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The Pharmacogenetics of Opioid Metabolism: A Clinical Perspective

Yatindra Kumar[1], Sudhir Singh Gangwar[1], Mudit Kumar[1], Sachin Kumar[1], Brajesh Kumar[1*]

[1]Department of Pharmacy, GSVM Medical College, Kanpur, UP-208002

***Corresponding Author E-mail: brajesh_saurabh@rediffmail.com**

ABSTRACT

The given review provides an extensive overview of the pharmacogenetics of opioid metabolism as viewed through the prism of animal-based clinical studies, focusing on genetic variability as the fundamental aspect of drug response modulation. By taking an approach of synthesizing findings of rodent and canine, the paper aims at focusing on crucial metabolic enzymes of CYP2D, CYP3A, and UGT1A/2B, and membrane transporter ABCB1 (P-glycoprotein) in order to understand how naturally existing or induced experimentally genetic polymorphisms interact with opioid biotransformation, analgesic efficacy, and adverse effect profile. As an example, the variations in CYP2D isoforms across rat strains have strong implications on codeine-to-morphine conversion, and MDR1-deficient canines exhibit an enhanced sensitivity of the central nervous system towards opioids because of poor efflux capability. Such learnings are incredibly significant, not only to veterinary medicine itself, as a way to dose opioids by breed, but also to human drug development, which relies heavily upon animal models in preclinical screening and risk measures. The review also singles out research gaps that are critical such the lack of Genomic databases to animals and limited genetic diversity within experimental populations. It recommends that more cross-species studies need to be done, and multi-omics methods should be integrated and that more humanized animal models need to be generated to increase translation correctness. Finally, the knowledge of pharmacogenetic processes in animals improves different safety, efficacy and species-specific therapeutic approaches to opioid therapy.

Key Words:

Pharmacogenetics, Opioid Metabolism, CYP450 Enzymes, ABCB1 Transporter, Animal Models, Veterinary Pharmacology

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1. INTRODUCTION

Veterinary Opioids Veterinary use of Opioids in managing pain and as anesthesia adjuncts is widely accepted in practice and preclinical research. Inter-subject or inter-species variability in opioid effectiveness and side-effect phenomenon, however, has prompted research into the possibility of underlying genetic influence on how the opioids are metabolized[1]. Pharmacogenetics, the effect genetics has on individual drug metabolism and reaction, has come up as a significant instrument of finding out all this interindividual and interspecies variation. In animal models (including rodents, canines, and non-human primates), important information on the enzymes and transporters taking place in opioid pharmacokinetics and pharmacodynamics has been gained. OPs can be significantly metabolized by enzymes,

including cytochrome P450 (CYCYP2D and CYCYP3A families), UDP-glucuronosyl-transferases (UGTs) and the efflux transporter P-glycoprotein, and this has important consequences on drug absorption, distribution, and elimination. The investigation into such genetic variation of animals also forms an excellent basis to the use of veterinary medicine and to translational biomedicine.

