

Appendices

Appendix 1: Information for Clinics and Clients

Appendix 1-1: Poster for Studies A and B



ROYAL ADELAIDE
HOSPITAL



THE UNIVERSITY
OF ADELAIDE
AUSTRALIA

Are you aged between 18 and 45?

★ Going to start **methadone** treatment?

Not pregnant or lactating?

Not intolerant to erythromycin?

Not taking monoamine oxidase

inhibitors or methadone in the last two weeks?

Not participating in another clinical research project?

Hair longer than 1cm?

★ Would you be willing to participate in the study "Clinical Pharmacology of Methadone during Induction onto Maintenance Treatment"?

💰 You could earn up to **\$1000** if you attend all contact days required and provide blood, breath and urine samples as requested. You will also be assisted with transport.

☎ If interested please contact: Erin (8303 5985)

OR C/O Charlotte (0417083295)

Appendix 1-2: Information sheet for Study A Subjects

INFORMATION SHEET FOR RESEARCH SUBJECTS

Study Title:

Study A. Clinical pharmacology of methadone during induction onto methadone treatment.

Methadone has been shown to be very effective as maintenance treatment for former heroin users. In Australia some 30,000 people are now being successfully maintained on methadone. The transition period when a heroin user moves to methadone can be problematic. During this period (generally the first two weeks after stopping heroin) there is a small risk of unexpected death.

The purpose of this study is to try to find out which factors could cause such deaths so as to make the transition from heroin use to methadone maintenance safer.

To be eligible to take part in this study, you will need to:

- (i) be about to commence methadone maintenance;
- (ii) be considered by the Drug and Alcohol Services Council staff to be suitable for methadone maintenance;
- (iii) be between 18-45 years;
- (iv) cooperate with study procedures, some of which will be carried out at the Royal Adelaide Hospital;
- (v) tell the researchers running the study what sort of other drugs or medicines you are taking;
- (vi) not be pregnant or breast feeding;
- (vii) not be in any other current research project;
- (viii) not to have a major psychiatric illness;
- (ix) not be intolerant to erythromycin (a commonly used antibiotic).

What this study involves:

1. The doses of methadone which you will receive will be determined by the standard clinic practice and will not be influenced by the researchers carrying out this study.
2. Over the course of the study, several procedures will be carried out. These are:

(a) Blood sampling.

On the first day the blood will be collected through a small plastic tube which has been inserted into one of your veins. All subsequent blood samples will be collected through a needle prick. The total amount of blood over the seven week study will be 405 ml, which is equivalent to a Red Cross Blood Bank transfusion donation. The blood will be analysed for the following: how much methadone, morphine, benzodiazepines are circulating in your blood; other components of your blood/body which are involved in methadone breakdown; measurement of some genes which are involved in how methadone works.

Appendix 1-2: Information sheet for Study A Subjects continued

(b)Erythromycin breath test.

Methadone is broken down in the body at different rates by different people. This might be one reason why some people, when they start methadone, might get into difficulties. The erythromycin breath test measures the activity of the enzyme which breaks down methadone which governs how effectively methadone is removed from the body. For this test you will be given a very small quantity of radioactive erythromycin into a vein and then be asked to blow air for a short period (1-2 breaths) into a balloon eleven times over the next 90 minutes. The radioactive gas captured in the balloon will indicate the body's capacity to break down methadone. The total dose of radiation exposure is extremely small and should be seen in the context of normal radiation exposure as part of everyday living. As part of everyday living, people are exposed to naturally occurring background radiation and receive a dose of 2000 to 3000 μSv (microsieverts) each year. The Sievert is the unit in which radiation is expressed. The effective dose from the radioactive erythromycin in this study is about 10 to 40 μSv (equivalent to an extra 1.8 to 7.3 days' natural exposure). No harmful effects of radioactive erythromycin have been demonstrated and the risk at this dose is negligible.

(c)Injection of stable-labelled methadone.

Five mg of your day 1 and your day 40 methadone doses will be administered intravenously as stable-labelled methadone. Stable-labelled methadone is identical to normal methadone in all respects as regards action, side effects and how the body handles it. The only difference is that one of the atoms is modified in such a way that we can measure how the body eliminates methadone. This test can differentiate between those who eliminate methadone very efficiently and those who eliminate methadone less efficiently. There are no additional risks from the stable-labelled methadone which do not occur with ordinary methadone.

(d)Measurement of methadone effects.

- (i) You will be asked about how methadone is affecting you; in particular whether you are experiencing withdrawal, the effect of methadone on your mood and feeling of well-being.
- (ii) Measurement of pupil diameter with a video camera.
- (iii) Measurement of blood pressure, heart rate and respiration. Respiration will be recorded as the rate over one minute and how much oxygen and carbon dioxide is circulating in your blood. This latter procedure will be carried out two ways. For the oxygen measurement, a small thimble-like device will be placed on one of your fingers and this automatically records how much oxygen is circulating. For carbon dioxide, a small tube is inserted into one of your nostrils and the carbon dioxide exhaled by you is measured by the machine to which the tube is connected. Neither procedure is painful or uncomfortable.

Appendix 1-2: Information sheet for Study A Subjects continued

- (iv) Urine sampling to screen for other drugs that you might be taking.
- (v) A small sample of your scalp hair (50 hairs, 1 cm long), will be cut with scissors at the scalp. The hair will be used to determine how much heroin you have been using in the previous months.

