THE EFFECT OF THE PERIPHERALLY ACTING OPIOID RECEPTOR ANTAGONIST, NALOXONE METHIODIDE, ON OPIOID INDUCED RESPIRATORY DEPRESSION

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DECLARATION:

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Tanya Lewanowitsch

February 2004

ACKNOWLEDGEMENTS:

There are two reasons why acknowledgements are placed at the beginning of a thesis. Firstly, it is the most popular page in the whole document. Very few people will read a whole thesis, but I challenge you not to have a peak at this page (keep in mind that you are reading an acknowledgements page right now). Secondly, the acknowledgements are the most important section in a thesis. Without the people mentioned on these pages the thesis may never have existed, or at least not in its final form. These are the people that help you through the hard times and share the good times. Their contributions are remembered every time someone reads this section. This is the very least I can do to thank those who have contributed to my PhD experience.

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STATEMENTS OF AUTHORSHIP AND CONTRIBUTION:

Publication 1:

Naloxone methiodide reverses opioid induced respiratory depression and analgesia without withdrawal.

Lewanowitsch T & Irvine RJ

European Journal of Pharmacology (2002) 445: 61-67.

Author Contribution:

Miss Lewanowitsch was involved in the experimental design, conducted all of the experimental procedures, statistical analysis and graphical presentation of the data collected, and prepared the manuscript for submission.

Doctor Irvine was involved in the experimental design, interpretation of the data collected and preparation of the manuscript.

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Publication 2:

Naloxone and its quaternary derivative, naloxone methiodide, have differing affinities for μ, δ, and κ opioid receptors in mouse brain homogenates.

Lewanowitsch T & Irvine RJ

Brain Research (2003) 964: 302-305.

Author Contribution:

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Doctor Irvine was involved in the experimental design, interpretation of the data collected and preparation of the manuscript.

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Publication 3:

Reversal of morphine, methadone and heroin induced respiratory depression and analgesia by the quaternary opioid antagonist, naloxone methiodide.

Lewanowitsch T, Miller JH, Irvine RJ

Drug and Alcohol Dependence (2004) In Review.

Author Contribution:

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Associate Professor Miller provided assistance with the whole body barometric plethysmography experiments and was involved in the preparation of the manuscript.

Doctor Irvine was involved in the experimental design, interpretation of the data collected and preparation of the manuscript.

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Publication 4:

Use of radiotelemetry to evaluate respiratory depression produced by chronic methadone administration.

Lewanowitsch T, White JM, Irvine RJ

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Author Contribution:

Miss Lewanowitsch was involved in the experimental design, conducted all of the experimental procedures, statistical analysis and graphical presentation of the data collected, and prepared the manuscript for submission.

Professor White was involved in the interpretation of the data collected and preparation of the manuscript.

Doctor Irvine was involved in the experimental design, assisted with the radiotelemetry surgery, and contributed to the interpretation of the data collected and preparation of the manuscript.

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ABBREVIATIONS & SYMBOLS:

A.D.	Anno Domini (in the year of the Lord)
AD_{50}	Antagonist dose that produces 50% of maximum effect
AUC	Area under the curve
B.C.	Before Christ
cAMP	Cyclic adenosine 3'5'-monophosphate
CSF	Cerebro-spinal fluid
C_{max}	Maximum concentration
CNS	Central nervous system
CO_2	Carbon dioxide
δ	Delta opioid receptor
DALDA	H-Tyr-D-Arg-Phe-Lys-NH_2
DADLE	D-Ala^2-D-Leu^5-enkephalin
DADTII	[D-Ala^2]deltorphin II
DALA	[D-Ala^2-Met^5]enkephalinamide
DAMGO	D-Ala^2-N-Me-Phe^4-Gly-ol^5-enkephalin
[Dmt^1]DALDA	[2',6'-dimethyltyrosine]Tyr-D-Arg-Phe-Lys-NH_2
DPDPE	D-$Pen^{2,5}$-enkephalin
DPLPE	D-Pen-L-Pen-enkephalin
DPPC	Disaturated phosphatidylcholine
DRG	Dorsal respiratory group
EC_{50}	Effective concentration that produces 50% of maximum effect
ED_{50}	Effective dose that produces 50% of maximum effect
ε	Epsilon opioid receptor
H^+	Hydrogen ion

