The Use of Oxycodone for Analgesia Post Caesarean Section:
Maternal Plasma Levels, Breast Milk Levels and Neonatal Levels;
Survey of Use in Australian and New Zealand Obstetric Units.

by

Suzette May Seaton
B. Pharm

Submitted in the fulfilment of the requirements for the degree of
Master of Medical Science

November 2008

University of Tasmania
Declaration of Originality

The material presented in this thesis is original and contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and, to the best of the candidate’s knowledge and belief, no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any information that infringes copyright.

........................................... (November 2008)

Suzette Seaton
B. Pharm., AACPA, Dip. Man. (FMI)
Statement of Authority to Access

This thesis may be made available for loan and limited copying in accordance with the Copyright Act 1968 and the Amendments to the Copyright Act 2006.

........................................... (November 2008)

Suzette Seaton
Abstract

Drug transfer to the feeding infant and the safety of a transferred drug are important considerations for clinicians, yet there is a paucity of reliable studies in humans. Drug product manufacturers are not mandated to provide studies on the transfer of their products into human milk and may advise that the drug not be used in breastfeeding mothers, due to lack of information. This often leads to the cessation of the drug, resulting in suboptimal treatment of the mother, or the highly undesirable outcome of cessation of breastfeeding.

There was a perception that the opioid analgesic drug, oxycodone, was becoming a popular choice for oral analgesia post-Caesarean section. A review of the literature revealed no information or recommendations for its use in this setting, and manufacturers advised that the drug should not be used in breastfeeding.

Fifty breastfeeding mothers, taking oxycodone, had blood and breast milk samples analysed for oxycodone levels at 24-hourly intervals after Caesarean section. Forty-one neonates had blood samples analysed at 48 hours and 72 hours after delivery.

Oxycodone was detected in milk of all mothers taking any dose of the drug in the previous 24 hours. The maximum level recorded in milk was 168 ng/ml. There was a strong linear correlation between the maternal blood levels and the milk levels and there was evidence of persistence of oxycodone in the milk of some mothers, up to 37 hours after the last maternal dose. Oxycodone was detected in the plasma of one neonate of 41 tested.
The risk of neonatal exposure was assessed to be minimal in the three days post
delivery because of the low volumes of milk ingested by neonates in this period.
The benefits of providing effective and convenient analgesia to aid successful
initiation of breastfeeding and enable mothers to care for their babies would appear
to outweigh the risks of infant exposure to oxycodone in this early period.

The findings in this study are not generalisable to the transfer of oxycodone into
mature milk, or exposure of older infants whose mothers may be taking this drug.
It would be prudent to be cautious and monitor infants for signs of sedation, poor
feeding, gastrointestinal symptoms and respiratory depression if mothers are on
large doses of oxycodone.

To determine current practice with respect to the use of oxycodone and other drug
components of multimodal analgesia post-Caesarean section 25 Fellows of the
Australian and New Zealand College of Anaesthetists completed an on-line survey.
Responses indicated that 50 percent of women in metropolitan hospitals and 95
percent in rural/regional hospitals, in the survey sample, would receive oral or
rectal oxycodone post-Caesarean section. The popularity of oxycodone as a choice
for analgesia in this setting supports the importance of this study.
Acknowledgments

I would like to acknowledge the valuable assistance of my supervisors, without whom this work could not have begun or progressed to a meaningful conclusion; Professor Judith Walker for being always available for regular meetings and for her invaluable guidance and positive encouragement on writing and construction of this thesis; Dr Mark Reeves for his assistance with research methodology, statistical advice and patient editing of papers for submission; and Professor Stuart McLean for his contribution to determining a suitable analytical method, despite considerable trial and error, and co-ordinating the human and physical resources required for sample analysis.

I also extend my thanks to Professor Noel Davies for his invaluable input into a chemical extraction method; and for his time spent on HPLC analysis of our samples; and Dr Alison Featherstone and Sue Brandon for chemical extraction of samples.

This work would not have been possible without the assistance of Dr Albert Shugg and Dr Amol Daware (paediatricians), in collecting neonatal blood samples; the midwives and nursing staff of the North West Private Hospital in collecting milk and maternal blood samples; and Richard Hanlon and staff of North West Pathology Services in collecting, storing and shipping samples.

Finally I wish to sincerely thank all the mothers who consented to participate in this study, for their contribution to the advancement of knowledge about the safety of drugs in breast-feeding.