Timetable.

1. The total study duration will be seven weeks.

2. Day 1. You will attend Warinilla per standard clinic practice and be met by an investigator, before collecting your methadone dose and being accompanied to the Royal Adelaide Hospital. Before taking your first methadone dose, a plastic tube will be inserted into one of your forearm veins. A blood (10 ml), hair and urine sample will be collected. The erythromycin breath test will be administered. The methadone dose will then be administered as follows: 5 mg will be given as stable-labelled methadone and the remainder of your dose will be given as the oral solution.

Further blood samples (7 ml) will be collected through the plastic tube at 5 minutes, 0.25, 0.5, 1, 2, 3, 4, and 6 hours after the methadone dose. Your withdrawal score, measurement of mood, pupil diameter, respiratory rate, heart rate, blood pressure, oxygen and carbon dioxide content in the body will be measured before the methadone dose and at 0.25, 1, 3, 4, 6 hours after the dose.

3. Days 2-14. You will return to collect your methadone dose from Warinilla and be accompanied to the RAH once each day. At the RAH a 7 ml blood sample will be collected before your daily dose and three hours after the dose. At each of these times the same methadone effects (withdrawal score, mood measurement, pupil diameter, respiratory rate, heart rate, blood pressure, oxygen and carbon dioxide content) will be measured.

4. Day 40. The same procedure as for day 1 will be repeated.

5. Days 41-49. The same procedures as for days 2-14 will be repeated.

Confidentiality.

All information collected from you during this study is completely confidential. The information will be coded so that you cannot be identified. The clinic will not be given any information about you or your study test results unless you want them to have this information. The study will not affect your treatment at the clinic. Research staff may access your clinic case notes but only to write down essential information such as your study treatment dates or the information relevant to the study, such as any illnesses or medications you may have had.

Appendix 1-2: Information sheet for Study A Subjects continued

Leaving the study.

You are free to drop out of the study at any time and for any reason. You do not have to tell anyone your reason. If you do drop out, this will not affect your treatment at the clinic in any way.

Effects, side effects and inconvenience of the study procedures.

- (a) The insertion of the plastic tube into the vein and the needle pricks may cause temporary pain. There is a slight risk of bruising at the site of the plastic tube insertion and the remote risk of clotting (especially with erythromycin) or infection in the vein. These risks are reduced because we only use qualified people to do the procedures.
- (b) Erythromycin. When given for the treatment of infection (between 250 and 500 mg every 6 to 8 hours for several days), the following can occur; (commonly): nausea, vomiting, abdominal pain, diarrhoea, headache, breathlessness, cough, fungus infections, (infrequently): clotting of a vein, rash, (rarely): anaphylaxis, acute respiratory distress, Stevens-Johnson syndrome (severe skin reaction), hepatitis, psychiatric disturbances, hearing loss, severe diarrhoea, heart rhythm disturbances. It is highly unlikely that any of these adverse effects will occur following the two single 0.059 mg doses (a minute fraction of the dose used for treatment of infection) of erythromycin. As already mentioned, the radiation exposure following the erythromycin breath test is negligible.
- (c) Stable-labelled methadone poses no additional risk which would not occur with ordinary methadone.
- (d) Whilst the 7 week study involves considerable inconvenience to you, it is possible that you may derive benefit in that your induction on to methadone will be more closely monitored than is the usual practice.

Payment/costs.

You will be paid a total of \$1,000 if you complete the 7 week study. If you drop out before finishing the study, you will be paid \$100 for completing days 1-14.

Appendix 1-2: Information sheet for Study A Subjects continued

SUMMARY PLAN OF THE STUDY:

Day	Events/activities
1	Standard clinic practice at Warinilla, met by investigator, collection of methadone dose, accompanied to Royal Adelaide Hospital. Hair, urine and blood (through a plastic tube) collection; erythromycin breath test; first methadone dose; methadone effect measures; time at the Royal Adelaide Hospital about 8 hours
2-14	Blood collection (by needle prick) before and 3 hours after methadone dose; methadone effect measures
40	As for day 1
49	As for days 2-14

If you have any questions, please ask the clinic staff, the researchers conducting this study, Ms Charlotte Smith (mobile: 0417083295), Ms Erin Murray (phone: 8303 5571) and/or or feel free to contact the Principal Investigator, Professor Jason White (8303 5987 or at Warinilla Clinic).

The 24 hour phone number of Warinilla Clinic is 8130 7500.

You may also contact the Chairman of the Research Ethics Committee of the Royal Adelaide Hospital, who is Dr. Michael James. His phone number is 8222 5345.

Appendix 1-3: Consent Form for Study A Subjects

CONSENT FORM FOR RESEARCH SUBJECTS

Study Title: Study A. Clinical pharmacology of methadone during induction onto methadone treatment.

1. I (please print) hereby consent to take part in the research project entitled *Study A. Clinical pharmacology of methadone during induction onto methadone treatment*. I have read the Information Sheet entitled *Study A. Clinical pharmacology of methadone during induction onto methadone treatment* and understood its contents. I have had the nature and purpose of the research project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is freely given.
2. I understand that I may not directly derive any clinical benefit from taking part in the research project.
3. I understand that while information gained during the research project may be published, I will not be identified and my personal results will remain confidential.
4. I understand that I may withdraw from the research project any stage and that this will not affect my medical care, now or in the future.
5. I understand the statement concerning financial compensation to me for taking part in the research project.
6. I have had the opportunity to discuss taking part in the research project with a family member or friend.
7. I am not participating in any other research project.

