CLINICAL APPLICATIONS OF PHARMACOLOGY

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Introduction

The study of how medications interact with living things is known as pharmacology. It also covers the drug's background, source, dosage forms, administration strategies, physicochemical properties, absorption, distribution mechanism of action, biotransformation, excretion, clinical applications, and side effects. Clinical pharmacology is a type of clinical trial that analyses the drug's preferred mode of administration and safe dosage range in people. From preclinical to clinical studies, drug development is a lengthy and complex process. Saudi Arabia (KSA) is becoming more interested in promoting innovation, research, and indigenous content, including clinical trials. There are now about 650 registered clinical trials in Saudi Arabia, with the number expected to grow. The safe and effective use of medications is an important element of drug development and clinical studies. Clinical pharmacology is important for making informed decisions during the drug development process since it focuses on the effects of drugs in humans. Clinical pharmacology encompasses pharmacokinetics, pharmacodynamics, and pharmacogenomics. (Mahato, 2017). It's a growing topic with a variety of uses in drug development, such as establishing optimal doses for Phase I, II, and III studies, evaluating bioequivalence and biosimilar research, and organizing clinical trials (Rodríguez-Fuentes, 2021). The drug development process will be improved more efficiently, and the pipeline will quicken, by including clinical pharmacology and regulatory agency needs into the study. Indirect patient care is also used to customize treatment using clinical pharmacology. To optimize patient dosing on an individual level, tools including therapeutic drug monitoring, pharmacogenomics, and model-informed precision dosing are used. Clinical pharmacology is a science that is underutilized in Saudi Arabia, and it is believed that vital to raise awareness of its applications and potential among the scientific community and healthcare professionals. The use and uses of

clinical pharmacology in drug development and clinical care are discussed in this review paper. Drug development is a long and complicated process that includes everything from the preclinical to the clinical trials (Abdullah Alsultan, 2020).

From drug discovery to preclinical investigations and finally structured clinical trials, drug development is a lengthy, difficult, and expensive process. There is a growing interest in supporting innovation, research, and local content in Saudi Arabia (KSA). Attracting pharmaceutical companies and contract research organizations to conduct clinical trials in Saudi Arabia is a top priority. There are now over 650 clinical studies registered in Saudi Arabia. This figure is thought to be quite low. As an example, Poland has approximately 6400 registered clinical studies, while having a similar gross domestic product and population. There are increased efforts in KSA to increase the number of clinical trials conducted, and therefore the number is expected to increase. Before 2009, clinical trials in KSA were not regulated by any government body. Clinical trials conducted at respective locations were self-regulated by local Institutional Review Boards. The Clinical Trials Administration was founded by the Saudi Food and Drug Authority in 2009. All investigators and sponsors have been obliged to register early-phase clinical studies (Phase I, II, and III) with the Saudi Clinical Trials Registry and acquire SFDA permission prior to study beginning since 2013 (Satoskar, 2020). The safe and effective use of pharmaceuticals is an important principle in drug research, clinical trials, and regulation. Clinical pharmacology is critical for making well-informed decisions during the drug development process. Pharmacokinetics, pharmacodynamics, and pharmacogenomics are all areas of clinical pharmacology that study the effects of medications on humans. These fields have grown at an exponential rate over the last two decades, and they are currently used in both preclinical and clinical drug research. Determine the first-in-human dose, determine the right

dose for Phase II and III studies, dosing in special populations, assessing bioequivalence and biosimilar studies, drug, and food interaction research, and create and conduct clinical trials, to name a few. Around half of the clinical pharmacology, information is contained in the package insert. Clinical pharmacologists are in charge of testing new drugs that have been developed experimentally (Mehrotra N, 2016).

As mathematical modelling and simulation have become an integral part of the field and are increasingly used in drug development, many aspects of clinical pharmacology have become more quantitative (also known as pharmacometrics). Model-Informed Drug Development is a way for assisting in drug development decision-making by utilizing data from a variety of sources, including real-world data, clinical studies, and preclinical research. One of the goals of the United States Food and Drug Administration (US FDA) was Model Informed Drug Development, which was incorporated in the Prescription Drug User Fee Amendments of 2017. Clinical pharmacology can also be used to personalize medicine for patients in direct patient care. To optimize patient dose, tools such as therapeutic drug monitoring (TDM), PGx, and precision can be employed, as well as an Individualized Model dosage. The goal is to promote and educate healthcare professionals and the scientific community about the discipline of clinical pharmacology, which is still neglected in Saudi Arabia. Clinical pharmacology is a helpful tool in optimizing medication safety and efficacy in clinical trials during drug development and patient care from a regulatory, research, and industrial standpoint. In this review paper, it discusses clinical pharmacology's applications in clinical drug development and direct clinical care, as well as provide an update on Saudi Arabia's drug development rules and procedures. (Lavé T, 2016).