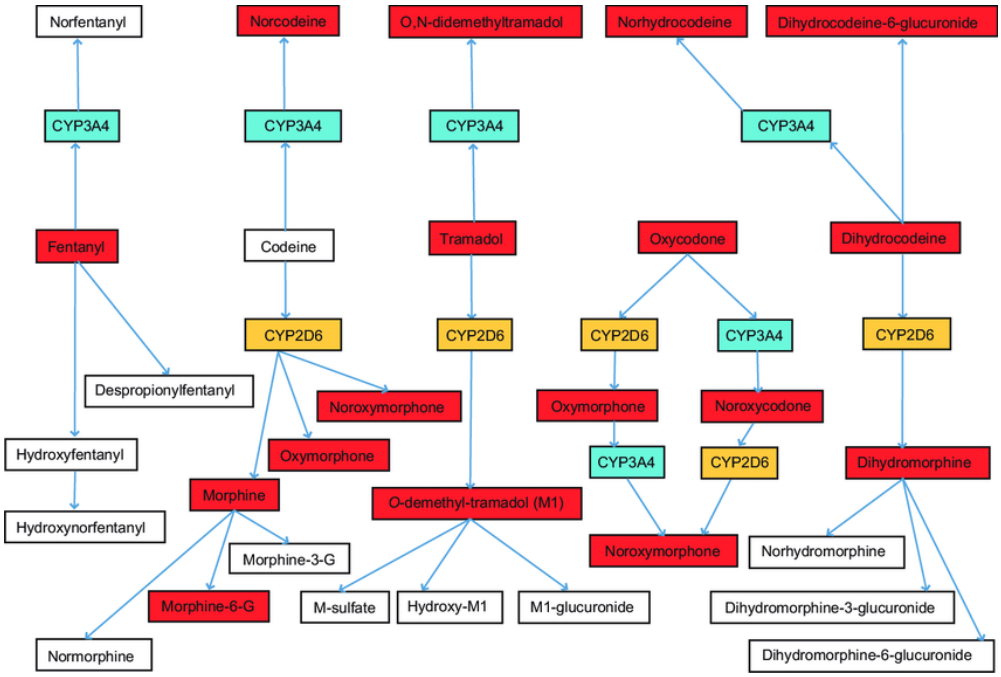

Figure 1: Opioids Metabolism[2]

However, the field of pharmacogenetics in veterinary and experimental animal models has been understudied with compared to that in human medicine although of late there has been an increasing interest. We conducted a review of major findings in the animal studies to assess the implication of genetic polymorphisms on the metabolism of efficacy and toxicity of popular opioids. Whether it is the differences in strain in rats or the tendency or sensitivity of certain breeds of dogs in regards to opioids, animal studies will pave a special opportunity to unravel the exact genetics of opioid response at a molecular level. We would like to demonstrate the clinical and translational value of pharmacogenetic information through the patterns of gene expression, enzyme activity, as well as transporter functionalities on an opioid animal investigation. The insights gained into these factors could help manage the pain better in veterinary practice and thereby have a stronger predictive capacity of preclinical models employed in the development of new opioid therapies[3].

1.1.Background and Context

Opioids are still some of the widely used pain relievers in animal care and research facilities, but their application in the clinical field is hampered by the large inter-individual and interspecific differences in drug response. In part, such variability can be defined by genetic differences that influence the process of opioid metabolism and its distribution within the body. Pharmacogenetic profiling has been able to clarify these differences in the human field but the same level of complexity is yet to be honed in the realm of animals. However, animal investigations have uncovered genetic factors namely those with regard to hepatic enzymes and membrane-bound transporters which significantly influence opioid efficacy and safety[4].

1.2.Objectives of the Review

- To analyze genetic factors (CYP, UGT, ABCB1) affecting opioid metabolism in animals.
- To evaluate methods like knockout models and breed comparisons.
- To examine breed/strain-specific opioid responses in rodents and dogs.
- To assess translational relevance for human drug development.
- To highlight pharmacogenetics' role in safer veterinary opioid use.

1.3.Importance of the Topic

Since the opioid crisis has been in power to influence pharmaceutical research and regulation, improved insight into the metabolism of opioids in animal models also becomes more appropriate. In the veterinary practice, however, species or breed-specific genetic profiles have the potential of helping to reduce this, by creating a personalised pain management program. Animal models are also essential in preclinical drug testing and thus to increase reliability and decrease translation failure rates in defining clinical trials, genetic variability should be considered in animal models. This puts the need to implement pharmacogenetics in animal studies of opioids not just a scientifically persuasive idea but rather a clinical necessity[5].