Signed Date

I certify that I have explained the nature and procedures of the research project to and consider that he/she understands what is involved.

Signed Date

Status in Project

Appendix 1-4: Information Sheet for Study B Subjects

INFORMATION SHEET FOR RESEARCH SUBJECTS

Study Title:

Study B. Predicting methadone stabilization doses during induction onto MMT.

Methadone has been shown to be very effective as maintenance treatment for former heroin users. In Australia some 30,000 people are now being successfully maintained on methadone. The transition period when a heroin user moves to methadone can be problematic. During this period (generally the first two weeks after stopping heroin) there is a small risk of unexpected death.

The purpose of this study is to try to find out which factors could cause such deaths so as to make the transition from heroin use to methadone maintenance safer.

To be eligible to take part in this study, you will need to:

- (i) be about to commence methadone maintenance;
- (ii) be considered by the Drug and Alcohol Services Council staff to be suitable for methadone maintenance;
- (iii) be between 18-45 years;
- (iv) cooperate with study procedures, some of which will be carried out at the Royal Adelaide Hospital;
- (v) tell the researchers running the study what sort of other drugs or medicines you are taking;
- (vi) not be pregnant or breast feeding;
- (vii) not be in any other current research project;
- (viii) not to have a major psychiatric illness;
- (ix) not be intolerant to erythromycin (a commonly used antibiotic).

What this study involves:

1. The doses of methadone which you will receive will be determined by the standard clinic practice and will not be influenced by the researchers carrying out this study.
2. Over the course of the study, several procedures will be carried out. These are:

(a) Blood sampling.

On the study days blood will be collected through a small plastic tube which has been inserted into one of your veins. The total amount of blood over the six week study will be no more than 70 ml, which is much less than a Red Cross Blood Bank transfusion donation. The blood will be analysed for the following: how much methadone, morphine, benzodiazepines are circulating in your blood; other components of your blood/body which are involved in methadone breakdown; measurement of some genes which are involved in how methadone works.

Appendix 1-4: Information Sheet for Study B Subjects continued

(b) Erythromycin breath test.

Methadone is broken down in the body at different rates by different people. This might be one reason why some people, when they start methadone, might get into difficulties. The erythromycin breath test measures the activity of the enzyme which breaks down methadone in the body which governs how effectively methadone is removed from the body. For this test you will be given a very small quantity of radioactive erythromycin into a vein and then be asked to blow air for a short period (1-2 breaths) into a balloon eleven times over the next 90 minutes. The radioactive gas captured in the balloon will indicate the body's capacity to break down methadone. The total dose of radiation exposure is extremely small and should be seen in the context of normal radiation exposure as part of everyday living. As part of everyday living, people are exposed to naturally occurring background radiation and receive a dose of 2000 to 3000 μSv (microsieverts) each year. The Sievert is the unit in which radiation is expressed. The effective dose from the radioactive erythromycin in this study is about 10 to 40 μSv (equivalent to an extra 1.8 to 7.3 days' natural exposure). No harmful effects of radioactive erythromycin have been demonstrated and the risk at this dose is negligible.

(c) Measurement of methadone effects.

- (i) You will be asked about how methadone is affecting you; in particular whether you are experiencing withdrawal, the effect of methadone on your mood and feeling of well-being.
- (ii) Measurement of pupil diameter with a video camera.
- (iii) Measurement of blood pressure, heart rate and respiration. Respiration will be recorded as the rate over one minute and how much oxygen and carbon dioxide is circulating in your blood. This latter procedure will be carried out two ways. For the oxygen measurement, a small thimble-like device will be placed on one of your fingers and this automatically records how much oxygen is circulating. For carbon dioxide, a small tube is inserted into one of your nostrils and the carbon dioxide exhaled by you is measured by the machine to which the tube is connected. Neither procedure is painful or uncomfortable.
- (iv) Urine sampling to screen for other drugs that you might be taking.
- (v) A small sample of your scalp hair (50 hairs, 1 cm long), will be cut with scissors at the scalp. The hair will be used to determine how much heroin you have been using in the previous months.

Appendix 1-4: Information Sheet for Study B Subjects continued

Timetable.

1. The total study duration will be six weeks. You will need to make yourself available on day 1 and day 40 of this period for up to four hours on each of these days.
2. Day 1. You will attend Warinilla per standard clinic practice and be met by an investigator, before collecting your methadone dose and being accompanied to the Royal Adelaide Hospital. Before you take your first methadone dose, a plastic tube will be inserted into one of your forearm veins. A blood (10 ml), hair and urine sample will be collected. The erythromycin breath test will be administered. The methadone dose will then be given. Further blood samples (7 ml) will be collected through the plastic tube, a quarter of an hour, one hour and three hours after the methadone dose. At the time of each blood sample (before and after methadone administration) your withdrawal score, measurement of mood, pupil diameter, respiratory rate, heart rate, blood pressure, oxygen and carbon dioxide content in the body will be measured.
3. Day 40. The same procedure as for day 1 will be repeated.

Confidentiality.

