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Toxicology and Therapeutics: The Fine Line between Poisons and Medicines

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***Abstract*---** The connection between therapeutics and toxicology is characterized by a key scientific concept; the same drug can act as either a toxicant or a drug with respect to the dosage, exposure circumstances, susceptibility in the biology, and clinical circumstances. This review discusses that fine line incorporating the toxicological and pharmacological views of dose-response relationship, pharmacokinetics and toxicokinetics, molecular mechanisms of action and the therapeutic window. It covers the origins of therapeutic benefit and toxic harm when interacting with shared cellular and molecular targets, such as receptors, enzymes, and nucleic acids and highlights the key mechanisms of toxicity including oxidative stress, mitochondrial dysfunction, apoptosis, and necrosis. The review also discusses the target specificity, controlled dosing and optimization of exposure used to differentiate therapeutic action and toxicity. The cases of classical and modern toxins such as digoxin, arsenic trioxide, botulinum toxin, chemotherapeutic agents, opioids, and so on, where the opposite to therapy is toxicity but, in these circumstances, its biological cause, can confirm that the latter is not the opposite of the former. The regulatory approval, safety margins, pharmacovigilance, medication errors, risk of overdose, and the increasing role of personalized medicine to decrease adverse outcomes are also discussed in the article. The developmental trends to consider in the future, including precision toxicology, use of artificial intelligence in predicting toxicity, designing safer drugs, and use of biomarker-based approaches in evaluating drug safety are discussed as new methods of enhancing the decision-making process in therapy. In general, the review finds that dose is the conclusive determinant of is-the-agent-healing medicine or is-the-agent-toxic medicine and that the balance between therapeutic good and toxic evil requires an understanding of the mechanisms that goes deep.

***Keywords*---** Toxicology; Therapeutics; Dose-response relationship; Therapeutic window; Drug safety; Poisoning.

INTRODUCTION

Toxicology has been historically defined as the science of poisons, but in contemporary biomedical use can be better thought of as the science of the adverse effects of biological conditions that occur due to exposure to a chemical, biological or physical agent under specified circumstances. This contemporary opinion underlines that being toxic does not fundamentally belong to a substance and that toxicity is a relative concept and is further influenced by dose, exposure timing, exposure path, vulnerability, and the environmental conditions (1).

Therapeutics on the contrary deals with the deliberate therapeutic use of biologically active substances to prevent, regulate or treat sickness. In modern pharmacology, treatment effectiveness varies with the choice of drug as well as the dose and regimen that can result in benefit and still have an acceptable safety margin (2).

The dose-response principle is the conceptual link of toxicology to therapeutics. A biologically active substance could be non-toxic, therapeutic, or even toxic and this is why the domains of toxicology and therapeutics must be regarded as complementary to each other as opposed to antagonistic (3).

This concept is generally summed up using the Paracelsian dictum, the dose makes the poison, which still serves as a basis of current toxicological arguments. Despite modern-day science uncovering not only more complexities like low-dose effects, but also mixed exposures and interindividual variability, the Paracelsian concept still serves as the main

explanation behind these toxin and medicine-involving domains of the same compound (4).

This change is particularly well-explained by the historical development of botulism toxin. Having been initially feared as one of the most potent biological toxins, botulinum toxin subsequently proved to be a successful therapeutic substance in severely-concentrated doses against neuromuscular, pain-controlled and cosmetic indications, proving the ability of a controlled dose to convert a previously deadly toxin into a useful medicine (5).

Another vivid demonstration of toxicology-therapeutics continuum is arsenic. Although arsenic trioxide has long been recognized as a classical poison, under stringent dosing control, it has become effective in contemporary regimens against acute promyelocytic leukemia, in which, despite highly toxic dosing, major therapeutic effects and high response rates have been demonstrated in specific patient populations (6).

The significance of the subject in drug development cannot be overstated; dose selection is a determination process in the area of translational medicine. Dose-ranging experiments done in the modern world are essential to phase II, and a faulty dose selection during phase II can destroy subsequent efficacy experiments and safety interpretation, making quantitative dose-response analysis an indispensable part of rational drug design (7).

