PHARMACOLOGY OF MORPHINE AND THE ACTIVE METABOLITE MORPHINE 6-GLUCURONIDE:

A COMPARISON OF PHARMACOLOGICAL AND CLINICAL EFFECTS

being a thesis submitted to the

University of Auckland

for the degree of

Doctor of Medicine

in the Faculty of Medicine

by

Paul Ivan Thompson

Imperial Cancer Research Fund

Department of Medical Oncology

St Bartholomew's and Homerton Hospitals

London, United Kingdom

1991

To Bronwyn

ABSTRACT

Morphine is an effective potent analgesic. However the side effects of nausea, constipation and sedation are seen frequently. Respiratory depression is not such a common problem clinically but is the most potentially dangerous toxicity. An analgesic inducing equivalent analgesic potency without these toxicities would be particularly valuable.

Morphine 6-glucuronide (M6G), one of the major metabolites of morphine, has analgesic activity in animals and animal studies have suggested an improved therapeutic index. The initial study in this thesis confirms the analgesic activity of M6G in man and the pharmacokinetic profile after intravenous and oral administration has been determined. The elimination half life is approximately 1.6 hours with the rate of clearance closely correlating with creatinine clearance. Oral bioavailability at approximately 5%, however, is poor due to its hydrophilic nature.

In an effort to more critically examine the comparative emetic potency of M6G and morphine, both compounds were administered to the ferret, a known emetic model for man. Surprisingly M6G had a greater emetic potency in this model. A pilot pharmacokinetic study performed on the ferret revealed that M6G is only a very minor metabolite accounting for approximately only 1% of the metabolic product of morphine compared to 10% in man. It is possible that other aspects of opiate handling are also different, and reminds us of the importance in studying the drug handling of any

animal model used for the testing of any drug, particularly when metabolites are thought to play a role in clinical effect.

No patients or volunteers in the initial open studies in man experienced any nausea or sedation. This observation prompted a double-blind randomized study comparing the analgesic potency, respiratory depression, nausea and sedation induced by morphine and M6G in normal volunteers. This study confirmed that M6G has an increased analgesic potency in man when compared to morphine and causes significanctly less respiratory depression, nausea and sedation.

It has been previously hypothesized that the μ opioid receptor with lower affinity for morphine, the $\mu 2$ receptor, is responsible for the majority of morphine toxic side-effects, including respiratory depression. The last study presented in this thesis utilises radioligand binding studies to determine the opioid receptor binding affinities of morphine and M6G at the $\mu 1$, $\mu 2$, total μ and delta opioid receptors. This reveals that M6G has a 5-fold lower binding affinity to the putative $\mu 2$ opioid receptor and hence provides a possible explanation for the decreased toxicity seen compared to morphine.

In light of the findings in man above, further investigation of this active morphine metabolite is therefore indicated as M6G could prove particularly beneficial to those patients with severe underlying pulmonary disease and for obstetric use.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

There are many people without whom the studies performed in this thesis would not have been possible. I would first like to acknowledge the patients who participated in the open pharmacokinetic study who realized the study was performed particularly for the possible benefit of patients in the future rather than themselves. Similarly I would like to thank the nursing, medical and technical staff of the ICRF Medical Oncology Unit at St Bartholomew's and Homerton Hospitals, and the other volunteers who participated in the volunteer pharmacokinetic and analgesic efficacy studies.

I am particularly grateful to Dr Maurice Slevin who originally conceived the idea of investigating morphine 6-glucuronide in the ICRF Medical Oncology Unit and who supervised me during the undertaking of this research. In the many times when seemingly insurmountable difficulties arose he always pointed me in the right direction, and continually enthused me to complete this work. Dr Richard Osborne began the work with morphine 6-glucuronide and provided me a basic knowledge of the subject, ideas and many references.

To Simon Joel, the principal biochemist of the Homerton Hospital Oncology Laboratory, I give very special thanks. He was of invaluable assistance in arranging for assays to be performed, but particular in being an infallible technical problem solver. I am also indebted to Duncan Trew and Naina Patel who each performed many drug assays. I would also like to thank Mary MacLean, pharmacist, who prepared drug

solutions for the double-blind randomized study and buffer solutions for the normal volunteer studies.

One of the studies presented in this thesis was performed in the Physiology Department of St Georges Hospital Medical School under the guidance of Dr Paul Andrews who provided a source of constant enthusiasm, friendship and technical expertise, and to whom nothing was too much trouble. I am deeply indebted to he and Dr Sharon Bingham who also gave many hours of her time and considerable expertise.

I am also grateful to Dr JA Wedzicha, Respiratory Medicine Physician, for advice on assessment of respiratory function and the use of her department and equipment. I am also extremely grateful to Leonette John, senior respiratory physiology technician, for her time, expertise and enthusiasm.

The study on the opioid receptor binding profiles of morphine and morphine 6-glucuronide was performed in the Department of Chemical Endocrinology of St Bartholomew's Hospital and I am indebted to them, particularly to David Hucks and Dr Lorraine McLoughlin for their hard work and patience in teaching me the technical aspects of the assays. I am also grateful to Professor Leslie Rees and Dr Ashley Grossman for their timely advice and use of their department.

I also wish to thank Professor Jim Malpas for the opportunity of working within the ICRF Department of Medical Oncology at St Bartholomew's Hospital, and Dr Peter

Wrigley who gave much timely advice during my time there and allowed his patients to participate in the studies.

The performance of these studies and the writing of this thesis resulted in countless night and weekend hours spent away from my wife Bronwyn and young children William, Andrew and Anna. My most grateful thanks go to them for their unending patience and understanding.