All information collected from you during this study is completely confidential. The information will be coded so that you cannot be identified. The clinic will not be given any information about you or your study test results unless you want them to have this information. The study will not affect your treatment at the clinic. Research staff may access your clinic case notes but only to write down essential information such as your study treatment dates or the information relevant to the study, such as any illnesses or medications you may have had.

Leaving the study.

You are free to drop out of the study at any time and for any reason. You do not have to tell anyone your reason. If you do drop out, this will not affect your treatment at the clinic in any way.

Effects, side effects and inconvenience of the study procedures.

- (a) The insertion of the plastic tube into the vein and the needle pricks may cause temporary pain. There is a slight risk of bruising at the site of the plastic tube insertion and the remote risk of clotting (especially with erythromycin) or infection in the vein. These risks are reduced because we only use qualified people to do the procedures.
- (b) Erythromycin. When given for the treatment of infection (between 250 and 500 mg every 6 to 8 hours for several days), the following can occur; (commonly): nausea, vomiting, abdominal pain, diarrhoea, headache, breathlessness, cough, fungus infections, (infrequently): clotting of a vein, rash, (rarely): anaphylaxis, acute respiratory distress, Stevens-Johnson syndrome (severe skin reaction), hepatitis, psychiatric disturbances, hearing loss, severe diarrhoea, heart rhythm disturbances. It is highly unlikely that any of these adverse effects will occur following the two single 0.059 mg doses (a minute fraction of the dose used for treatment of infection) of erythromycin. As already mentioned, the radiation exposure following the erythromycin breath test is negligible.

Appendix 1-4: Information Sheet for Study B Subjects continued

Payment/costs.

You will be paid a total of \$200 if you complete the 6 week study. If you drop out after the first day, you will be paid \$50 for completing day 1.

If you have any questions, please ask the clinic staff, the researchers conducting this study, Ms Charlotte Smith (mobile: 0417083295), Ms Erin Murray (phone: 83035571) and/or or feel free to contact the Principal Investigator, Professor Jason White (8303 5987 or at Warinilla Clinic).

The 24 hour phone number of Warinilla Clinic is 8130 7500.

You may also contact the Chairman of the Research Ethics Committee of the Royal Adelaide Hospital, who is Dr. Michael James. His phone number is 8222 5345.

Appendix 1-5: Consent form for Study B Subjects

CONSENT FORM FOR RESEARCH SUBJECTS

Study B. Predicting methadone stabilization doses during induction onto MMT.

1. I (please print) hereby consent to take part in the research project entitled *Study B. Clinical pharmacology of methadone during induction onto methadone treatment*. I have read the Information Sheet entitled *Study B. Clinical pharmacology of methadone during induction onto methadone treatment* and understood its contents. I have had the nature and purpose of the research project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is freely given.
2. I understand that I may not directly derive any clinical benefit from taking part in the research project.
3. I understand that while information gained during the research project may be published, I will not be identified and my personal results will remain confidential.
4. I understand that I may withdraw from the research project any stage and that this will not affect my medical care, now or in the future.
5. I understand the statement concerning financial compensation to me for taking part in the research project.
6. I have had the opportunity to discuss taking part in the research project with a family member or friend.
7. I am not participating in any other research project.

Signed Date

I certify that I have explained the nature and procedures of the research project to and consider that he/she understands what is involved.

Signed Date

Status in Project

Appendix 1-6: Project Summary Sheet for Clinic Staff Use

METHADONE INDUCTION PROJECT SUMMARY SHEET

PATIENT SELECTION CRITERIA

- Patients request methadone treatment & are suitable according to standard criteria
- Age range 18-45 years
- Male or female
- Willing to participate in the study

PATIENT EXCLUSION CRITERIA

- Pregnant or lactating
- Major psychiatric illness
- HIV positive
- Intolerant to erythromycin
- Abnormal liver function tests
- Intake of monoamine oxidase inhibitors in past two weeks
- Hair length less than 1cm (50 req)
- Participation in another clinical research project

STUDY DAYS

	STUDY A <i>10 patients</i>	STUDY B <i>20 patients</i>
DAY	\$1000	\$200
Day 1	Warinilla attendance Samples: Hair, urine, blood Erythromycin IV + breath tests Methadone: oral + <i>part IV</i> Pharmacodynamics recorded	Warinilla attendance Samples: Hair, urine, blood Erythromycin IV + breath tests Methadone: oral <i>only</i> Pharmacodynamics recorded
Days 2-14	Warinilla attendance as nec. Samples: Blood Methadone: oral only Pharmacodynamics recorded	<i>No study involvement</i>
<i>26 day break</i>	<i>No study involvement</i>	<i>No study involvement</i>
Day 40	Warinilla attendance as nec. Samples: Urine, blood Erythromycin IV + breath tests Methadone: oral + <i>part IV</i> Pharmacodynamics recorded	Warinilla attendance as nec. Samples: Urine, blood Erythromycin IV + breath tests Methadone: oral only Pharmacodynamics recorded
Days 41-49	Warinilla attendance as nec. Samples: Blood Methadone: oral only Pharmacodynamics recorded	<i>No study involvement</i>
	Partial completion: Days 1-14 = \$100 total	Partial completion: Day 1 only = \$50