On the preclinical level, predictive toxicology is driven by the same question: how can exposure potentially harmful to humans be recognized before they become injured without loss of compounds with therapeutic potential? Precise microphysiological in vitro models and models of human relevance have thus been created to enhance the forecasting of substance reaction and decrease the disparity amid preclinical toxicity indicators and clinical results (8).

The role of involving toxicological prediction in pharmaceutical development is also becoming pertinent in terms of clinical safety. According to new research in computational toxicology, in silico prediction, target-based screening and data-driven safety modelling are emerging as key instruments of predicting adverse effects earlier in development and of mitigating the risk of chemical promising therapeutic programmed failed due to unknown toxicity (9).

Regarding the size of the Medicines-poisons boundary, the importance of the issue on a problem of public-health is equal since the pharma-poisoning is a significant health problem around the world. Recent evidence of reviews has revealed frequent instances of medicinal products as the causal agents of poisoning accidents in both a high income as well as a low-middle-income context, reaffirming that therapeutic use of drugs should be always comprehended with its associated risks of overdose, abuse, and accidental ingestion (10).

The subject is not also limited to medicines but also applies to society-wide toxicological costs. Toxic exposures on pollution still result in millions of deaths on a global scale supporting the concept that dose, exposure control, and hazard management are pharmacological concerns, but also priorities of central concern by the populace (11).

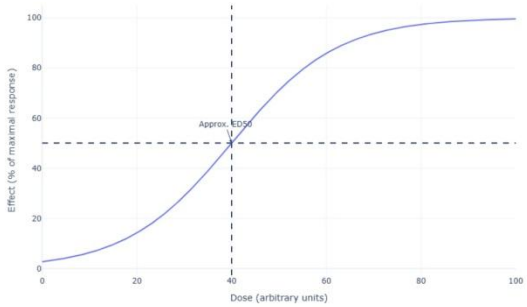

Figure 1. Conceptual graded dose–response curve showing the progressive increase in biological effect with increasing dose and the approximate location of the median effective dose (ED50).

Fundamental Concepts in Toxicology and Therapeutics

Dose–Response Relationship

A dose response relationship refers to the extent of variation in the strength of probability of a biological effect as the exposure to the biological reaction is increased. This relationship is applied in therapeutics to give an estimated range of dose at which efficacy increases and the level at which the extra exposure involves more risk than benefit; in toxicology to interpret hazard and threshold behavior, and the change in behavior where adaptive response becomes injury (12).

One important conclusion of dose-response science is that one cannot arbitrarily choose dose. Most informative when the dose level is based on consideration of kinetics, internal exposure and human relevance, toxicological studies would be conducted with excessively high or unreasonably chosen doses which would mislead interpretation and diminish the usefulness of toxicological results in determining real-world safety application (13).

Some of the best know quantitative descriptors are ED50 and LD50. ED50 is defined as the dose that causes a particular desired effect in half of a test population, and LD50 is defined as the lethal dose in

half of a test population, and has found little use except in preclinical toxicology; these numbers can help demonstrate that efficacy and lethality are potentially next to each other on the same conceptual dose curve (14).

The therapeutic index develops this reasoning by stating the margin between the effective exposure and harmful exposure. Narrow therapeutic index medications are those where disease causing toxicity can be reached by minimal change in dose or systemic concentration and vice versa, therefore, signifying more stringent bioequivalence requirements, increased monitoring vigilance, and caution in clinical dose change (15).

As a continuing clinical pharmacology phenomenon, therapeutic window is thus not thought of as a set number but a moving target. The goal of model-informed dose optimization strategies is to expand or more fully exploit that window by optimizing schedules, exposing, and maintaining efficacy whilst reducing toxicity, especially in agents with a narrow benefit-risk profile (16).