2. PHARMACOGENETIC INSIGHTS INTO OPIOID METABOLISM: EVIDENCE FROM ANIMAL MODELS

Pharmacogenetics of opioid metabolism has been studied in animals and genetic polymorphism, including CYP2D, UGT1A/2B, and ABCB1 variants, have been noted to provide a critical influence of drug efficacy, clearance, and penetration of CNS. Through the techniques of knockout mouse, breed comparison in the dog and radiolabeled imaging in primates the scientists have found out associations of great importance in the genotype-phenotype. This research is the advantage of controlled conditions and the availability of high-quality gene-editing instruments as well as their disadvantage, which is the interspecies difference, the scarcity of genetic diversity in animal models, and the lack of thorough genomic databases, limiting translation into human populations.

Table 1: Summary of Key Studies on Pharmacogenetics and Opioid Use Disorders[6]

Author(s)	Study	Focus Area	Methodology	Key Finding
Burns et al. (2019)[7]	Molecular imaging of opioid and dopamine systems	Neurobiology of Opioid Use Disorders (OUD)	Molecular imaging (PET scans)	Genetic variations affect opioid receptor function and dopamine signaling, impacting OUD risk.
Chan (2019)[8]	Drug metabolism and pharmacogenetics	Pharmacogenetics in Anesthesia and Analgesia	Conceptual and clinical review	CYP450 polymorphisms significantly influence opioid metabolism and perioperative drug response.

Cornett et al. (2020)[9]	Pharmacogenomics of pain management	Pain pharmacogenomics and drug metabolism	Literature review	Genetic polymorphisms in CYP2D6 and opioid receptors guide personalized opioid pain management.
Crews et al. (2021)[10]	CPIC guideline for CYP2D6, OPRM1, and COMT genotypes and opioid therapy	Clinical implementation of pharmacogenetic testing	Evidence-based guideline development	Genotype-guided opioid prescribing can optimize therapy and reduce adverse effects.
Crist, Clarke, & Berrettini (2018)[11]	Pharmacogenetics of opioid use disorder treatment	Pharmacogenetics in OUD treatment	Review of treatment response and gene associations	OPRM1 and ABCB1 polymorphisms influence medication response (e.g., methadone, buprenorphine).

2.1.Summary of Key Studies

There is an increasing number of studies that establish pharmacogenetics of opioid metabolism in animals, with strong consideration of the main impact that genetic polymorphisms produce in opioid pharmacokinetic and pharmacodynamic variations. These experiments are also paradigms to learn the mechanisms that are usually preserved in the human context[12].

- **Cytochrome P450 2D (CYP2D) in Rats and Dogs**: The different forms of the gene CYP2D have been known to play a major role in determining the occurrence of metabolic activation of prodrugs such as codeine to morphine. In rods, morphine has varying bioavailability leading to increased or reduced analgesic properties and this occurs because of differences in CYP2D isoforms. The same goes with canine researchers that find that different breeds of dog have varying levels of activity in CYP2D, implying genetically different metabolism levels belong to different dogs.

- **UDP-glucuronosyltransferases (UGT1A and UGT2B) in Guinea Pigs and Mice**: Such phase II enzymes are important in the regulation of opioid elimination. Morphine is converted to morphine-3-glucuronide and morphine-6-glucuronide by glucuronidation, and morphine-6-glucuronide retains analgesia in morphine. Difference in UGT expression level and activity in the animal models affects the efficiency as a therapeutic agent and toxicity profile of morphine.

- **ATP-binding cassette transporter B1 (ABCB1/MDR1) in Dogs and Mice**: The gene produces P-glycoprotein which is a transporter at cell membrane that actively pumps opioids out of brain. Analysis of dogs with MDR1 mutation (e.g. Collies and Australian Shepherds) indicates higher central nervous system (CNS) concentrations of opioids such as loperamide and fentanyl, making them susceptible to neurotoxicity. Likewise, WT mice exhibit reduced CNS sensitivity to opioids whereas knockout mice lacking functional ABCB1 have amplified CNS responses to opioids that is indicative of the

gene importance in restricting the opioid bioavailability in the central nervous system (CNS)[13].