Evaluation and Development of drugs

Drugs Evaluation and Development Clinical pharmacologists have made significant contributions to the evaluation of existing pharmaceuticals and the development of new ones. Paul Martini released a treatise called Methodology of Therapeutic Investigation in 1932, which summarized his experience in scientific drug evaluation and perhaps made him the "first clinical pharmacologist. “Martini discussed the use of placebos, control groups, stratification, rating scales, the "n of 1" trial design, and the need to estimate sample size and establish baseline conditions before starting a trial. He was also the first to create the term "clinical pharmacology." Clinical trial design has also benefited from Gold's and other academic clinical pharmacologists' contributions. Sheiner has stated that various advances in the use of statistical approaches for drug evaluation are still needed, and that clinicians must reclaim control over clinical trials to guarantee that the most important concerns are addressed (Arthur J. Atkinson Jr., 2012).

The method of developing new drugs in the United States. Drug development today is a complicated process that is traditionally separated into preclinical research and development and numerous stages of clinical development. When a drug candidate is found and put through in vitro and animal research, The FDA receives an investigational new drug application (IND). Phase I clinical development begins once the IND is approved, with limited healthy volunteers or patient investigations. These studies aim to establish a range of tolerated doses and characterize the drug candidate's pharmacokinetics and initial toxicity profile. Suppose these results warrant further development of the compound. In that case, short term Phase II studies are conducted in a selected group of patients to IND NDA PHASE I PHASE II PHASE III Clinical Development

Preclinical Development Dose Escalation and Initial PK Proof of Concept and Dose-Finding Large Efficacy Trials with PK Screen Animal Models for Efficacy Assay Development Animal PK and PD Animal Toxicology PK and PD Studies in Special Populations Chemical Synthesis and Formulation Development. (PK means pharmacokinetic studies; PD means drug effect or pharmacodynamics research.) To collect evidence of treatment efficacy and investigate patients' therapeutic and toxic reactions to various dosing regimens (Luo, 2020).

Longer Phase III trials are designed using these dose-response relationships to validate treatment efficacy and document safety in a wider patient population. The information gathered during preclinical and clinical testing is subsequently included in a New Drug Application (NDA) submitted to the FDA for approval. Before the NDA is authorized and the medicine can be commercialized, the FDA may require clarification of research data or more trials. Following NDA clearance, adverse drug reaction monitoring and reporting are required. Studies to support FDA licensing for additional therapeutic indications or direct consumer sales "over-the-counter" (OTC) may be conducted following NDA clearance. Despite the fact of the pharmaceutical industry holds the majority of the expertise and resources required to generate novel therapies, clinical investigators in academia have played an important role in lobbying for drug development. In 1910, dopamine was created for the first time. Despite this, it was not until 1963 that Leon Goldberg and his colleagues gave solid evidence that dopamine-induced vasodilation was mediated by binding to a previously unidentified receptor (Shiroiwa, 2017).

Clinical Pharmacology Applications in Clinical Drug Development

- **Phase I studies**

The process of developing a new medicinal agent is multi-phased, including ethical, scientific, and financial problems. Clinical development success is about 10% of the time, and only a small percentage of medications make it past clinical trials. Phase 1 clinical trials are vital in turning experimental findings into clinical applications and in determining whether or not promising new treatments should be pursued. Phase 1 trials, often known as first-in-human studies, are intended to test experimental new medications as well as novel combinations of dose schedules for FDA-approved drugs. Healthy volunteers are usually the target population of Phase 1 clinical trials. They are the optimum population for evaluating clinical pharmacology because they enable for evaluation of the drug's safety profile without interference from pathological conditions. Basic PK information regarding a potential drug candidate can be obtained via clinical investigations with healthy volunteers. They boost the study's enrolment rate and address ethical concerns about enrolling patients to receive the experimental new medicine at sub therapeutic levels in order to collect safety data (Scannell JW, 2012).

The British Pharmacological Society performed a survey that found that recruiting healthy participants for clinical studies is largely safe. At an extremely low rate (0.04%), some people had life-threatening incidents (33). This raises ethical concerns about exposing healthy volunteers to dangers without any possible health benefits during early drug research. According

to a meta-analysis of non-oncology phase 1 trials, 34 of the 11,028 healthy subjects experienced severe adverse events, with 50% of these events not being attributed to the study drug or research procedure; furthermore, no deaths or life-threatening events were reported, indicating that healthy subjects are a suitable population for non-oncology phase 1 studies and that investigating the safety of drugs on healthy participants is relatively safe. Healthy volunteers, on the other hand, are not suitable for cancer treatment studies due to the narrow therapeutic index of cytotoxic medications and the possibility of long-term DNA damage. Patients with advanced cancer who have had no response to other treatments are a better potential population for evaluating the dose toxicity profile, determining the recommended Phase II dose, providing preliminary evidence of benefit, and identifying a specific target population in this circumstance. Major goals include defining the optimal dose and schedule for Phase II studies, assessing safety and tolerance, characterization of PK and PD of the new therapeutic candidate or innovative combination of authorized medications, and determining the suitable dose and schedule for Phase III investigations (Table 1). Micro dosing is used in Phase 0 trials (early Phase 1 trials), which allows for safer, faster, and less expensive first-in-human research by exposing healthy volunteers to sub therapeutic drug doses (Orme M, 1989).

