral drug called 'Stallon' for staphylococcal infections in 1954. This drug killed 102 people and more than a hundred people were permanently affected. He was sentenced to two-year imprisonment and fined one million Franks. It contains 15 mg of Diiododiethyl tin and 100 mg of Isolinoleic acid. Symptoms started with severe headache on the fourth day of ingestion along with vomiting, diplopia, abdominal colic and urinary retention. In severity it ranged from clouding of consciousness, coma and residual paraplegia. Necropsy had revealed cerebral edema.

A French pharmacologist, Professor F. Caujolle, showed that organic tin salts had a delayed effect which made the routine toxicity tests useless. It clearly pointed out the need for

delayed toxicity studies in animals (25) and regulated human clinical trials.

Thalidomide

Thalidomide is first licensed for use in the UK in 1958. William McBride , had written to the Lancet medical journal after noticing an increase in the number of deformed babies (phocomelia) born at his hospital. All mothers had a history of Thalidomide use. (26)

The use of thalidomide as a tool in developmental biology led to important discoveries in the biochemical pathways of limb development. (27)

Thalidomide inhibits TNF-α, IL-6, IL-10, and IL-12 production, modulates the production of IFN-γ, and enhances the production of IL-2, IL-4 and IL-5 by immune cells. It increases lymphocyte count, co stimulates T cells, and modulates natural killer cell cytotoxicity It also inhibits NF-κB and COX-2 activity. The mortality rate in neonates with thalidomide-induced abnormalities is about 40%. (28)

Thalidomide was banned from clinical use in 1960s. It has emerged again as a potential antiangiogenic therapeutic agent in relapsed or refractory multiple myeloma and several other cancers. Strict precautions need to be exercised for use in females of child bearing age. Pregnancy must be excluded by a negative pregnancy test (one test within 10–14 days and again ≤24 hours before treatment initiation). Repeat pregnancy tests are to be done during therapy period, if used. Despite all of this, Thalidomide use is a cause of concern among health professionals as well as the general population.

Diethylstilbestrol (DES)

It is a synthetic non steroidal estrogen used to prevent miscarriages by stimulating synthesis of estrogen and progesterone in the placenta. It was synthesized in 1938. It was the cause of vaginal cancer; during pubertal female children of women who had taken DES while pregnancy. This drug was banned by FDA, for its use during pregnancy. (29)

Did DES (Diethylstilbestrol) Cause People To Be Transgender?

It was also used for the treatment of symptoms arising during the menopause and following ovariectomy, and for senile (atrophic) vaginitis and vulvar dystrophy. Diethylstilbestrol was used as a morning after pill for postcoital emergency contraceptive. It has also been used for the prevention of postpartum breast engorgement, for dysfunctional menstrual cycles, and for the treatment of female hypogonadism. Prostate cancer in men also witnessed the use of DES, though rarely.

It was used in postmenopausal women with breast cancer.

In 1971, it was found that DES created a rare vaginal tumor called "clear cell carcinoma" — not in the women who took the medication, but in girls and women who had been exposed to Diethylstilbestrol years earlier while they were in their mothers' wombs.

DES sons have a higher rate of testicular cancer, infertility, and urogenital abnormalities. (30)

Maternal Exposure To Diethylstilbestrol During Pregnancy And Increased Breast Cancer Risk In Daughters

Susceptibility to breast cancer is determined not only through inherited germline mutations but also by epigenetic changes induced by alterations in the hormonal environment during fetal development is gaining increasing support. Daughters of mothers who took synthetic estrogen diethylstilbestrol (DES) during pregnancy have two times higher breast cancer risk than women who were not exposed to it. The mechanisms likely involve epigenetic alterations, such as increased DNA methylation and modifications in histones and microRNA expression. (31)

Diethylstilbestrol and Autism

Recent studies have presented the hypothesis that *in-utero* exposure to DES and also other synthetic estrogens and progestogens, which all are endocrine disruptors, contribute to the pathogenesis of psychiatric disorders, especially Autism Spectrum Disorders (ASD). (32).

Data and families from the HHORAGES cohort were used also to study the molecular basis of the causal link between *in-utero* exposure to synthetic estrogens and the occurrence of psychiatric illnesses. (33)

Neurodevelopmental Disorders And Genital Malformations

Concomitant neurodevelopmental impairment and male genital malformations (disorders of sex development, DSD) have been observed in children exposed *in utero* to DES. Chen et al. reported that boys with cryptorchidism were more likely to receive a diagnosis of ASD (HR 1.24). Similarly, using nationwide Israeli healthcare data, Rotem et al. highlighted a correlation between male genital malformations and ASD (odds ratio of 1.62) (34,35).

