European Journal of Pharmaceutics and Biopharmaceutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review Article

Canine gastrointestinal physiology: Breeds variations that can influence drug absorption

Hayley Oswald, Michele Sharkey, Devendra Pade, Marilyn N. Martinez *

US FDA Center for Veterinary Medicine, Rockville, MD 20852, United States

ARTICLE INFO

Article history:
Received 3 June 2015
Revised 1 August 2015
Accepted in revised form 20 September 2015
Available online xxxx

Keywords:
Dog
Gastrointestinal physiology
GI transit time
Permeability
Absorption

ABSTRACT

Although all dogs belong to *Canis lupus familiaris*, the physiological diversity resulting from selective breeding can lead to wide interbreed variability in drug pharmacokinetics (PK) or in oral drug product performance. It is important to understand this diversity in order to predict the impact of drug product formulation attributes on *in vivo* dissolution and absorption characteristics across the canine population when the dog represents the targeted patient population. Based upon published information, this review addresses breed differences in gastrointestinal (GI) physiology and discusses the *in vivo* implications of these differences. In addition to the importance of such information for understanding the variability that may exist in the performance of oral dosage forms in dogs for the purpose of developing canine therapeutics, an appreciation of breed differences in GI physiology can improve our performance prediction of oral drug formulation performance when we extrapolate bioavailability results from the dog to the humans, and vice versa. In this literature review, we examine reports of breed associated diversity in GI anatomy and morphology, gastric emptying time (GET), oro-cecal transit time (OCTT), small intestinal transit time (SITT), large intestinal transit time (LITT), intestinal permeability, sodium/potassium fecal concentrations, intestinal flora, and fecal moisture content.

© 2015 Published by Elsevier B.V.

1. Introduction

Due to hundreds of years of selective breeding and domestication, the dog as a species has diverged both genotypically and phenotypically. All dogs belong to *Canis lupus familiaris*, yet the physiological diversity resulting from this selective breeding has led to the potential for wide interbreed variability in drug pharmacokinetics (PK) and in oral drug product performance. Thus, it is important to understand the physiological differences that can occur across the canine population.

Given the importance of this information, we undertook an extensive literature search of the published information pertaining to breed-associated diversity in gastrointestinal (GI) anatomy and physiology. Parameters evaluated include the following:

- Anatomical features
  - Small intestinal length and diameter
  - Intestinal villus morphology
- Physiological processes
  - Gastric emptying time (GET)
  - Oro-cecal transit time (OCTT)
  - Small intestinal transit time (SITT)
  - Large intestine transit time (LITT)
- Absorption factors
  - Fecal moisture content
  - Electrolyte absorption
  - Intestinal flora
  - Intestinal permeability

The lack of published information on the relationship between breed and basal fluid volumes, mucous layer thickness, bile salt composition, and regional pH necessitated its exclusion from this review.

The studies described in this review utilized a variety of testing methods. Since the experimental methodology can greatly

Abbreviations: PK, pharmacokinetics; GI, gastrointestinal; GET, gastric emptying time; OCTT, oro-cecal transit time; SITT, small intestinal transit time; LITT, large intestinal transit time; TTT, total transit time; MTTT, mean total transit time; ADME, absorption, metabolism, distribution and elimination; MP, Miniature Poodle; GD, Great Dane; SS, Standard Schnauzer; GS, Giant Schnauzer; L/R, lactulose to rhamnose urinary ratio; MG, 3-O-methyl-D-glucose; WMC, wireless motility capsule; OABT, ^{13}C-octanoic acid breath test; BIPS, barium impregnated polyethylene spheres.

* Corresponding author. Tel.: +1 240 402 0635; fax: +1 240 276 9538.
E-mail address: marilyn.martinez@fda.hhs.gov (M.N. Martinez).

http://dx.doi.org/10.1016/j.ejpb.2015.09.009
0939-6411/© 2015 Published by Elsevier B.V.

UNCORRECTED PROOF

influence conclusions derived from any given investigation, we considered the potential for study-design bias in the cited literature and we applied caution when generating inter-study comparisons. Where inconsistencies appeared to exist, we tried to identify the potential underlying causes.

This review represents a first step in an effort to understand the potential range of drug exposures that can occur when a drug or drug formulation is introduced into the general canine population.

2. Anatomical features

Potential breed differences in intestinal drug absorption can occur as a consequence of *in vivo* factors controlling gut permeability, drug solubility, and *in vivo* product dissolution. This in turn can be influenced by population diversity in anatomical features such as intestinal length, intestinal villus morphology, GI transit time, and those variables that influence the gut luminal environment. Although we have segregated the discussion into discrete topics, it is important to recognize that the GI tract should be viewed from the perspective of an interacting and dynamic system.

2.1. Small intestinal length and diameter

The total length of the canine small intestine is comprised approximately 10% duodenum, 85% jejunum and 5% ileum [1]. The dog small intestine is lined by villi and does not show the presence of the permanent folds (plicae circulares) that serve to increase the effective absorptive surface area of humans and primates. This difference is important to consider when extrapolating data on canine drug absorption and intestinal segmental absorption (e.g., as can be generated with the use of physiologically based pharmacokinetic models) to intestinal absorption predictions in humans.