Table 1. Key Dose–Response Parameters in Toxicology and Therapeutics

Parameter	Definition	Clinical Importance
Dose–response relationship	The association that exists between an administered dose/exposure and the size/likelihood of a biological effect.	Lays the foundation of the balanced action between efficacy and toxicity and rational dose ranges.
ED50	The amount of drug to induce the required effect on half of the mice that are being studied.	Assists in estimating pharmacologic potency and aids with first dose choice.
TD50	The concentration resulting in a toxic effect in half of the examined group.	Helps determine the time of onset of adverse effects at population level.
LD50	The potential dose that will result in death in half a test population, primarily, preclinical toxicology.	Historically: Compared the acute lethality and the toxic potency.
Therapeutic Index (TI)	A measure of safety usually expressed as TD 50/ ED 50.	Measures the size of the safety margin between benefit and toxicity.
Therapeutic Window	The practical exposure range over which good is obtained at a toxicity level that is not unacceptable.	Guides dose adjustment, monitoring and personalized therapy.

Source: Compiled by the author from the dose–response and therapeutic-window literature (12-16)

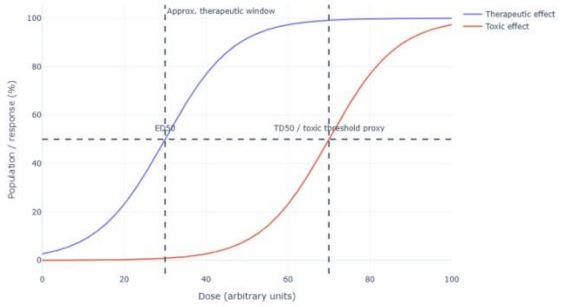

Figure 2. Conceptual comparison of therapeutic and toxic dose–response curves, illustrating the approximate therapeutic window between beneficial and harmful exposure ranges.

Pharmacokinetics and Toxicokinetics

Both pharmacokinetics and toxicokinetics address the time course of absorption, distribution, metabolism and excretion (ADME), though are used to answer different practical questions. Pharmacokinetics in therapies describes the movement of a therapeutic agent into the blood and tissues, the biotransformation and the excretion of the substance in a manner that permits a clinician to attain the effects of a therapeutic agent and to minimize its side effects. A similar ADME framework applies to toxicokinetics to measure internal exposure of exposure to a potentially harmful substance, and to relate external dose to tissue concentrations, biologically effective dose and final toxic response. That is why ADME is the dynamic transition between the exposure administered or environmentally received and therapeutic activity and toxic risk (16).

It is the difference in clinical and regulatory context of the interpretation of those kinetic laws rather than the discrete existence of those separate kinetic laws that constitutes the main difference between drug behavior and toxin behavior. Drugs are knowingly given with formulation, dose, and route whereas toxicants could enter the body unintentionally, irregularly, and through inhalation, intake, absorption

through the skin, or through mixed routes. Moreover, most toxic effects arise due to the saturation of metabolism or the overloading of detoxification pathways or the production of reactive intermediates, so the internal exposure to toxicants is nonlinear and becomes less predictable at high doses. That is why, the interpretation of toxicokinetics gives specific stress to dose dependency, bioactivation, saturation, as well as dependency between external exposure and target-organ load (17)

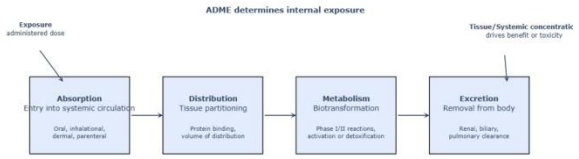

Figure 3. Schematic overview of ADME pathways in pharmacokinetics and toxicokinetics.

Mechanisms of Toxicity vs Therapeutic Action

Cellular and Molecular Targets

At the cellular scale, therapeutic action and toxicity would have to start with the interaction between a chemical agent and biological targets. These include: receptors, enzymes, ion channels, membrane lipids, transporters, structural proteins and nucleic acids. Increasingly modern toxicology is aware that toxicity is usually triggered as a disruption of signaling as opposed to apparent gross tissue eventuality; a chemical can initially induce an alteration in cellular communication, transcriptional regulation, or coordination of metabolism before manifesting itself in the form of visible toxicity. This perception aids in explaining the fact that the same molecule could do positive pharmacology adjustment at one concentration of the drug and cell dysregulation at a different concentration (18).