The work was published in the Journal of Clinical Investigation and titled "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers." In 2005, the US Food and Drug Administration issued guidelines. It gives researchers a regulatory framework for estimating the maximum recommended starting dose (MRSD) for healthy volunteers, based on determining the no-observed adverse effects level (NOAEL) in preclinical studies, then converting mg/kg dosing from animal species to humans using allometric scaling factors to get the human equivalent dose. Another technique is to

include all available in vivo and in vitro data into the EMA-accepted minimal anticipated biological effect level (MABEL) to choose the safe starting dose and escalation in first-in-human clinical studies. The NOAEL- or MABEL-derived human-relevant dose is adjusted by applying appropriate safety margins to limit the risk associated with the first dose administered to humans (Iasonos A, 2017).

- **Drug-drug interaction and bioequivalence studies**
- Drug-drug interactions are studied to see if they are mediated by metabolism or transporters. The researchers want to see if the experimental drug affects the PK of the other Coad ministered drugs or the other way around and if the interaction is clinically meaningful. After in vitro tests reveal a potential interaction, clinical drug-drug interaction studies are conducted. Prospective clinical drug-drug interaction investigations are routinely conducted in healthy volunteers as stand-alone studies. They are undertaken early in the drug development process during Phase I investigations and do not belong to any single phase. A powerful index perpetrator known to inhibit or stimulate a specific metabolizing enzyme or transporter is used to determine drug interaction. The area under the curve or the percentage change in plasma concentration will determine the magnitude of the interaction. A change in AUC of 20% or more is usually regarded clinically significant (Prueksaritanont T, 2013).
- **Application in Clinical Care**

By reviewing novel medications for institutional pharmacy and therapeutic committees, clinical pharmacology can assure the safe and effective use of drugs in clinical care, performing therapeutic drug monitoring (TDM) and applying genotype-guided dosing and dosing in special populations. In addition, model-informed precision dosing, a new field incorporating different

specialties within clinical pharmacology, considers several factors (e.g., demographic, genetic, disease, and environmental factors) to select the optimal dose to maximize efficacy and minimize toxicity. The disciplines are summarized shortly (Polasek TM, 2018).

- **Therapeutic Drug Monitoring (TDM)**

Therapeutic Drug Monitoring is a clinical tool used to individualize therapy for patients. It is usually applied to drugs with a narrow therapeutic index and high between-subject variability. Other essential factors to consider are the availability of rapid and cost-effective drug assays and understanding the concentration-response relationship. Therapeutic Drug Monitoring is routinely performed for vancomycin, aminoglycosides, tacrolimus, cyclosporine, phenytoin, and valproic acid. There is a significant focus on using Therapeutic Drug Monitoring to inform dose adjustment decisions for additional medicines. Antimicrobials and anticancer medications, such as anti-HIV therapies, antifungals, beta-lactams, antituberculous treatments, busulfan, and tyrosine kinase inhibitors, are especially susceptible to this. These medications are used to treat life-threatening disorders, and there is typically no obvious PD or clinical criterion to assess a patient's response to treatment. Despite the fact that the requirements for Therapeutic Drug Monitoring apply to several of these medicines, Therapeutic Drug Monitoring is still not widely employed, due to a lack of assay availability (Ashbee HR, 2014).

Conclusion

Clinical pharmacology holds the promise of improving patient care, drug development, and drug regulation. The recommendation is to expand the role and scope of clinical pharmacology and to

educate more scientists in this field. It is moving away from a ‘one-size-fits-all’ approach to personalized medicine in clinical practice. There is a need to individualize treatment based on patient-related differences, such as demographic information and genetic variability. As modern clinical care implements precision medicine, the integration and utilization of PGx and model-informed precision dosing in clinical practice will become essential. Both PGx and model-informed precision dosing can significantly improve clinical outcomes and reduce the cost of care. There is a significant space to improve when conducting clinical trials. KSA performs only 0.21% of global clinical studies, more than the other Arab states, excluding Egypt. The contribution of KSA in clinical studies does not reflect the resources available in the country. It necessitates the establishment of research groups to identify issues and create a sustainable infrastructure for clinical research.

Because of the level of development of the healthcare system, the significant annual expenditure on healthcare, the availability of world-class medical facilities, the presence of nationally and internationally trained investigators, and the rapid growth of the pharmaceutical industry, an increasing number of sponsors are investing in the KSA healthcare system. Insufficient finance, insufficient clinical pharmacology training, a lengthy ethical approval process, difficulty finding study participants, and a lack of experienced researchers conducting clinical trials are all obstacles to the advancement of clinical research in Saudi Arabia. It suggests forming a Saudi Clinical Practice Consortium, which would be in charge of performing therapeutic trials and developing clinical recommendations specific to each community. This collaboration would also be in charge of making customized recommendations to each community, as well as developing and validating genetic biomarkers in regional locales.

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