Appendix 2: Paperwork for Client Files

Appendix 2-1: Case Report Form for Day 1 and Day 40 of Study A

Planned Time	Actual Time	Procedure	Sig	Date:		ID:		Sig:	
				Blood	Pupil	Symptoms	POMS	Respiratn	O ₂ Saturation
0:00	:	Urine Sample							
0:10	:	Hair Sample							
0:30	:	Cannula Inserted							
0:35	:	Blood for Genetics							
0:37	:	Blood for LF, Haematology							
0:40	:	Blood							
0:50	:	Erythromycin Infusion							
0:53	:	Breath Sample							
0:58	:	Breath Sample							
1:00	:	Cease Infusion							
1:05	:	Breath Sample							
1:10	:	Breath Sample							
1:15	:	Breath Sample							
1:20	:	Breath Sample							
1:30	:	Breath Sample							
1:35	:	PM, S, P, R, OS							
1:45	:	Breath Sample							
2:00	:	Breath Sample							
2:20	:	Breath Sample							
2:30	:	Administer Dose (i.v.)							
2:30	:	Administer Dose (p.o.)							
2:35	:	Blood							
2:40	:	Cease IV dose							
2:45	:	Blood, PM, S, P, R, OS							
3:00	:	Blood							
3:30	:	Blood, PM, S, P, R, OS							
4:30	:	Blood							
5:30	:	Blood, PM, S, P, R, OS							
6:30	:	Blood, PM, S, P, R, OS							
8:30	:	Blood, PM, S, P, R, OS							

Abbreviations:

OS/O₂ Saturation – Oxygen Saturation

R/Respiratn – Respiration

P/POMS – Profile of Mood States

Sig – Signature

LF – Liver Function

PM/Pupil – Pupil Measurement

S/Symptoms – Methadone Symptoms Checklist

Appendices

Appendix 2-2: Case Report Form for Days 2-14 and Days 41-49 of Study A

Planned Time	Actual Time	Dose:	Sig	Date:	ID:	Sig:	Blood	Pupil	Symptoms	POMS	Respiratn	O ₂ Saturation
0:00	:	Cannula Inserted										
0:05	:	Blood										
0:10	:	PM, S, P, R, OS										
0:45	:	Administer Dose (p.o.)										
3:45	:	Blood										
3:50	:	PM, S, P, R, OS										
4:30	:	Tests Ceased										

Abbreviations:

OS/O₂ Saturation – Oxygen Saturation
 PM/Pupil – Pupil Measurement
 Sig – Signature

P/POMS – Profile of Mood States
 R/Respiratn – Respiration
 S/Symptoms – Methadone Symptoms Checklist

Appendices

Appendix 2-3: Case Report Form for Day 1 and Day 40 of Study B

Planned Time	Actual Time	Procedure	Sig	Date:		ID:		Sig:	
				Blood	Pupil	Symptoms	POMS	Respiratn	O ₂ Saturation
0:00	:	Urine Sample							
0:10	:	Hair Sample							
0:30	:	Cannula Inserted							
0:35	:	Blood for Genetics							
0:37	:	Blood for LF, Haematology							
0:40	:	Blood							
0:50	:	Erythromycin Infusion							
0:53	:	Breath Sample							
0:58	:	Breath Sample							
1:00	:	Cease Infusion							
1:05	:	Breath Sample							
1:10	:	Breath Sample							
1:15	:	Breath Sample							
1:20	:	Breath Sample							
1:30	:	Breath Sample							
1:35	:	PM, S, P, R, OS							
1:45	:	Breath Sample							
2:00	:	Breath Sample							
2:20	:	Breath Sample							
2:30	:	Administer Dose (p.o.)							
2:45	:	Blood, PM, S, P, R, OS							
3:30	:	Blood, PM, S, P, R, OS							
5:30	:	Blood, PM, S, P, R, OS							

Abbreviations:
 OS/O₂ Saturation – Oxygen Saturation
 PM/Pupil – Pupil Measurement
 Sig – Signature

LF – Liver Function
 P/POMS – Profile of Mood States
 R/Respiratn – Respiration
 S/Symptoms – Methadone Symptoms Checklist

Appendix 2-4: Pharmacodynamics Notes Sheet

RAH 020327a Study ___ Patient # _____ Date ___/___/___

Laboratory Evaluations: PHARMACODYNAMICS

Sample date Study day Actual time Study time	___/___/___ Day ___ :___ hr ___ min	For any clinically significant results, please explain
Pupil Diameter (mm)		
Blood pressure		
Heart Rate		
Respiratory Rate (/min)		
Oxygen Saturation		
POMS		
-Total Mood Disturbance	/168	
-Tension/Anxiety	/36	
-Depression/Dejection	/60	
- Anger/Hostility	/48	
-Vigor/Activity	/32	
-Fatigue/Inertia	/28	
-Confusion/Bewilderment	/28	
-Friendliness	/28	
Methadone Checklist		

Appendix 2-5: Profile of Mood States Questionnaire

NOTE: This appendix is included on page 297 of the print copy of the thesis held in the University of Adelaide Library.

Appendix 2-6: Methadone Symptoms Checklist

CLINICAL PHARMACOLOGY OF METHADONE INDUCTION

INITIALS SUBJECT ID DATE

STUDY: _____ DAY _____ TIME _____ HOURS SINCE DOSE _____

METHADONE SYMPTOMS CHECKLIST

Please indicate how you are feeling right now. Put a ✓ in the appropriate box for each symptom.