Despite the observed variability, the length of the duodenum, jejunum and ileum is positively correlated with canine body size. This was confirmed in a postmortem investigation of 55 dogs where measurements had been taken on body weight (range 5–33 kg) and intestinal segmental length. The relationships between lengths of the various intestinal segments were further confirmed by the positive correlation observed between ileal and jejunal lengths (Fig. 1a–d) [2].

2.2. Intestinal villus morphology

The dog small intestinal villi are typically long (villus height >500 μm) and cylindrical or tongue-like in shape [3]. Baum et al. harvested full thickness biopsies from the GI tracts of 28 dogs of different ages and measured the histomorphologic differences (jejunum and colon) across canine breeds of various ages [4]. Adult dog (age ⩾2 years) body weight was assigned using an online resource (www.wikipedia.org; American Kennel Club). Time to reach full adult body weight was estimated as 10 months for toy, small and medium breeds and 15 months for giant breeds [5]. Thus in the data published by Baum et al. (2004), all dogs of 2 years and

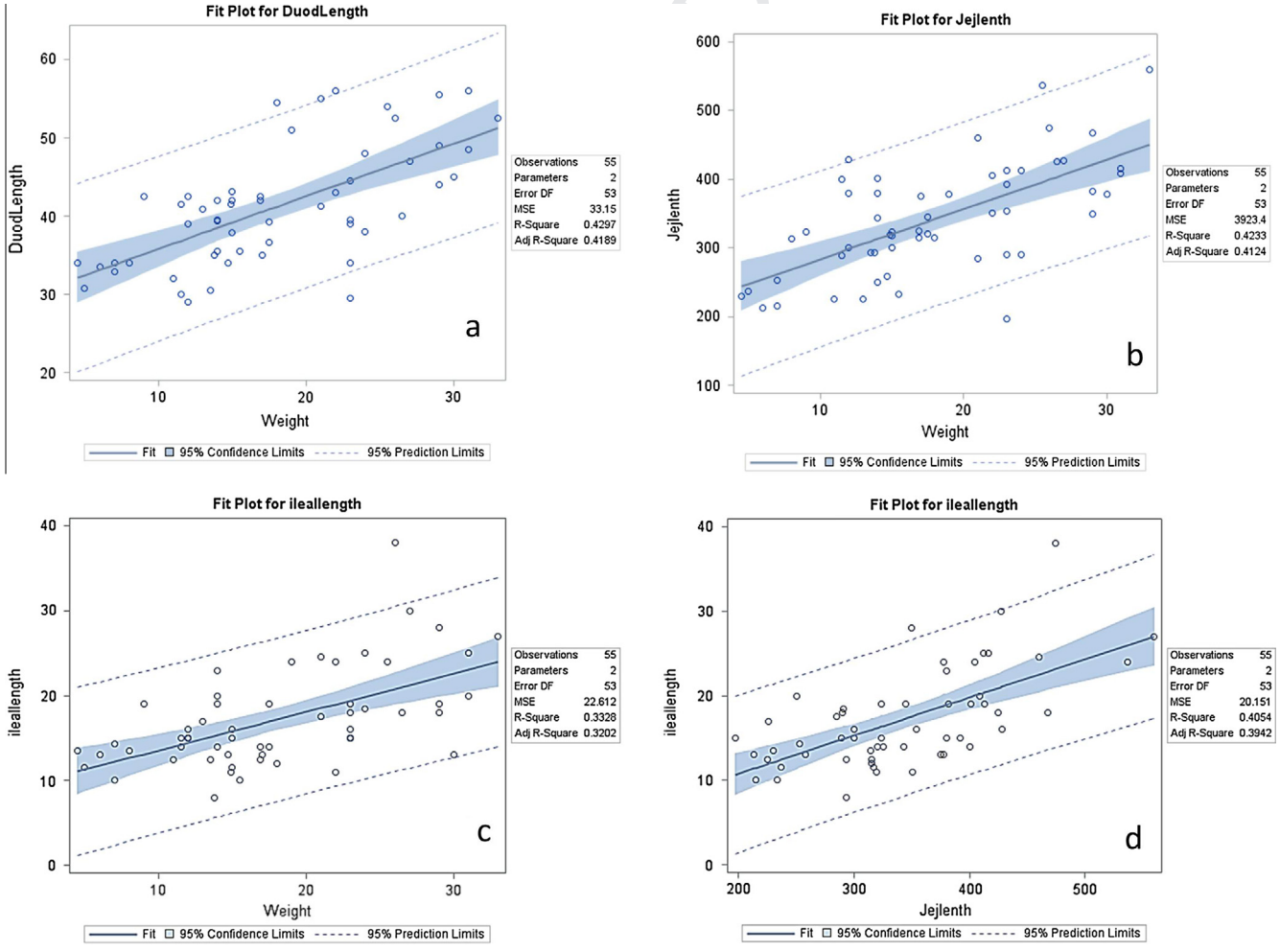

Fig. 1.

Please cite this article in press as: H. Oswald et al., Canine gastrointestinal physiology: Breeds variations that can influence drug absorption, Eur. J. Pharm. Biopharm. (2015), http://dx.doi.org/10.1016/j.ejpb.2015.09.009

Download English Version:

https://daneshyari.com/en/article/8412953

Download Persian Version:

https://daneshyari.com/article/8412953

Daneshyari.com