Some of the most essential molecular targets include receptors, enzymes and DNA. Interactions involving receptors can be therapeutically employed where the actions are selective, reversible and dose controlled, whereas they may induce harm where the actions are either excessive in stimulating or blocking. Inhibition of enzymes may result in anticipated pharmacology, as is the case with most targeted drugs, or severe toxicity in situations where critical metabolic pathways are blocked. DNA damage has a unique role in toxicology since genotoxic damage can be a cause of mutation and chromosome changes, cancer, or inherited cellular alteration. Due to this reason, modern safety science tends based more towards a quantitative assessment of the genotoxic dose-response behavior as opposed to simple designation of compounds as either simply as being genotoxic or non-genotoxic (19).

Mechanisms of Toxicity

The commonest mechanisms of toxic injury, which are widely shared in the organ systems, involve oxidative stress. It occurs when the rate of production of reactive oxygen species surpasses that of antioxidant defenses leading to the loss of lipids, proteins, and membranes through lipid peroxidation, oxidation of proteins, membrane instability, enzyme dysfunction, amplification of inflammation, and DNA damage. Oxidative signaling is a normal physiological process, but once gone excessively, redox imbalance would turn what is a normal adaptive cellular process into a safe tissue-damaging form of mechanism. This highlights the typical use of oxidative stress as a downstream pathway in hepatotoxicity, nephrotoxicity, neurotoxicity and cardiotoxicity caused by drugs, industrial chemicals and environmental contaminants (20).

Another central process that can predetermine the fate of injured cells is mitochondrial dysfunction that can be either a recovery process or death. Toxicants can compromise the electron transport chain, disrupt membrane potential, disrupt calcium homeostasis, decrease ATP production, and elevate the number of oxidants produced by mitochondria. In cases of energy failure which is partial or the damage is controlled, then apoptosis can occur in the cell; in cases where damage is too severe and bioenergetic collapse is very high then in such cases it is more likely that it occurs through necrosis. Since mitochondria are a unification of metabolism, oxidative balance, and death signaling, their disruption is a key mechanistic crossroads between toxic exposure and organ dysfunction. The same importance is why there has been an increase in scientific interest in mitochondrial biomarkers as premature or early indicators of chemical injury (21).

Mechanisms of Therapeutic Action

Specificity, controllability, and predictability are the main differences between therapeutic action and toxicity. An effective medicine is not merely a biologically active substance but one whose association with a target is selective enough, strong enough and reproducible enough to have an effect which is beneficial without unacceptable collateral damage. Current pharmacology simply has significant focus on specificity in receptors, tissue selection, regulation of pathways, displays of exposure-response and pharmacodynamic particularly. The absence of biological disruption is not the aim, but rather a constraint of the desired pathway within a clinically useful range in which a

desired pathway is perturbed greater than the undesired one. In this regard, therapeutics may be considered to be controlled biology, and toxicity is uncontrolled or excess biology (22).

The practical mechanism that maintains this difference in real patients is controlled dosing. The choice of dose, the optimization of schedule, and the monitoring of the concentration and the exposure modeling are all created to maintain the drug exposure at a range where the target engagement is not harmful but beneficial. This is of particular importance in the case of agents whose exposure response curve is steep, there is variability in inter-patient, or if the adverse effect is exposure-linked. The use of model-informed dose optimization has thus become a particularly significant approach with contemporary therapeutics, in that it aids clinicians to optimize the chances of benefit, whilst minimizing the risk of toxicity in case of under-exposure, or of failure in treatment in case of over-exposure (23).