RIGHT NOW

	NONE	MILD	MODERATE	SEVERE	EXTREME
Constipation					
Sweating					
Trouble urinating					
Reduced desire for sex					
Nausea (feeling sick)					
Decreased Appetite					
Hallucinations					
Dry mouth					
Feeling tired					
Methadone dose not holding					
Chest pains					
Swelling of feet or ankles					
Diarrhoea					
Itchy skin					
Need to urinate					
Vomiting					
Increased appetite					
Nervousness					
Bleeding gums					
Feel awake					
Pain down left arm					
Numbness in hands or feet					
Heartburn					
Itchy nose					
Want to drink alcohol					
Dizziness					

Appendix 2-6: Methadone Symptoms Checklist continued

RIGHT NOW

	NONE	MILD	MODERATE	SEVERE	EXTREME
Headache					
Runny or stuffy nose					
Want to drink (not alcohol)					
Trouble thinking clearly					
Yawning					
Feelings of coldness					
Stomach cramps					
Runny eyes					
Confusion					
Muscle spasms / twitching					
Blurred vision					
Aches and pains					
Heart pounding					
Tense muscles					
Goose pimples					
Pleasant feeling in stomach					
Feeling high					
Increased desire for sex					
Craving					
Decreased appetite					
Feeling unhappy					
Feeling anxious					
Feeling irritable					
Feelings of weakness					
Hot flushes					
Restlessness					
Salivation					
Other (please write symptom)					

Appendix 3: Documentation for Experimental Work

Appendix 3-1: LC-MS Methadone Assay Checklist

LCMS ASSAY CHECKLIST

- Decide on run samples, fill out run sample sheet.
- 10ml tapered bottom tubes x sample no. x 2
- Set up column, get baseline plot started
- Separate tubes into two lots and number accordingly
- Add 200µl each of 5mM HCl to one lot
- Cover with tissue and set aside
- To second set:
 - Add 100µl of Internal Standard to each tube
 - Add 400µl of 0.1M NaCO₃ to each tube
 - Add 900µl of blank plasma
 - and 50µl of Standard or QC.... d0
 - and 50µl of Standard or QC.... d6
- OR
 - Add 1ml of subject plasma sample
- In fume hood, add 5ml organic extraction solvent each from bottle tap
- Tighten caps, rotary mix for a minimum of 20 minutes: _____ to _____
- Centrifuge @ 3250rpm for 5 mins
- Take, tip, and return each sample to the centrifuge
- Centrifuge @ 3250rpm for 5 mins
- In fume hood use transfer pipettes to transfer top organic layer

Better to leave some behind than to contaminate
- Vortex samples for a minimum of 1 minute
- Centrifuge @ 3250rpm for 10 mins
- Aspirate upper organic layer & remove entirely, leaving acid bubble behind

Better to lose some than to contaminate
- Leave to air for minimum 30 mins: _____ to _____
- Transfer acid bubble to HPLC micropipette tube/vials
- Fill out run detail sheet, then start run

Appendix 3-2: LC-MS Methadone Assay Sample Sheet

SAMPLE DETAILS

LC-MS assay for (R)- and (S)-methadone d₀ (²H₀) and d₆ (²H₆)

DATE :

EXPERIMENT DESCRIPTION :

Sample #	Description	Sample Vol (mL)	Sample #	Description	Sample Vol (mL)
1	S1	1.0	31		
2	S2	1.0	32		
3	S3	1.0	33		
4	S4	1.0	34		
5	S5	1.0	35		
6	S6	1.0	36		
7	S7	1.0	37		
8	S8	1.0	38		
9	BLANK	1.0	39		
10	HQC-1	1.0	40		
11	HQC-2	1.0	41		
12	MQC-1	1.0	42		
13	MQC-2	1.0	43		
14	LQC-1	1.0	44		
15	LQC-2	1.0	45		
16			46		
17			47		
18			48		
19			49		
20			50		
21			51		
22			52		
23			53		
24			54		
25			55		
26			56		
27			57		
28			58		
29			59		
30			60		

Appendix 3-3: LC-MS Methadone Assay Run Sheet

SAMPLE DETAILS

LC-MS assay for (R)- and (S)-methadone d₀ (²H₀) and d₆ (²H₆)

DATE :

EXPERIMENT DESCRIPTION :

MOBILE PHASE :

10 : 90 : 0.5 : 0.7 Acetonitrile : Water : Triethylamine : Glacial Acetic Acid
Final pH should be 5.40±0.1

COLUMN : Cyclobond I RSP 2000 150x2.1mm

FLOW RATE : 0.175 mL/Min

PumpA psi
PumpA psi
Corona Needle Current μA

INJECTION VOLUME : uL

DETECTION : Mass-Spectrometry

RUN TIME : minutes

Injct. #	Samp. #	Description	Injct. #	Samp. #	Description
1			31		
2			32		
3			33		
4			34		
5			35		
6			36		
7			37		
8			38		
9			39		
10			40		
11			41		
12			42		
13			43		
14			44		
15			45		
16			46		
17			47		
18			48		
19			49		
20			50		
21			51		
22			52		
23			53		
24			54		
25			55		
26			56		
27			57		
28			58		
29			59		
30			60		