2.2.Methodologies and Findings

A range of experimental methodologies has been employed in animal pharmacogenetic studies to dissect the influence of specific genes on opioid metabolism:

- **Pharmacokinetic Modeling, and Pharmacodynamic Modeling:** Modeling of the effects of opioids is done by injecting the drug and measuring the proportion of the drug concentration in the plasma. A number of important pharmacokinetic parameters like the half-life, clearance, and volume of distribution are then extracted. These parameters are then compared amongst various genotypes or between strains to determine the difference in the metabolic process[14].

- **Genotyping and Gene Knockout Studies:** Genomic analysis determines functional polymorphism of drug-metabolizing genes. Knockout models, more so in mice (e.g. CYP3A-null or MDR1-null), play a crucial role in establishing causative associations between particular genes and the changes in drug metabolism or response. As an example, CYP3A knockout mice are associated with finding a decreased clearance and hypersensitivity towards fentanyl and buprenorphine.

- **Comparative Breed-based Studies in Dogs:** by breed (e.g. Greyhounds with lower CYP activity) vs. Labradors) studies among the dogs have found severe pharmacokinetic differences in opioid disposal. These variations are said to be caused by the mutation of genes like MDR1-1Del deletion mutation, which causes the defective functioning of the P-glycoprotein[15].

- **Radiolabeled Tracer and Imaging Studies of Non-human Primates:** Non-human primates can benefit advanced imaging like PET, SPECT and other forms of radiolabeled opioids giving real time information of the drug distribution, receptor binding and CNS penetration. The translational value of these methods is high and it is attributed to physiological similarities between primates and humans.

2.3.Critical Evaluation

Strengths:

- **Experimental Restriction:** Animals provide control in study of genetic backgrounds, doses of drugs and experimental conditions in the environment creating great experimental restriction. This increases the credibility of genotype to phenotype correlations.

- **Mechanistic Insights with Gene Editing:** Availability of sophisticated technologies e.g. CRISPR/Cas9 has allowed specific underpinnings to be altered and has allowed real mechanistic insights into drug metabolism. Take an example, gene specific UGT knockouts may be used to determine the effect of individual isoform in morphine conjugation[16].

- **Ethical and Logistical Possibility:** Some of these experimental techniques, like, brain microdialysis or hepatic enzyme induction can be more ethically and logistically practical in animals compared to human beings.

Weaknesses:

- **Interspecies Variations:** Although animal research can inform the mechanism, the lack of certainty is related to the physiological, receptor localization, and enzymatic expression differences between species that decrease the applicability of animal research into humans. As an example, CYP isoforms are widely different in the substrate-specificity and inducibility between rodents and humans[17].
- **Minor genetic variability in non model species:** The majority of animal studies are carried out using inbred strains or select breeds and therefore lack variability in comparison with the human populations. This restricts the universalism of results and hinders the extrapolation of results to the population.
- **The absence of comprehensive genomic databases:** There are no comprehensive genomic databases, such as genome-wide association studies (GWAS) and 1000 Genomes in animals as found in humans. This reduces the capability to determine and make correlations with naturally occurring genetic variants and drug response observed in wider populations.

3. MECHANISTIC PATHWAYS INFLUENCING OPIOID PHARMACOKINETICS IN ANIMAL MODELS

Genetics plays an important role in opioid metabolism in animals, especially as far as enzymes and transport proteins are concerned in processing drugs and distribution to body tissues. Opioids are mainly oxidized at the phase I stage by cytochrome P450, which is mainly the CYP2D and CYP 3A[18]. They are enzymes to activate such prodrugs as codeine into active opioid morphine. There is a large strain- and breed-related variability in their activity and some strains of rodents and a range of dog breeds have a different potency, duration and toxicity of effect of drugs. Similarly, opioids are conjugated in phase II by UGT1A1 and UGT2B7 and in the form of glucuronides, e.g. M3G and M6G, which have variable activity and toxicity between species. As an example, there is increased formation of M6G in guinea pigs, which augment the analgesic effects, whereas additional M3G is synthesized in rats, which may reduce the efficacy level.