Table 2. Mechanisms of Toxicity vs Therapeutic Action

Mechanism	Toxic Effect	Therapeutic Use Example
Overstimulation or over blockage of receptors.	Respiratory depression, arrhythmia, paralysis, endocrine disruption	Opioid analgesia, Beta-adrenergic blockade, Botulinum toxin therapy.
Enzyme inhibition	Metabolic failure, cholinergic crisis, impaired detoxification	ACE blockers, acetylcholinesterase-inhibitors, antimetabolites.
DNA interaction / damage	Mutagenesis, carcinogenic risk, myelosuppression	Cytotoxic chemotherapy in cancer treatment
Oxidative stress	Lipid peroxidation, inflammation, membrane injury, organ toxicity	Some anticancer strategies intentionally exploit ROS-mediated vulnerability
Mitochondrial dysfunction	ATP depletion, apoptosis, necrosis, multiorgan injury	Selected antineoplastic mechanisms and apoptosis-directed therapies
Target-specific pathway	Usually beneficial, but off-target	Monoclonal antibodies, kinase inhibitors,
modulation with controlled exposure	toxicity appears if exposure rises excessively	receptor-selective drugs

Examples of Substances: Poison vs Medicine

Classical Examples

Digitalis, particularly digoxin has always been one of the most understandable albeit classical examples of the thin line between medicine and poison. Being a cardiac glycoside, it has been extensively used in patients with a few types of heart failure and atrial fibrillation due to a combination of positive inotropic and neurohumoral properties. But its utility cannot be separated by its toxicity: gastrointestinal, neurological, conduction and life-threatening arrhythmias can have manifestations when or upon an increase in exposure or a predisposition. The digoxin clinical narrative thus exemplifies an ultimate toxicological fact: a drug can be potentially useful therapeutically, in fact due to the biological toxicity that causes the drugs to become dangerous (24).

An equally vivid historical and clinical paradox is that of arsenic. Even centuries ago, it was only a well-known poison, however, due to the potential of a better understanding of the molecular pathogenesis of the mentioned disease, arsenic trioxide was a revolutionary treatment in acute promyelocytic leukemia. The fact that it has been, and still is, used in modern therapeutic use is not a contradiction of toxicology, but a direct application with it: arsenic is and will be cytotoxic with differentiating effects and can be targeted to malignant cells, but only at carefully defined dosages, with protocolized and patient-selected monitoring. The triumph of APL with arsenic trioxide proves the fact that the lines between the poison and the medicine are not drawn according to the culture reputation, however based on the mechanism, dosage, indication and control (25).

Of the deadliest examples of a toxin turned into a finely-tuned therapeutic device, may be the case of Botox toxin. It is one of the strongest biologic toxins ever known but small, localized and highly standardized dosages have now been widely used in neurology, rehabilitation, pain medicine, urology, dermatology and aesthetics medicine. Its therapeutic benefits are based on the identical basic mechanism of its toxicity: the inhibition of the release of the acetylcholine at cholinergic nerve terminals. This distinction is in dose, localization, product standardization and medical control. Botox toxin thus is perhaps the best contemporary exemplar of the way that toxicology and therapeutics overlap as opposed to diverging (26).

Modern Drugs with Narrow Therapeutic Window

A good number of the current anticancer drugs intersect this thin boundary as well. Cytotoxic chemotherapy is not a safe treatment; it is biologically gentle; it is convenient, since its toxic action can be focused, so far as possible, on proliferating malignant cells. It results in an automatic small therapeutic margin, particularly to drugs like busulfan, 5-fluorouracil, and methotrexate, in which the exposure difference between patients can be quite large and toxicity levels that are extreme are closely associated with extreme toxicity. This is why therapeutic drug monitoring has emerged as empirical evidence-based approach to groups of cytotoxic agents to help clinicians personalize dosage and minimize chances that drug treatment will shift towards underexposure or perilous overexposure. (27).