BIA 10-2474 safety trial

In January 2016, during a drug safety trial conducted in France, one person died and four became ill after taking BIA 10-2474—a drug that works on the endocannabinoid system and was intended for a range of diseases. Endocannabinoids play a dual role as protective as well as causative agents in certain diseases. They have important roles related to the central nervous system (CNS), including learning, memory, emotional processing, as well pain control, inflammatory and immune response, and as a biomarker in certain psychiatric disorders. Fatty acid amide hydrolase (FAAH) hydrolyses the endocannabinoids and inhibitors can lead to extended endocannabinoid activity (36).

The altered activity of fatty acid amide hydrolase (FAAH), an enzyme of the endocannabinoid system, has been implicated in several neuropsychiatric disorders, including major depressive disorder (MDD). It is speculated that increased brain FAAH expression is correlated with increased depressive symptoms. (37)

The **BIA 10-2474** study was to assess the safety and tolerability of BIA 10–2474 after single and multiple oral doses and to investigate the effect of food on the pharmacokinetic (PK) and pharmacodynamics (PD) of BIA 10–2474. A total of 128 participants were enrolled in this trial, out of which ninety were dosed with the FAAH inhibitor and the others were given a placebo. Volunteers who were subjected to multiple doses of test drugs were adversely affected them were admitted to hospital, out of which one of the volunteers was declared brain dead and the other four, out of the remaining five were said to have irreversible brain damage. (38)

The first volunteer complained of headache and dizziness and was sent to the hospital, Biotrial physicians failed to follow up, and they continued administering scheduled doses to the rest of the participants in the cohort. The first participant went on to receive an MRI showing brain death, and four others fell ill during the interim. After eventually learning of the death, Bio trial stopped the study.

Regulatory studies were carried out to investigate the effects of the FAAH inhibitor BIA 10–2474 on fertility, embryo-fetal toxicity, and pre-and post-natal development in rats and rabbits. Despite some reductions in sperm count in rats from 50 mg/kg, there were no major changes in male fertility up to 100 mg/kg. In female rats administered up to GD6, there were

increases in pre-implantation loss at 50 and 100 mg/kg but neither post-implantation loss nor early embryonic development was affected.

In rabbits, the same maternal toxicity was seen but there were no effects in this species on post-implantation loss or fetal body weights. There were no teratogenic effects clearly due to BIA 10–2474 and developmental milestones and behavior of offspring were not affected. (39)

A recent report of tragic mishap in Phase I clinical trial of BIA 10–2474, an FAAH inhibitor came as a major setback to researchers.(40)

TGN1412 fiasco

In 2006, a phase I clinical study was conducted for a CD28 superagonist antibody TGN1412 in six human volunteers. After the very first infusion of a dose 500 times smaller than that found safe in animal studies, all six participants experienced life-threatening conditions involving multiorgan failure for which they were moved to the intensive care unit.

Earlier this month eight healthy volunteers in a phase I trial received a T cell agonist at Parexel's clinical pharmacology research unit at Northwick Park Hospital, London (41)

This was the first human trial of TeGenero's TGN1412, a new humanised monoclonal superagonist of the CD28 T cell surface receptor, designed to mitigate autoimmune and immunodeficiency disease (42).

CD28 superagonist antibodies can cause activation and proliferation of regulatory T cells regardless of the signal received by the T-cell receptor. Regulatory CD4+CD25+ T cells play an important role in the prevention of autoimmune diseases (43)

Activation of regulatory T cells by antigens is controlled by co-stimulatory signal from antigen-presenting cells, mainly dendritic cells (DC) where antigen is presented by MHC complex of DC to T cells via T-cell receptor. (44)

Activation of regulatory T cells can be useful for the treatment of a variety of autoimmune diseases and cancer and they were investigated for their therapeutic potential in different animal models for their superagonist activity (45)

ROCKET trial

This was an open-label, Multiple Cohort, Single-arm, Multi-center Trial to Determine the Safety, Feasibility and Efficacy of JCAR015 in Adult Subjects With B-cell Acute Lymphoblastic Leukemia. Juno Therapeutics, Inc. (Nasdaq: JUNO), a biopharmaceutical company focused on re-engaging the body's immune system to revolutionize the treatment of cancer.This Phase II clinical trial of JCAR015 in adult patients with relapsed or refractory B cell acute lymphoblastic leukemia, known as the "ROCKET" trial is now withdrawn. Development of JCAR015 has been discontinued after two patients suffered cerebral edema and one patient died.(46)

Cafe study

This egregious example is of a clinical study gone terribly wrong. In 2003, a judge ordered 26-year-old Dan Markingson, a patient of psychosis with homicidal tendencies, to be involuntarily committed at the recommendation of University of Minnesota physician Stephen Olson, MD. Dr. Olson then persuaded the judge to release Markingson—on the condition that he be enrolled in Dr. Olson's treatment program.