The presence of transport proteins like P-glycoprotein (encoded by the ABCB1 (MDR1) gene) is crucial to the regulation of the central nervous system (CNS) penetration of the opioids. Mutation of MDR1 that cause loss of protein function (commonly inherited in herding dog breeds, such as Collies) disrupts the protective role of the BBB, which increases opioid levels in the brain and the risk of neurotoxicity[19]. The mice knockout experiments provide support to analogous CNS extravagant outcomes. There is also breed- and strain-specific differences in the expression of metabolic enzymes influencing further pharmacokinetics, and pharmacodynamics, such as differences between Sprague-Dawley and Wistar rats. These genetic differences also emphasize the necessity of choosing the animal models in pharmacogenetics research thoroughly, so that the results of a study can be fully reliable and applicable.

3.1.Cytochrome P450 Enzymes and Opioid Oxidation

Cytochrome P450 is an enzyme system and especially the CYP2D and CYP3A subfamily, to the phase I opioid metabolism in animals[20]. These enzymes contribute to the oxidative metabolism of opioids, including production of active products of prodrugs such as codeine, morphine.

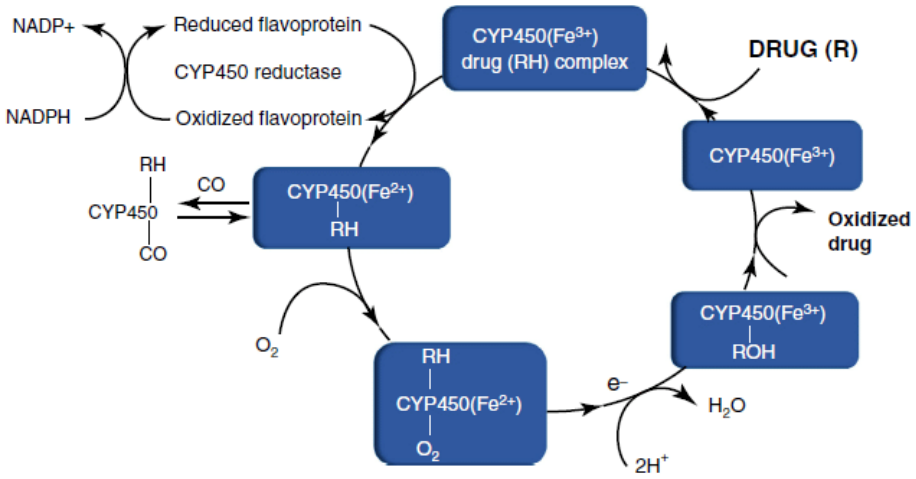

Figure 2: Cytochrome P450 Enzymes[21]

- CYP 2D isoforms (e.g., CYP2D1, CYP2D2) in rodent can be highly strain dependent regarding analgesic potency and systemic drug exposure. Equally, CYP3A inactive or less active metabolites are broken down by CYP3A into fentanyl and other synthetic opioids.
- In dogs, specifically Greyhounds and other breeds, the activity and expression of CYPs enzymes varies considerably, hence problems in the rates of drug metabolism arise. Polymorphisms or deletions in such genes may cause slower or faster opioid metabolisms, which alters the strength as well as the duration of opioid effects.
- Also, these polymorphisms may affect the detoxification and leave the animals with the less metabolic capacity more vulnerable to the opioid-mediated toxicity[22].

3.2.Conjugation via UGT Enzymes

Phase II In phase II, opioid class, such as morphine, is conjugated into glucuronide metabolites by UDP-glucuronosyltransferase (UGT enzymes) including UGT1A1 and UGT2B7[23].

- These enzymes in rat and guinea pig catalyze the oxidation of morphine to morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G). M3G is practically dormant or even suppresses analgesia whereas M6G tend to maintain or increase opioid effects.
- The M3G/M6G ratio which is species and strain dependent can have a significant impact on analgesic efficacy as well as toxicity.
- e.g. guinea pigs exhibit more M6G formation which can potentiate analgesic effects, whereas rats are more likely to form M3G, which can decrease efficacy, or produce more side effects.
- Variations in UGT genes of the enzymes alter the opioid clearance rates and systemic exposure due to the expression levels of the enzymes being affected by genetic variations.