Table 3. Representative Examples of Substances that Function as Both Poisons and Medicines

Substance	Toxic Dose / Toxic Exposure	Therapeutic Dose / Therapeutic Exposure	Clinical Use
Digoxin	Supratherapeutic toxicity; the toxicity increases with accumulation, kidney dysfunction and interactive drugs.	Individualized, low dose, oral therapy with clinical and, where indicated, serum-level surveillance.	Heart failure; rate control in atrial fibrillation
Arsenic trioxide	Exposure-related toxicity can be QT prolongation, hepatic and differentiation-associated toxicities.	Dosing intravenously via protocol within the specialized hematology.	Acute promyelocytic leukemia
Botulinum toxin type A	There is no universal human or toxic dose; the systemic dissemination or overexposure may lead to generalized weakness and botulism- like results.	Unit-based, indication-specific localized injection by trained clinicians	Dystonia, spasticity, hyperhidrosis, migraine, aesthetic indications
Cytotoxic chemotherapy (e.g., methotrexate, busulfan, 5-FU)	Overexposure can result in severe marrow suppressive effects, mucosal injury, organ toxicity or neurotoxicity.	Scheduling doses that are regimen specific, with therapeutic drug monitoring of selected drugs.	Hematologic and solid malignancies
Opioids (e.g., morphine class)	It is patient-specific, with an overdose causing sedation, respiratory depression, and death.	Individualized titrated dosing for analgesia	Severe acute or chronic pain

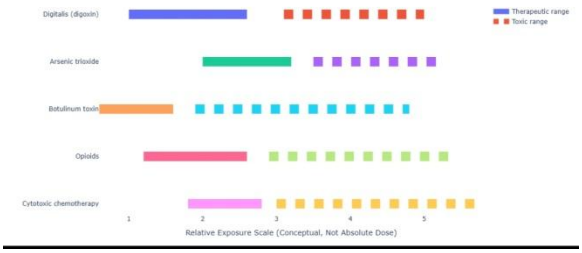

Figure 4. Conceptual comparison of toxic and therapeutic exposure ranges for selected poison–medicine examples.

Therapeutic Window and Drug Safety

The therapeutic window is the range of exposure over which a drug is likely to cause a significant benefit with no more than acceptable toxicity. With a wide window, tolerant of routine dosing tends to be the rule; with a narrow one, an alteration of half measures in terms of absorption, distribution, metabolism, elimination, adherence, co-prescribed medication, or vulnerability of the patient can cause a shift between efficacy and harm. The clinical significance of this principle can be seen by analgesia existing along the exposure continuum with sedation and respiratory depression and the μ-receptor-mediated loss of respiratory drive is the primary lethal risk of opioid therapy and overdose to normal physiology. Practically, the safety of drugs in a narrow range is facilitated through an individualized titration, the identification of susceptibility elements, monitoring, prevention of interaction with other interacting sedatives, and containment of reversal strategies in case of necessity (28).

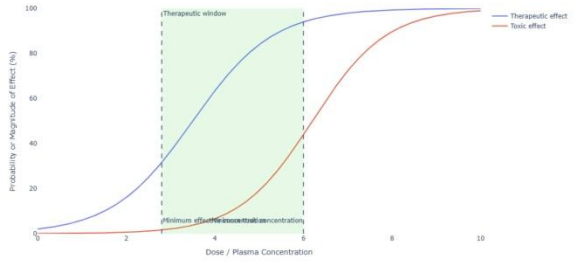

Figure 5. Therapeutic window diagram illustrating the interval between minimal effective exposure and toxic exposure.

Risk Assessment and Clinical Toxicology

Toxicity Testing

Identifying the risk of a particular medicine in clinical practice starts to be scrutinized way before it comes into regular clinical use. The aim of preclinical toxicity testing is to detect target-organ toxicity, define dose-response interactions, identify safety signals, which might affect initial dosing in humans, and optimize the benefit-risk relationship, prior to extensive clinical exposure. However, more and more one is not dependent on just one method but is both combined with mechanistic toxicology, computational prediction, in vitro systems, animal studies and translational interpretation to enhance human relevance. Clinical trials then extrapolate this process; translating preclinical concern to a monitored human experience to enable the characterization of adverse events, exposure-response interaction and population dissimilarity under increasingly less controlled real-world circumstances (29).