This study was funded by the Clifford Craig Medical Research Trust.
# Table of Contents

Declaration of Originality I

Statement of Authority to Access II

Abstract III

Acknowledgments V

Chapter 1 - Caesarean Section, Analgesia and Breastfeeding 1

1.1 Introduction 1

1.2 Context 2

1.3 Emergence of The Questions 3

1.4 Preliminary Literature Search 4

1.4.1 What is oxycodone? 4

1.4.2 Current recommendations 6

1.4.3 Importance of further study 8

1.5 Pilot Drug Usage Evaluation 8

1.5.1 Objective 8

1.5.2 Method 9

1.5.3 Summary of results 10

1.5.4 Discussion 12

1.5.5 The use of analgesics in breast-feeding mothers 13

1.5.6 Conclusion 14

1.6 Scope 15

1.7 Research Questions and Hypotheses Posed 16

1.7.1 Study of breastfeeding mothers and neonates 17

1.7.2 Survey of Australian and New Zealand obstetric units 20

1.8 Roles of Key Personnel 21

1.9 Definition of Terms 23
Chapter 2 - A Journey Through the Literature

2.1 Overview

2.2 Search Terms and Literature Sources

2.3 Transfer of Drugs into Breast Milk
   2.3.1 Drug concentration in maternal plasma
   2.3.2 Milk to plasma ratio
   2.3.3 Protein binding
   2.3.4 Lipid solubility
   2.3.5 Molecular size
   2.3.6 pH, pKa and ionisation of drugs

2.4 Infant Exposure to Drugs in Breast Milk

2.5 Physicochemical Characteristics and Pharmacokinetics of Oxycodone
   2.5.1 Adults
   2.5.2 Neonates and infants

2.6 Oxycodone Use in Paediatrics

2.7 Oxycodone – Toxicity and Harm

2.8 Analgesic Practice Following Caesarean Section
   2.8.1 Surveys of analgesic practice following Caesarean section

2.9 Studies of Drug Excretion into Breast Milk in the Obstetric Setting
   2.9.1 Studies of oxycodone excretion into breast milk

2.10 Impact of Analgesic Drugs on Initiation of Breastfeeding

2.11 Methods of Analysis of Oxycodone and its Metabolites in Biological Samples

2.12 Summary
Chapter 3 — Methodology

3.1 Introduction

3.2 Oxycodone in Maternal Plasma, Breast Milk and Neonates

3.2.1 Ethics approval

3.2.2 Study design

3.2.3 Selection of participants

3.2.4 Exclusion criteria

3.2.5 Recruitment

3.2.6 Data collection

3.2.7 Sample collection and storage

3.2.8 Sample analysis

3.2.9 Data analysis

3.2.10 Methodological assumptions

3.2.11 Methodological limitations

3.3 Survey of Obstetric Units in Australia and New Zealand

3.3.1 Ethics approval

3.3.2 Survey design and delivery

3.3.3 Piloting the survey

3.3.4 Selection of participants

3.3.5 Data collection

3.3.6 Recruitment

3.3.7 Data analysis

3.3.8 Methodological limitations

3.4 Summary
Chapter 4 – Analysis of Samples: Materials and Methods

4.1 Introduction 83
4.2 Collection and Storage of Samples 84
4.3 Extraction and Analysis of Oxycodone and Noroxycodone 85
   4.3.1 Materials and reagents 85
   4.3.2 Initial method 87
   4.3.3 Final method 88
4.4 Preparation of Standards and Internal Standards 88
4.5 Preparation of Plasma and Breast Milk Samples 90
4.6 HPLC-MS Instrument Details 91
4.7 Assay Validation and Determination of Limits of Quantitation 92
4.8 Comment on Initial Trials 98
4.9 Summary 99

Chapter 5 – Presentation and Evaluation of Results 100

5.1 Introduction 100
5.2 Oxycodone in Maternal Plasma, Breast Milk and Neonates 101
   5.2.1 Sample population demographics 101
   5.2.2 Oxycodone breast milk vs. maternal plasma levels 101
   5.2.3 Neonatal oxycodone levels 106
   5.2.4 Maternal oxycodone dose, plasma and breast milk levels 106
   5.2.5 Clearance of oxycodone from breast milk following multiple dosing 109
   5.2.6 Maternal sedation, neonatal sedation and feeding attachment 113
5.3 Analgesia Post-Caesarean Section in Australian and New Zealand
   Obstetric Units 115
   5.3.1 Survey participant demographics 115
5.3.2 Oxycodone use post-Caesarean section

5.3.3 Drug preference for multimodal analgesia post-Caesarean section

5.3.4 Modification of drug choice in breastfeeding mothers

5.3.5 Effect of research findings on analgesic practice post-Caesarean Section

5.4 Discussion – Oxycodone in Maternal Plasma, Breast Milk and Neonates

5.4.1 Oxycodone breast milk vs. maternal plasma levels

5.4.2 Neonatal oxycodone levels

5.4.3 Maternal oxycodone dose, plasma and breast milk levels

5.4.4 Clearance of oxycodone from breast milk

5.5 Discussion – Analgesia Post-Caesarean Section in Australian and New Zealand Obstetric Units

5.5.1 Oxycodone use post-Caesarean section

5.5.2 Drug preference for multimodal analgesia post-Caesarean section

5.5.3 Modification of drug choice in breastfeeding mothers

5.5.4 Effect of research findings on analgesic practice post-Caesarean Section

5.6 Summary

Chapter 6 – Summary and Conclusions

6.1 Overview

6.2 Summary of Findings

6.2.1 What is known about drug excretion into breast milk?

6.2.2 What is known about oxycodone excretion into breast milk?
6.2.3 What has been learned about oxycodone excretion into breast milk?