Appendix 3-4: HPLC Methadone Assay Checklist

METHADONE ASSAY CHECKLIST

- Decide on run samples, fill out run sample sheet.
- 10ml tapered bottom tubes x sample no. x 2
- Set up column, get baseline plot started
- Separate tubes into two lots and number accordingly
- Add 200µl each of 5mM HCl to one lot
- Cover with tissue and set aside
- To second set:
 - Add 100µl of Internal Standard to each tube
 - Add 400µl of 0.1M NaCO₃ to each tube
 - Add 100µl of Standard or QC....
 - and 900µl of blank plasma
 - OR
 - Add 1ml of subject plasma sample
- In fume hood, add 6ml organic extraction solvent each from bottle tap
- Tighten caps, rotary mix for a minimum of 20 minutes: _____ to _____
 - Run Reference Mix Sample, 100µl of 150µl
- Centrifuge @ 3250rpm for 5 mins
 - Run HCl Test Sample, 100µl of 150µl
- Take, tip, and return each sample to the centrifuge
- Centrifuge @ 3250rpm for 5 mins
- In fume hood use transfer pipettes to transfer top organic layer

Better to leave some behind than to contaminate
- Vortex samples for a minimum of 1 minute
- Centrifuge @ 3250rpm for 10 mins
- Aspirate upper organic layer & remove entirely, leaving acid bubble behind

Better to lose some than to contaminate
- Leave to air for minimum 30 mins: _____ to _____
- Transfer acid bubble to HPLC micropipette tube/vials
- Fill out run detail sheet, then start run

Appendix 3-5: HPLC Methadone Assay Sample Sheet

SAMPLE DETAILS

DATE :

EXPERIMENT DESCRIPTION :

Sample #	Description	Sample #	Description
1		31	
2		32	
3		33	
4		34	
5		35	
6		36	
7		37	
8		38	
9		39	
10		40	
11		41	
12		42	
13		43	
14		44	
15		45	
16		46	
17		47	
18		48	
19		49	
20		50	
21		51	
22		52	
23		53	
24		54	
25		55	
26		56	
27		57	
28		58	
29		59	
30		60	

Appendix 3-6: HPLC Methadone Assay Run Sheet

SAMPLE DETAILS

DATE :

EXPERIMENT DESCRIPTION :

MOBILE PHASE : 9:11:80 Methanol:Acetonitrile:1% Triethylamine
pH 5.60

COLUMN : Cyclobond I RSP 2000 250x4.6mm

FLOW RATE : 1.0 mL/Min **BACK PRESSURE :** x 100 kgf/cm²

INJECTION VOLUME : uL

DETECTION : 210 nm **RANGE :** 0.005 aufs

RUN TIME : minutes

Inject. #	Samp. #	Description	Inject. #	Samp. #	Description
1			31		
2			32		
3			33		
4			34		
5			35		
6			36		
7			37		
8			38		
9			39		
10			40		
11			41		
12			42		
13			43		
14			44		
15			45		
16			46		
17			47		
18			48		
19			49		
20			50		
21			51		
22			52		
23			53		
24			54		
25			55		
26			56		
27			57		
28			58		
29			59		
30			60		

Appendix 3-7: Erythromycin Injection Preparation Instructions for RAH Pharmacy

CYTOCHROME P450 CYP3A4 ACTIVITY
-ERYTHROMYCIN BREATH TEST-

Erin Murray 20/08/02
(08) 8303 5985

¹⁴C-erythromycin Preparation

REQUIRES

- 4 μ Ci of ¹⁴C-erythromycin (*N*-methyl-¹⁴C, 55mCi/mmol; NEN Life Science Products Inc, Boston, MA, USA)
-2.5ml provided = approximately 60 doses
- 5 ml of normal (0.9 %) saline
- 5 ml syringe
- 0.22 μ m sterile filter

Action:

- Dilute 40 μ l dose of ¹⁴C-erythromycin into 5 ml normal saline
- Load into a 5 ml syringe
- Attach a low-volume 0.22 μ m sterile
- Remove air from filter, obtain total weight of syringe

Appendix 3-8: Erythromycin Validation Information Sheet

INFORMATION SHEET FOR RESEARCH SUBJECTS

The purpose of this study is to validate the Erythromycin Breath Test.

To be eligible to take part in this study, you will need to:

- (x) not be intolerant to erythromycin (a commonly used antibiotic).
- (xi) be aged between 18 and 45 years old.

What this study involves:

(a) Erythromycin breath test.

Methadone and other drugs are broken down in the body at different rates by different people. This might be one reason why some people, when they start methadone, might get into difficulties. The erythromycin breath test measures the activity of the enzyme which breaks down these drugs in the body and governs how effectively they are removed from the body. For this test you will be given a very small quantity of radioactive erythromycin into a vein and then be asked to blow air for a short period (1-2 breaths) into a device up to twelve times over the next 90 minutes. The radioactive gas captured will indicate the body's capacity to break down methadone. The total dose of radiation exposure is extremely small and should be seen in the context of normal radiation exposure as part of everyday living. As part of everyday living, people are exposed to naturally occurring background radiation and receive a dose of 2000 to 3000 μSv (microsieverts) each year. The Sievert is the unit in which radiation is expressed. The effective dose from the radioactive erythromycin in this study is about 10 to 40 μSv (equivalent to an extra 1.8 to 7.3 days' natural exposure). No harmful effects of radioactive erythromycin have been demonstrated and the risk at this dose is negligible.

Confidentiality.