Poisoning and Management

Clinical toxicology starts by understanding that poisoning can be acute, delayed, repeated, or chronic as well as the understanding that clinical toxicology must first stabilize the patient prior to it trying to neutralize the poison. The fundamental tenets airway, breathing, circulation, neurological assessment, supportive care, prevention of further absorption where appropriate, enhancement of elimination in special cases and antidotal therapy where a defined approach of eliminating it is available. Acute poisoning usually requires immediate resuscitation and early antidotes, as opposed to chronic poisoning, which usually requires the end of exposure, observation of progressive organ damage, and follow-up. Antidotes are thus very important and yet can only work in the presence of good supportive and toxicological care; most useful is naloxone in the case of opioids, atropine and pralidoxime are the most common in the case of organophosphates, digoxin-specific antibody fragments are most useful in the case of severe digoxin toxicity, leucovorin in the case of methotrexate (30).

Table 4. Selected Poisons and Their Antidotes

Poison	Mechanism	Antidote
Opioids	μ-receptor agonism causing central respiratory depression	Naloxone
Organophosphates	Cholinergic excess acetylcholinesterase inhibition.	Atropine + pralidoxime
Digoxin	Na^+/K^+-ATPase inhibition with dysrhythmia risk	Digoxin-specific antibody fragments
Methotrexate toxicity	Antagonism of folic acid and dysfunction of DNA synthesis.	Leucovorin; glucarpidase selected severe cases
Arsenic poisoning	Multisystemic cellular toxicity and enzyme inhibition and oxidative damage.	Chelation therapy in appropriate poisoning scenarios
Botulism	Blockade of acetylcholine release at cholinergic synapses	Botulinum antitoxin

Regulatory and Safety Considerations

Regulatively, the difference between a poison and a medicine is formalized by use of benefit -risk assessment and not by classification by virtue or nature of the substance. The streamlined approval process of new drugs and biological products in the United States, which is guided by the FDA, has a framework based on a systemic evaluation of the therapeutic background, projected advantages, actual and possible hazards, and plans that can be followed in order to handle these hazards. This implies that the acceptance is not made due to the inherent safety of a substance, but rather the evidence of its usage in a set of conditions, where the perceived benefits of the usage overridden the noticed harms (31).

The centralized marketing authorisation route is used in the European system with a single application being evaluated scientifically and with success, a single authorisation is granted to the Union market. The emerging guidelines on pre-authorisation in EMA thus provide a clear understanding that such an

undertaking is very much organized and demands initial regulatory contacts, seamless dossier establishment and adherence to the changing legal and scientific imperatives in order that a medicinal product successfully seeks the centralised route (32).

The main feature of this regulatory thinking is safety margins, as the permission of the use will not be on the basis of demonstrating activity, but provision of the limits of exposure within which the use will be ethically or clinically acceptable. The modern practice of benefit-risk methodology supports the idea that regulators have to consider disease context, substitutes, uncertainties in evidence, harmfulness and plausibility of management of the risk, then decide that a profile of a given medicinal product is acceptable. Practically, this is to turn regulatory science into a formal extension of toxicology: it expresses mechanistic and clinical uncertainty as a judgment to act upon whether controlled therapeutic use should be done (33).

Post-marketing surveillance is also essential since even high-quality pre-approval trials are not always sufficient to ascertain all of the different rare, delayed, and interaction-related adverse drug reactions or those unique to the population. Pharmacovigilance systems thus build on the toxicological scrutiny of a drug sooner aftermarket launch via spontaneous reporting, signal recognition, risk management plans, and post-authorisation scrutinization. Of particular relevance is the case of substances whose toxicity is only realized in the conditions mandate by real-life circumstances of co-morbidity, polypharmacy or long-run exposure, and in which the additional evidence of post-marketing is thus a significant protection to patient safety and responsiveness to regulation (34).

Impact on Clinical Practice and Patient Safety

The poison-medicine boundary is frequently overstepped in routine clinical care, but not due to the change in the substance, but rather as a result of the use process dying. The various types of medication errors that can occur include; giving the wrong medication, incorrect dose, incorrect patient, incorrect timing, or improper monitoring that can turn an otherwise effective treatment into avoidable injury. Extensive evidence demonstrated that drug related harm continues to be widespread throughout healthcare facilities, and preventable harm occurs very often throughout the prescribing and monitoring processes, making secure medication systems as significant as the pharmacological effect itself (35).