6.2.4 What drug choices are available for analgesia post-Caesarean section?

6.2.5 What has been learned about analgesic use for management of pain post-Caesarean section in Australian and New Zealand practice?

6.2.6 Are these choices compatible with breastfeeding?

6.3 Conclusions

References
Appendices

Appendix A – Noroxycodone levels in maternal plasma and breast milk

Appendix B – Ethics approval “Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: relationships between drug dose, breast-milk levels and neonatal plasma levels”

Appendix C (i) – Oxycodone Study Clinical Report Form

Appendix C (ii) – Oxycodone Study Patient Information Brochure

Appendix C (iii) – Oxycodone Study Patient Information Sheet

Appendix C (iv) – Oxycodone Study Consent Form

Appendix C (v) – Oxycodone Study Pathology Request Form

Appendix D – Ethics approval “Oxycodone as a component of multimodal analgesia after Caesarean section: Survey of analgesic practice in Australian and New Zealand obstetric units”

Appendix E (i) - Survey of analgesic practice in Australian and New Zealand obstetric units – Survey Questions

Appendix E (ii) - Survey of analgesic practice in Australian and New Zealand obstetric units – Letter of Introduction

Appendix E (iii) - Survey of analgesic practice in Australian and New Zealand obstetric units – Reminder Letter

Appendix E (iv) - Survey of analgesic practice in Australian and New Zealand obstetric units – Comments Analysis

Appendix F (i) – Numerical data sets: maternal oxycodone and breast milk oxycodone

Appendix F (ii) – Statistical data for M:P ratios

Appendix G (i) – Cohort of individual participant with outliers
Appendix G (ii) – Oxycodone dose, dose to sampling times, plasma and breast milk levels for all participants 192

Appendix H – Maternal sedation, Neonatal sedation and feeding attachment 195

Appendix I – References relating to post-Caesarean section studies (1993-2007) 198

List of Figures

Figure 1.1 – Chemical structures of thebaine and oxycodone 4

Figure 4.1 – Calibration curves for the second run of samples 93

Figure 5.1 – Breast Milk vs Maternal Plasma Oxycodone 0-24 h
 – milk samples ≤ 150 min after plasma samples 104

Figure 5.2 - Breast Milk vs Maternal Plasma Oxycodone 24-72 h
 – milk samples ≤ 150 min after plasma samples 104

Figure 5.3 - Breast Milk vs Maternal Plasma Oxycodone 0-24 h
 – samples at the same time 105

Figure 5.4 – Maternal Plasma Oxycodone vs Total Daily Dose 0-24 h 107

Figure 5.5 – Breast Milk Oxycodone vs Total Daily Dose 0-24 h 107

Figure 5.6 – Analgesics Most Used 118

Figure A1 – Breast Milk NOR vs Maternal Plasma NOR
 - sampling at the same time 166

Figure A2 – Oxycodone and Noroxycodone Levels in Plasma and Milk 168
List of Tables

Table 1.1 – Pilot drug usage evaluation – data on analgesic usage 11
Table 3.1 – Summary of data and measurements 70
Table 4.1 – Standards for maternal plasma and breast milk analysis 89
Table 4.2 – Standards for neonatal plasma analysis 89
Table 4.3 – Calibration data for assay validation 97
Table 5.1 – Sample population demographics 101
Table 5.2 – Oxycodone dose ranges, observed maternal plasma oxycodone and breast milk oxycodone ranges and M:P ratios 102
Table 5.3 – Cohort of participants with breast milk oxycodone > 100 ng/ml 108
Table 5.4 – Participants with zero oxycodone plasma or breast milk levels or breast milk levels < 5 ng/ml at measurable point post dose 111
Table 5.5 – Participants with detectable oxycodone in breast milk ≥ 24 hours post last dose 112
Table 5.6 – Participants showing accumulation of oxycodone in breast milk 114
Table 5.7 – Survey participant demographics 115
Table 5.8 – Caesarean section rates and oxycodone use per participant hospital 117
Table 5.9 – Analgesics rated by overall response rating 120
Table 5.10 – Analgesia in participant hospitals with CS > 500 per annum 124
Table 5.11 – Analgesia in participant hospitals with CS < 500 per annum 125
Table 5.12 - Statistical correlation for milk and plasma data sets 130
Table 5.13 – Statistical correlation for plasma and milk levels vs 0-24 h oxycodone dose 135
**Table F1** – Numerical data sets: maternal oxycodone an breast milk oxycodone

**Table F2** – Statistical data for M:P ratios

**Table G1** – Cohort of individual participants with outliers

**Table G2** – Oxycodone dose, dose to sampling times, plasma and breast milk levels for all participants

**Table H1** – Maternal Sedation vs Oxycodone Dose

**Table H2** – Maternal Sedation vs Breast Milk Oxycodone Concentration

**Table H3** – Neonatal Feeding Attachment vs Breast Milk Oxycodone Concentration