HPLC	High performance liquid chromatography
ICAM-1	Intercellular adhesion molecule 1
i.c.v.	Intracerebroventricular
IDRS	Illicit drug reporting system
ι	Iota opioid receptor
IL-1	Interleukin-1
IL-6	Interleukin-6
i.m.	Intramuscular
i.p.	Intraperitoneal
i.t.	Intrathecal
IUPHAR	International Union of Pharmacologists
i.v.	Intravenous
J receptor	Juxta-capillary receptor
κ	Kappa opioid receptor
LD_{50}	Lethal dose that produces 50% of deaths
LH	Luteinizing hormone
M-3-G	Morphine-3-glucuronide
M-6-G	Morphine-6-glucuronide
MAPK	Mitogen-activated protein kinase
Metkephamid	Tyr-D-Ala-Gly-Phe-N(Me)Met-NH_2
MDR1	Multidrug resistance gene
Moguisteine	R,S)-2-(2-methoxyphenoxy)-methyl-3-ethoxycarbonyl-acetyl-1,3 thiazoladine
MPE	Maximum possible effect
MRP	Multidrug resistance associated protein family

μ	Mu opioid receptor
Naloxone	Naloxone hydrochloride
NIS	Sodium/iodide symporter
NK cells	Natural killer cells
NMDA	N-methyl-D-aspartate
NMR	Nuclear magnetic resonance
N/OFQ	Nociceptin/orphanin FQ
NOP	Nociceptin/orphanin FQ receptor
O_2	Oxygen
oatps	Organic anion transport proteins
OATs	Organic anion transporter
$PaCO_2$	Arterial blood CO_2 concentration
PaO_2	Arterial blood O_2 concentration
PCP	Phencyclidine
PC	Phosphatidylcholine
PCO_2	Partial pressure of CO_2
PET	Positron emission topography
PGP	P-glycoprotein
PI3K	Phosphatidylinositol-3 kinase
PK	Protein kinase
pO_2	Partial pressure of O_2
RT-PCR	Reverse transcriptase polymerase chain reaction
σ	Sigma opioid receptor
s.c.	Subcutaneous
SpO_2	Arterial O_2 saturation

T_3	Triiodothyronine
T_4	Thyroxine
Tg	Thyroglobulin
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
USA	United States of America
V_A	Alveolar Volume
VO_2	O_2 consumption
VRG	Ventral respiratory group
ξ	Zeta opioid receptor

ABSTRACT:

Fatal and non-fatal opioid overdoses resulting from opioid induced respiratory depression are a significant problem throughout the world. Whilst the opioid receptor antagonist, naloxone hydrochloride, can effectively reverse opioid overdoses, its use is limited because of the adverse effects it produces. These include severe withdrawal and the reversal of analgesia produced by opioid receptor agonists. In this project, the peripherally acting opioid receptor antagonist, naloxone methiodide, was investigated for its potential to reverse opioid induced respiratory depression without altering centrally mediated effects, such as withdrawal. In the publications presented in this thesis, naloxone hydrochloride and naloxone methiodide were shown to effectively reverse the decreases in respiratory rate produced by the administration of morphine, methadone and heroin in mice. Naloxone hydrochloride and naloxone methiodide also reversed the analgesia produced by these opioid receptor agonist treatments, but only naloxone hydrochloride induced significant withdrawal. The doses of naloxone methiodide required to produce the effects described above were higher than the naloxone hydrochloride doses required. Radioligand binding techniques indicated that this was due to a difference in the affinity of naloxone hydrochloride and naloxone methiodide for μ, δ and κ opioid receptor binding sites. Radioligand binding techniques were also used to confirm that naloxone methiodide, or its metabolites, could not readily cross the blood brain barrier. Therefore, the effects of naloxone methiodide appear to be mediated outside the central nervous system. The final publication aimed to extend our knowledge of opioid induced respiratory depression by utilising new radiotelemetry technology to test the efficacy of naloxone methiodide in rats

subjected to a chronic opioid administration regime. This experiment showed that circadian rhythm plays a role in the development of tolerance to the cardiorespiratory effects of continuous and chronic methadone administration, and that naloxone hydrochloride and naloxone methiodide treatment can increase respiratory rate and heart rate after this methadone administration. Therefore, naloxone methiodide can effectively antagonise the peripheral effects produced by opioid receptor agonists. Peripherally acting opioid receptor antagonists should be developed in the future to prevent or treat the adverse effects of opioid receptor agonists.