One of the most obvious clinical manifestations of therapeutic action and toxicity existing in the same continuum is the risk of overdose. This is also particularly true of opioids, since the effects of opioids, such as analgesia, sedation, and respiratory depression, are mediated by similar pharmacological pathways, and when the dose, patient susceptibility, or the presence of other sedatives changes even the margin of safety can be quickly narrowed. Recent prescribing rulings thus view opioid treatment as health and safety risk-management issue that must be carefully patient-selected, dose-tapered, benefit-assessed, and overdose prevention outlined through a well-defined methodology in the case of risk-factor presence (36).

Personalized medicine seeks to minimize precisely this type of avoidable damaging by tailoring the single patient to the biological and clinical attributes of the particular patient, as opposed to a trial population that represents the average patient. There is recent pharmacogenomic evidence indicating that pre-emptive genetic testing could be more effective and safer by directing drug selection and dosing prior to occurrence of severe adverse drug reactions. Personalized medicine in this respect is not toxicology, but the application of toxicological science to the individuals level to maintain exposure within the safest and most effective dose in each specific patient (37).

Future Trends

An important future pathway within this area is the emergence of precision toxicology, which aims to go beyond general judgements of hazard at the population level to mechanistically-informed, human-relevant, and exposure-specific prediction of toxic effects. This strategy combines new approach methodologies, systems biology, and more detailed data to determine who is at risk, when through which exposure conditions and by what biological pathways toxicity is likely to develop. With this paradigm in evolution, toxicology is likely to gain a more predictive, less empirical, and more closely connected with individualized therapeutic decisions (38).

Another significant change agent in the field of toxicity prediction is artificial intelligence. Recent reviews indicate that AI and machine learning can combine molecular structure, toxicity databases, target biology, and multimodal data to predict earlier acute and organ-specific toxicity changes than, or otherwise inaccessible by traditional workflows, early in development. Despite the current issues with data quality, model interpretability and regulatory confidence, AI powered toxicology is considered more and more as a tool to reduce late-stage failure rate and enhance the safety profile of candidate drugs prior to entering clinical trials (39).

Predictive toxicology and clinical predictability are likely to see increasing use as a higher-level design tool in safer drug design systems, not as a late-stage filter, decreasingly. The existing thinking in drug

development is that safety-related project failure is a top contributor to failure of drug development, and that in silico models, organ-on-chip, historic toxicity, and mechanism-conscious screening may be used to discover individual risky compounds earlier, and shift medicinal chemistry to safer prototypes. Such an upward trend reflects a larger change of reactive toxicology to design level prevention of toxicity (40).

Biomarkers of toxicity will also become conclusive in subsequent stage of therapeutic safety. The latest biomarker strategies are no longer restricted to the conventional clinical chemistry methods, but also encompass microRNAs, metabolomic clues, mechanistic cell-death biomarkers, imaging-based biomarkers, and organ-specific injury cues. They are important because they enable the detection of injury earlier, improve the distinction between adaptive and pathological biological responses, and become more informed when making decisions during the course of clinical development and clinical care. Nevertheless, they can only be broaderly adopted by validation, qualification, and context-specific regulatory acceptance (41).

CONCLUSION

Dose, exposure, biological context and the level of mechanistic knowledge used to apply a poison or a medicine ultimately determines the fine line between poisons and medicines. A compound does not become therapeutic by virtue of losing its toxic potential but the science, regulation and clinical judgment manage to keep the potential within an acceptable range of benefit. It is due to this reason that the future of toxicology and therapeutics is not in their separation but understanding and applying them mechanistically as a single entity and predictive modeling, individualized dosing and real-life monitoring of their effect in such a way that the good pharmacology can be maintained and the bad exposure is reduced. [42]

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N/A

Conflict of Interest

The author declare no conflict of interest.

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