3.3.Transport Proteins and Blood-Brain Barrier Penetration

ABCB1 gene codes P-glycoprotein (P-gp) transporter that plays a crucial role in preserving the integrity of the blood-brain barrier (BBB) through mediation of the active efflux of numerous opioids past the BBB into the central nervous system (CNS) and consequently the regulation of the availability in the CNS[24].

- Knockout mice deficient in ABCB1 have shown extremely elevated levels of opioids, such as morphine, fentanyl, and loperamide in the brain leading to over-dosed effects of the central nervous system, respiratory rate and sedation.

- Non-functional or absent P-glycoprotein is caused by mutation of the MDR1 (ABCB1) gene (e.g. MDR1-1Delta) in dogs, particularly herding breed (including Collie, Australian Shepherd and Shetland Sheepdog). These animals are hyper-responsive to centrally acting opioids and more susceptible to opioid kind of neurotoxicity[25].

- P-glycoprotein is considered to contribute to pharmacoresistance and opioid tolerance because it can lead to a growing efflux and a decrease of effective CNS concentrations with continuous treatment.

3.4.Breed and Strain Differences

A genetic background is a vital factor affecting opioid metabolism in animals, though outstanding breed differences and strain differences existed, that affected drug-metabolizing enzymes as well as drug transport proteins. In dogs, members of the breed including the Collies and the White Shepherds often have mutations on the MDR1 gene resulting in highly inactive P-glycoprotein[26]. This mutation is known to cause hyper-sensitivity to opioid including morphine and loperamide and to other drugs such as ivermectin and vincristine. Such animals are exposed to an increased risk of neurotoxicity and adverse drug reactions and thus require individual dosing schedules or the transfer to alternative treatment drugs[27].

Likewise, pharmacogenetic studies with rodent models, including Sprague-Dawley and Wistar rats, have high variations in the levels of expression of enzymes such as CYP and UGT. Strain differences affect as much pharmacokinetic factors (e.g. absorption rates, metabolism, and elimination rate) as pharmacodynamic effects (e.g. analgesic strength and efficacy of action). Hence, the natural genetic variability of animal strains or breeds should be given ample attention in developing preclinical studies due to its ability to greatly influence the results of the conducted experiments and constrains the applicability of the findings to other populations[28].

4. TRANSLATIONAL RELEVANCE OF ANIMAL PHARMACOGENETIC MODELS

Preclinical opioid drug development is important in animal pharmacogenetic models because it provides information on the effect of genetic differences in metabolism, efficacy and toxicity[29]. Transgenic rodents e.g. CYP and UGT knockout mice, and non-human primates offer the possibility of selective study of metabolic routes, with the non-human primates offering close physiological and enzyme equivalence with human subjects, facilitating the prediction of pharmacokinetics and pharmacodynamics[30]. One of the most important factors is species selection: rodents as an inexpensive model, canine model with MDR1 mutations to evaluate blood-brain barrier transport and neurotoxicity, and primates as a very high translational rate of drugs such as fentanyl and oxycodone. Such models influence the safer design of clinical trials and facilitate veterinary as well as human-regulatory activities, such as dose optimization and labeling with respect to genetic variation, thereby contributing to precision medicine and rational drug-approval approaches[31].