However, instead of treating Markingson, Dr. Olson enrolled him in a clinical study of Seroquel, in which Dr. Olson was serving as an investigator. Importantly, Markingson lacked the capacity to consent to study participation. Even more troubling, Dr. Olson delegated the administration of prescription drugs to a social worker named Jeanne Kenney, who was also responsible for monitoring potentially deadly adverse effects, including akathisia.

Thalidomide advance Research

Decades later, Thalidomide is being tried again for inflammatory skin conditions, such as cutaneous lupus, Behcet's disease, Crohn's disease, and many types of cancer. As research into thalidomide continued, doctors found that it helps regulate the body's germ-fighting immune system and helps control inflammation.

Studies also showed that thalidomide slows the process the body uses to create new blood vessels. Cancers use this same process to get the fuel they need to grow and spread. That research led the U.S. Food and Drug Administration (FDA) to approve the use of Thalidomide.

Diethylstilbestrol Research

Clear cell adenocarcinoma. DES daughters have about 40 times the risk of developing clear cell adenocarcinoma of the lower genital tract as unexposed women Subsequent research has shown that the risk of developing this disease remained elevated as these individuals aged into their 40s and 50s, but it continued to be rare (47)

Breast cancer. A 2011 study also found that a large cohort of DES daughters had nearly twice the risk of developing breast cancer at 40 years or older as unexposed women, but a 2019 follow-up study showed that their breast cancer risk has lessened over time.(48)

It is therefore possible that risk was increased for a limited time at middle age. However, a 2010 study from Europe found no difference in breast cancer risk between DES daughters and women not exposed to DES *in utero* (49)

Pancreatic cancer. A 2021 study found that DES daughters had about two times the risk of pancreatic cancer as women in the general population Research is ongoing to determine if the increased risk persists as these individuals get older.(50)

Cervical precancers. Studies show that DES daughters were about 2 times more likely to have high-grade cell changes in the cervix than females not exposed to DES *in utero*. Approximately 4% of DES daughters developed these conditions because of their exposure (51)

Thalidomide Memorial –To Remember is to Care

As of March 2022, 443 people are living with thalidomide impairments in the United Kingdom. In 2016, the Thalidomide Memorial –Day was unveiled in Wales to pay tribute to all of the lives impacted by thalidomide. Every year on 30 June, people come together to remember, and a roll call is given to those who have lost their lives in the previous 12 months.

FDA Synchronize medical products in a globalized environment.

The U.S. drug and medical product safety system, are on the verge of major transformations driven by the rapid evolution of science, technology, and the healthcare system.

Medical products are discovered, developed, authorized, marketed, transported, promoted, and used by practitioners, patients, and other consumers throughout much of the world. Many important information regarding the safety of these products can and does often, originate outside the United States. The Federal Food, Drug, and Cosmetic Act was adopted in 1938, following the Elixir Sulfanilamide disaster mentioned in the article. After the Thalidomide tragedy, FDA was given expanded regulatory authority to ensure the efficacy and safety of drugs.

The Regulation of Control Act byFDA

In 1901, during a diphtheria outbreak, several children were given a diphtheria antitoxin made from horses, the best treatment available at the time. Unfortunately, one of the horses used for the production of the serum was infected with tetanus. Seven children who received that antitoxin died. The next year saw the passage of the Biologics Control Act of 1902 (Virus, Serum, Antitoxin Act), which was designed to ensure the purity, potency, and safety of these and other biological products. In 1906, Upton Sinclair published *The Jungle*, an indictment of the meat-packing industry (52)

CONCLUSION

Management of drug disasters among the human population remains a major therapeutic challenge throughout the world. Drugs showing safety and efficacy in bio-clinical animal models may show very different pharmacological properties when administered to humans. Development of proper preclinical models which can efficiently predict drug behavior in humans is very essential prior to test a drug on a human subject. Tragedies suggest that phase I trials in healthy participants may be risky and a very stringent and detailed regulation needs to be in practice. Ethical concerns in phase I healthy participants and study subjects in other clinical trial phases should be diligently and mandatorily addressed. STALINON therapeutic disaster ,the Elixir Sulfanilamide tragedies—prompted US Congress to pass a bill mandating the safety of drugs 25 years later. The thalidomide tragedy led to the passage of new amendments in 1962 to ensure drug efficacy and greater drug safety. Diethylstilbestrol tragedy,TGN 1412,BIA 10-2474 ,seriously alerted FDA. The serious historical events, condemnatory details was gained that led to novel approaches for understanding, diagnosing, and managing drug-induced toxicities. Animal studies ,Human trials, Biomedical research conducted in ethical ways can reduce drug disasters to great extent.

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