All information collected from you during this study is completely confidential. The information will be coded so that you cannot be identified. No-one will be given any information about you or your study test results unless you want them to have this information. Research staff may access your clinic case notes but only to write down essential information relevant to the study, such as any illnesses or medications you may have had.

Leaving the study.

You are free to drop out of the study at any time and for any reason. You do not have to tell anyone your reason.

Effects, side effects and inconvenience of the study procedures.

- (e) The insertion of the plastic tube into the vein may cause temporary pain. There is a slight risk of bruising at the site of the plastic tube insertion and the remote risk of

Appendix 3-8: Erythromycin Validation Information Sheet continued

clotting (especially with erythromycin) or infection in the vein. These risks are reduced because we only use qualified people to do the procedures.

- (f) Erythromycin. When given for the treatment of infection (between 250 and 500 mg every 6 to 8 hours for several days), the following can occur; (commonly): nausea, vomiting, abdominal pain, diarrhoea, headache, breathlessness, cough, fungus infections, (infrequently): clotting of a vein, rash, (rarely): anaphylaxis, acute respiratory distress, Stevens-Johnson syndrome (severe skin reaction), hepatitis, psychiatric disturbances, hearing loss, severe diarrhoea, heart rhythm disturbances. It is highly unlikely that any of these adverse effects will occur following the two single 0.059 mg doses (a minute fraction of the dose used for treatment of infection) of erythromycin. As already mentioned, the radiation exposure following the erythromycin breath test is negligible.

If you have any questions, please ask the researchers conducting this study, Ms Erin Murray (phone: 83035571) and/or the Investigator, Professor Andrew Somogyi (8303 5987).

Appendix 3-10: Morphine Assay Checklist

MORPHINE ASSAY CHECKLIST

DATE: ___/___/___

- Set up column, get baseline plot started
(Flow=1 ml/min, Back pressure < 2000 psi)
- Decide on run samples, fill out run sample sheet.
- Run pH 2.0 buffer and Ref Mix Sample 50µl of 200µl
(100µl St, 30µl IT, 70µl pH2 Buf)
- 10 ml flat bottom tubes x sample no. x 2 and numbered accordingly
- Add 200 µl each of NaH₂PO₄ pH 2.0 to one lot, cover with tissue and set aside
- To second set:
 - Add 30 µl of Internal Standard to each tube
 - Add 500 µl of Sodium Bicarbonate Buffer to each tube
 - Add 100 µl of Standard or QC....
 - and 900 µl of blank plasma
 - OR
 - Add 1 ml of subject plasma sample
 - Or add 0.5 ml subject plasma sample + 0.5 ml H₂O
- In fume hood, add 6 ml chloroform to each from bottle tap
- Tighten caps, rotary mix for 15 minutes, from: _____ to _____
- Centrifuge @ 3250 rpm for 10 mins
- Aspirate off Aqueous Layer
- Add 500 µl Sodium Bicarbonate Buffer
- Vortex samples for 10 seconds
- Centrifuge @ 3250 rpm for 10 mins
- Aspirate Sodium Bicarbonate Buffer
- Transfer solvent into duplicate tubes with NaH₂PO₄
- Tighten caps, rotary mix for 10 minutes, from: _____ to _____
- Centrifuge @ 3250 rpm for 10 mins
- Aliquot 150 µl of acid bubble to HPLC micropipette tube/vials
- Fill out run detail sheet, then start run
- Save chromatograms
- Record E1, E2, Guard Cells, and Back Pressure

Cell	Range	Voltage	Value
E1			
E2			
Guard			

Back pressure: _____

Appendix 3-11: Morphine Assay Sample Sheet

Date: _____

Sample #	Description	Sample #	Description
1	R1	35	
2	R2	36	
3	R3	37	
4	R4	38	
5	R5	39	
6	R6	40	
7	R7	41	
8	R8	42	
9	LQC	43	
10	LQC	44	
11	HQC	45	
12	HQC	46	
13	Plasma Blank	47	
14		48	
15		49	
16		50	
17		51	
18		52	
19		53	
20		54	
21		55	
22		56	
23		57	
24		58	
25		59	
26		60	
27		61	
28		62	
29		63	
30		64	
31		65	
32		66	
33		67	
34		68	

Appendix 3-12: Morphine Assay Run Sheet

Date: _____

Inj#	Description	Vol	Inj #	Description	Vol
1			35		
2			36		
3			37		
4			38		
5			39		
6			40		
7			41		
8			42		
9			43		
10			44		
11			45		
12			46		
13			47		
14			48		
15			49		
16			50		
17			51		
18			52		
19			53		
20			54		
21			55		
22			56		
23			57		
24			58		
25			59		
26			60		
27			61		
28			62		
29			63		
30			64		
31			65		
32			66		
33			67		
34			68		

Appendix 4: An Additional Publication Associated with the Work Contained in this Thesis

Foster, D.J.R., Morton, E.B., Heinkele, G., Mürdter, T., and Somogyi, A. Stereoselective quantification of methadone and a d6-labelled isotopomer using high performance liquid chromatography-atmospheric pressure chemical ionization mass-spectrometry: application to a pharmacokinetic study in a methadone maintained subject.

Therapeutic Drug Monitoring 28 (4), August, 2006 pp. 559-567.

NOTE: This publication is included on pages 313 - 320 in the print copy of the thesis held in the University of Adelaide Library.

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