How to Choose Drug Dosage for Human Experiments Based on Drug Dose Used on Animal Experiments: A Review

UB Rajasekaran¹, US Krishna Nayak²
¹Research Scholar, Department of Orthodontics, AB Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, Karnataka, India, ²Head and Dean, Department of Orthodontics, AB Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, Karnataka, India

The orthodontic tooth movement is a biological response to orthodontic force. The biological response is very strongly-related to local bone metabolism. There is a strong evidence in the literature that bone metabolism can be altered by drugs. There are various studies published in dental journals on administration of drugs for the purpose of affecting orthodontic tooth movement both for augmentation of anchorage and to increase the rate of tooth movement. Most of these studies are animal studies. The aim of this article is to give insight to how to convert drug dose from animal studies to human trails. Dose per kilogram of body weight for one species is not the same for another species, it has to be converted first based on body surface area (BSA) normalization method. BSA correlates well across several mammalian species with several parameters of biology, including oxygen utilization, caloric expenditure, basal metabolism, blood volume, circulating plasma proteins, and renal function.

Keywords: Body surface area, Normalization method drug dose conversion, Kₘ factor

INTRODUCTION

The orthodontic tooth movement is a biological response to orthodontic force.¹ The biological response is very strongly-related to local bone metabolism.²,³ There is a strong evidence in the literature that bone metabolism can be altered by drugs.⁴⁻⁶ There are various studies published in dental journals on administration of drugs for the purpose of affecting orthodontic tooth movement as well as for augmentation of anchorage and retention. Most of these studies are animal studies.⁷⁻⁹ The problem in the application of these drugs for therapeutic purpose in human subjects or at least for the purpose of clinical trial is hesitated by many researchers mainly because of determining the effective dosage for humans. If drug influenced orthodontics incorporated into mainstream orthodontics, it will be a great addition to orthodontic biomechanics. The aim of this article is to give insight to how to convert drug dose from animal studies to human trails.

METHODOLOGY USED IN LITERATURE SEARCH

The database Medline-PubMed, was searched using the key terms “animal studies in orthodontics using drugs,” and “conversion of animal drug dosage for human studies in dentistry.” All articles published before December 2013 were included in the study. For the first search term, there were a total of 21 hits for the search. The second search term had 66 hits. This was further reduced 40 articles by setting a limit in PubMed search by limiting them to articles published in last 3 years. All the 61 articles including their bibliography section was studied and reviewed.

HOW TO CHOOSE DRUG DOSAGE FOR INITIAL ANIMAL STUDIES

1. Selection of appropriate animal species that best represents humans are selected.¹⁰
2. Based on toxicological studies, the lethal dose (LD) (dose per kilogram body weight that kills 50% of the test animals) is determined for that species.¹¹
3. Then LDₐ₀ is determined, that is when dose per kilogram body weight given to a group of the same species animals only 10% of the animals will die.¹²
4. The LDₐ₀ dose is administered to the animals for the experimental purpose.
5. When we observe the desired effects in the animals, the next step is to conduct human trails.

CAN WE USE LDₐ₀ DOSAGE FROM ANIMAL EXPERIMENTS TO CLINICAL TRIALS DIRECTLY?

1. Dose per kilogram of body weight for one species is not the same for another species, it has to be converted first based on body surface area (BSA).¹²,¹³

Corresponding Author:
Dr. UB Rajasekaran, Department of Orthodontics, AB Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, Karnataka, India. Phone: +91-8012537202/9845242020. E-mail: rajasekaranub@gmail.com
2. The formula used in human dosage calculation based on dose used in animal experiments is \((\text{animal} \cdot \text{K}_m\text{ factor divided by human } \text{K}_m\text{ factor})\) multiplied by animal dose (mg/kg); the K\text{m} factor, body weight (kg) divided by BSA (m\text{2}). The \text{K}_m\text{ values based on average BSA calculations for human, baboon, dog, monkey, rabbit, guinea pig, rat, hamster, and mouse:}^{14-20}
Values based on data from Food and Drug Administration (FDA) Draft Guidelines\textsuperscript{10} (Table 1)

3. The reason why we cannot convert the drug dosage as they relate to humans. The US FDA has begun to approve more researchers are now shifting away from animal-based LD test animals differs in important aspects to that of humans. Efforts toward designing more appropriate means of selecting drug dosages for human trials will be very advantageous in the near future.

## CONCLUSION

LD values for humans are best estimated by extrapolating results from human cell cultures. The degree of error from animal-extrapolated LD values is very large.\textsuperscript{21} The biology of test animals differs in important aspects to that of humans. Researchers are now shifting away from animal-based LD measurements. The US FDA has begun to approve more reliable non-animal methods in response to research cruelty concerns and the lack of validity/sensitivity of animal tests as they relate to humans.\textsuperscript{21} Currently, BSA-based dose calculation is the most appropriate method and is far superior to a simple conversion based on body weight.\textsuperscript{21} Efforts toward designing more appropriate means of selecting drug dosages for human trials will be very advantageous in the near future.

## REFERENCES