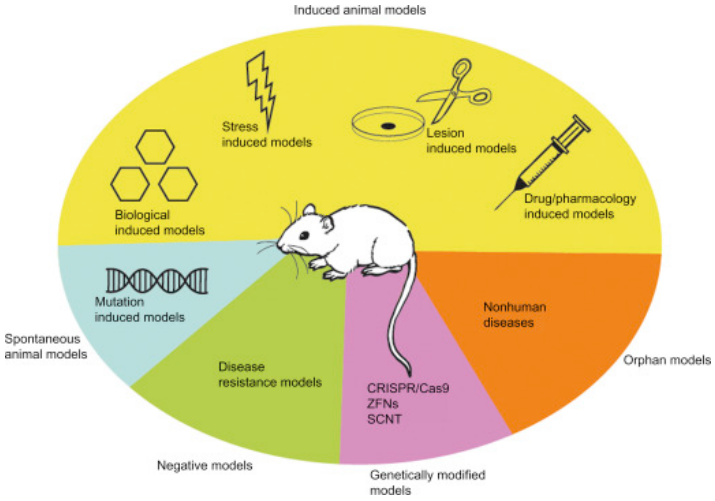

Figure 3: Animal pharmacogenetic models[32]

4.1.Role in Preclinical Drug Development

Animal pharmacogenetic models are important in preclinical phases of opioid drugs development as they offer much needed information about the genetic and molecular basis of opioid metabolism, efficacy and toxicity. Gene modified rodents like the CYP or UGT knockout mouse can also be used to provide an isolable means of studying the role of a given metabolic enzyme or transporter. These models assist in discovering the effect of metabolic pathway changes on the exposure of drugs into the system and the supply into the central nervous system. On the same note, the non-human primates are also very physiologically and metabolically similar to humans hence the process of predicting the pharmacokinetics and pharmacodynamics is more accurate[33]. By including pharmacogenetic information obtained in these animal models, the presence of possible adverse effects, dose-related toxicity, or limitations of efficacy can be detected at a very early stage of development, thus narrowing the path to drug candidates development and approach to a safer and evidence-based clinical trial stage in a human being.

4.2.Species Selection for Modeling Human Metabolism

The selection of animal species in pharmacogenetic research is vital, specifically, translation is impacted directly by species-specific variation in enzyme expression, receptor affinity, and function of drug transporters[34].

- Rodents are particularly the mice and rats and are common since they are cost effective and very manipulable in the genetic sphere. Although they do not have an actual human correspondent to CYP2D6, these forms such as CYP2D1 and CYP2D2 show up as functional surrogates. The metabolism of codeine, tramadol, and morphine have been reviewed extensively using knockout and transgenic rodents.
- Use of canines Canines and those with naturally occurring mutations of the MDR1 (ABCB1) gene are useful in investigating blood-brain barrier permeability and opioid induced neurotoxicity. As an example, Collies and Australian Shepherds with MDR1 deletions were used as a model of assessing opioids such as loperamide and fentanyl CNS penetration and safety margins.
- Non-primates like rhesus and cynomolgous monkey are more genetically and enzymatically related to human beings compared to humans, more so in CYP3A4, CYP2D6, and UGT2B7 enzymes. They have been of use in higher preclinical phases and are used to evaluate the uptake and circulatory changes of opioids like oxycodone and fentanyl, rendering data that is immediately relevant to the human clinical trial design.

The choice of species can therefore be informed by the metabolic or transporters target being tested and the translational proximity of the model to human physiology[35].

4.3.Implications for Regulatory Science

The result of pharmacogenetic studies of animal models not only influence the application of drugs studied in human beings, but it also forms an important implication in the veterinary field and approval processes governing it. To Veterinary drugs, the species-specific pharmacogenetic data play a vital role in formulating effective and safe dosing limits. As an example, opioid drugs in dogs should recognize breed sensitivities in terms of the MDR1 status. Further, regulatory authorities including the FDA, EMA, and the ICH are increasingly demanding pharmacogenetic information in preclinical investigation to aid the application of toxicological risk approximation, dose-selection, and prediction of at-risk-population at the initial stage of a first-in-human trial[36].

These studies also play a role in the development of drug labelling advice especially in groups with comparable human polymorphisms in these genes (e.g. poor metabolisers of CYP2D6 substrates). Altogether, strong animal model systems scatter the distance between the molecular level and the medical practice to facilitate the precision mode of treatment in human and veterinary medicine.

