UNIVERSITI PUTRA MALAYSIA

PHARMACOKINETICS OF IMIDOCARB IN NORMAL AND FEBRILE DOGS AND GOATS

ABDUL SALAM ABDULLAH

FPV 1983 7

PHARMACOKINETICS OF IMIDOCARB IN NORMAL AND FEBRILE DOGS AND GOATS

by

Abdul Salam Abdullah, D.V.M., M.S.

A Thesis

Submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy in the Faculty of Veterinary Medicine and Animal Science, Universiti Pertanian Malaysia

September 1983.

ABSTRACT

Disposition kinetics of imidocarb, an antiprotozoan drug, was studied in normal and febrile dogs and goats. Fever was induced using E. coli endotoxin, Trypanosoma evansi and Infectious Bovine Rhinotracheitis (IBR) virus. The objectives of the study were to compare the disposition kinetics of imidocarb in ruminant and monogastric species, and the influence of fever of different etiology on the disposition kinetics of this drug. The concentration of imidocarb in body fluids and tissues were measured by spectrophotometry.

The disposition kinetics of imidocarb in normal and febrile dogs and goats can be adequately described by a two-compartment open model. The apparent volume of the central compartment, V_c, was significantly lower ($P<0.01$) but the volume of distribution, $V_{d(area)}$ was significantly higher ($P<0.05$) in normal goats than in dogs. Higher volume of distribution and the ratio of imidocarb level in peripheral-to-central compartment in goats (6:1) prolonged elimination of the drug, resulting in considerably higher levels of the drug still present in the tissues 14 days after a single subcutaneous or intramuscular dose. Thus the withdrawal time of imidocarb was estimated to be 5-6 weeks in this food-producing species. Differences in the kinetic disposition of imidocarb in dogs and goats may be largely attributed to the anatomical and physiological differences in the gastrointestinal tract between the two species.

The results of the present study indicate that fever of different etiologies affected the disposition kinetics of imidocarb

differently. Plasma concentrations of imidocarb were higher than normal during endotoxin-induced fever but lower during Trypanosoma-induced fever. Although concentrations of imidocarb in the plasma of goats were not affected by the IBR viral-induced fever, the apparent volume of distribution, $V_{d(area)}$, and the steady-state volume ofdistribution, $V_{d(ss)}$, were significantly lowered as in the endotoxin-induced fever. Similarly, the above kinetic parameters as well as volume of central compartment, V_c, and the body clearances Cl_B were significantly higher ($P<0.01$) in dogs and goats during Trypanosoma-induced fever than in the normal animals although the plasma concentrations were substantially reduced during the febrile reaction. The microconstants were also affected differently by fever of different etiology. Nevertheless, half-life of imidocarb remained unaffected during the three febrile conditions.

Therefore, it could be hypothesized that fever of different etiology affected the disposition kinetics of imidocarb differently and the influence of fever on pharmacokinetics should be considered beyond the plasma concentrations and half-life of the drug itself. Furthermore, the pathophysiology of the disease and not just the febrile state should be considered when evaluating the influence of disease conditions on the disposition kinetics of a drug.

ACKNOWLEDGEMENT

I wish to acknowledge with deep gratitude my indebtedness to Professor J. Desmond Baggot, Chairman, Department of Pharmacology and Toxicology, School of Veterinary Medicine, University of California, Davis. I have relied to a great extent on his advice and have benefited from his unrivalled experience in pharmacokinetics.

The enormous guidance, contribution, support and encouragement given by Professor Syed Jalaludin Syed Salim and Professor Abdul Latif Ibrahim are deeply appreciated. I am also grateful to Dr. Sheikh Omar Abdul Rahman, Head of the Department of Pathology and Microbiology and Dr. Law Ah Theem, Faculty of Fisheries and Marine Science for their help. I am also indebted to all technical assistants of the Faculty of Veterinary Medicine and Animal Science, Universiti Pertanian Malaysia, especially Zainal Abidin Jamin for their excellent technical assistance and to Normadiah Sukaimi for her accurate typing of the original manuscript.

My gratitude to Universiti Pertanian Malaysia, Serdang, Selangor for funding this project, Schools of Veterinary Medicine, Murdoch University, Western Australia and University of California, Davis, U.S.A. for providing the laboratory and library facilities in completing this project.

Last but not least, I would like to express my sincere gratitude to my wife, Rahmah, daughters, Syazrah Nisydah and Syazrah Yuanidah for their understanding and patience with me in completing this project.

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES

LIST OF FIGURES