5. DISCUSSION

Genetic polymorphisms of enzymes such as CYP2D, CYP3A, UGT1A/2B, and ABCB1 have been illustrated in animal studies to strongly impact opioid metabolism and this has substantial effects on both efficacy and safety of drugs inter-species. These results are essential to both veterinary medicine and preclinical studies, since they can be used to customize opioid doses and better predict human behavior[37]. It has limitations, however, of small genetic databases, the use of inbred animal models and inability to access cross-species data, which limit wider application. Future studies need to be aimed at the extension of genetic data, investigating ethnically diverse people, using multi-omics procedures and creating humanized models to make pharmacogenetic research more transferable.

5.1.Interpretation and Analysis of Findings

An overview of the evidence available to date in animal studies shows clearly that genetic polymorphisms of enzymes like CYP2D, CYP3A, UGT1A/2B, and the ABCB1 transporter play an important role in the matter of opioid metabolism and efficacy and safety. Rodent and canine models indicate that the enzyme activity variance, which may be natural or artificially created, will raise the interindividual and interspecies differences in the pharmacokinetics and pharmacodynamics. An example is CYP2D isoforms in the rat that influences the bio transformation of codeine to morphine and in the MDR1-deficient dog, exaggerated CNS effects were seen based on the impaired efflux processes. The results support the usefulness of animal pharmacogenetic models to analyze complicated metabolic racetrackways and anticipate variable drug reactionivity[38].

5.2.Implications and Significance

Such pharmacogenetic considerations are of paramount importance to veterinary practice, preclinical drug development and human clinical trials. Breed sensitivity In veterinary practice, breed sensitivity can be used to optimize opioid dosing regimens based on a variety of factors including safety and effectiveness of pain management. In the preclinical setting, pharmacogenetic models allow a better prediction of how a drug will be metabolized in humans, increasing the delivery of opioid candidates through translation[39]. However, more and more areas of regulatory interest place those models in high regard to make recommendations

regarding the dosing and to define the genetically susceptible groups. Adding the pharmacogenetic information earlier in the pipeline has the potential to generate positive changes toward the decreased occurrence of adverse effects and decreased attrition associated with clinical trials.

5.3.Gaps in Knowledge and Future Research Directions

Irrespective of these developments, there are a number of gaps. There is scarcity of genomic databases in animal species which limits mapping of naturally occurring polymorphism in the populations. Inbred strain or certain breeds are used in most studies and this population is limited in genotypic variation required to assure generalization. Moreover, the comparative species data is usually unavailable; hence the direct translation of the finding into human context is quite cumbersome. Of priority in the future investigation would be:

- Growth of genetic databases of non-human organisms;
- This is done by the study of a variety of populations within and between species;
- The integration of genomics, proteomics and metabolomics, using multi-omics strategies;
- The creation of humanised animal models more accurate to the human pharmacogenetic response.

By filling these knowledge gaps, the reliability of animal models as translational resources will enhance and assist in the creation of safer and more customized opioid therapies in veterinary and human medicine[40].

6. CONCLUSION

Pharmacogenetic of opioid metabolism in animal models also forms a vital background to the effect of genetics variabilities on absorption, distribution, metabolism, and excretion of medicines. The presence of drugs like CYP2D, CYP3A, UGT1A/2B, and transporters like ABCB1 were found to make a big difference in the efficacy and safety of opioids, hence causing significant interindividual and interspecies discrepancy. The same insights can be particularly beneficial in veterinary practice, since responses do occur on a breed basis, which can guide safer and more practicable methods of pain management. In addition, the pharmacogenetic study in animals is also critical to preclinical drug development as this increases predictive validity of human drug response evaluation models. Although the genetic diversity and species-specific data remains limited in the current situation, the combination of genomic and multi-omics technologies, and the evolution of humanized animal models have a tremendous potential in optimizing methods of personalized medicine development. Altogether, a veterinary expertise on pharmacogenetics of animals is not only a step forward in the field of veterinary practice but it also fills the significant gaps in the field of translational studies on opioid therapeutics.

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