Metformin renal handling
PROTOCOL

Principal Investigators:	
Dr Dan Wright and Prof Rob Walker	School of Pharmacy and Department of Medicine, University of Otago
Co-investigators:	
Prof Stephen Duffull	School of Pharmacy, University of Otago
Associate Professor Tony Merriman	Department of Biochemistry, University of Otago
Associate Professor Matt Doogue	Department of Medicine Christchurch, University of Otago
Associate Professor Natalie Medlicott	School of Pharmacy, University of Otago
Dr Tracey Putt	Department of Medicine, University of Otago
Dr John Schollum	Department of Medicine, University of Otago

ABSTRACT

Metformin is the first line treatment for Type-2 diabetes. There is currently no clear consensus on the safe dosing of metformin in patients with impaired renal function. Published guidelines are inconsistent and lack a sound scientific basis to inform prescribing decisions. In addition, there is concern that individuals with impaired kidney function may be at risk of metformin over-exposure and severe side effects. The renal handling of metformin in patients with kidney dysfunction is poorly understood. Previous research by our group has shown that reduced glomerular filtration rate does not correlate with the renal clearance of drugs, such as metformin, that are eliminated primarily by tubular secretion. This project aims to clarify the impact of kidney function on metformin renal handling. This information will provide the scientific basis for a revised dosing guideline for patients with renal impairment.

PROTOCOL, IN BRIEF

Subjects will be recruited using print advertisements in the newspaper and from the renal clinic at Dunedin Hospital. The study will include volunteers stratified into three groups based on renal function: 1) Those with a stable eGFR of ≥ 60mL/min, 2) those with a stable eGFR ≥ 30 mL/min and < 60 mL/min, 3) those with a stable eGFR < 30mL/min. We intend to recruit 15 subjects into each renal function group for a total of 45 subjects.

Exclusion criteria;

1. Subjects who are unable or unwilling to give written informed consent
2. Subjects with Type 2 diabetes or who are currently taking metformin
3. Subjects with evidence of >25% change in eGFR in the past month
4. Significant asthma, heart failure or any condition associated with a fragile fluid balance (potential reaction to beta-blockade)
5. Pregnancy
6. Known allergy to medication classes; biguanides or aminoglycosides.
7. The concomitant use of drugs known or suspected to interact with the tubular transport of metformin or creatinine including: antibiotics (unless a 2 week washout),

beta-blockers, calcium channel blockers, antiarrhythmic drugs, H2 blockers, thiazide diuretics (unless a 7 day washout), antituberculosis drugs, and probenecid.

Subjects will be screened for exclusion criteria. Baseline information such as demographics and concomitant medicines will be recorded. Informed written consent will be obtained.

Study Day: Subjects will report to the research clinic, 9th floor, Department of Medicine, Dunedin Hospital, after an overnight fast. A blood sample will be taken for genotyping and for baseline plasma creatinine, urate, and cystatin C concentrations. Subjects will then receive a single dose of; 1) metformin 500mg orally, and, 2) gentamicin intravenously 40mg as an IV bolus. Oral medications will be administered with at least 250mls of filtered water and an intake of 100mL/hour for the next 4 hours will be maintained to ensure adequate urine output. Blood samples will be collected at the following times post drug administration: 15-30 minutes, 30-60 minutes, 90-120 minutes, 4, 6, 8 and 24 hours for the measurement of metformin, gentamicin, creatinine (3 samples), urate (3 samples), and cystatin C (1 sample). Timed urine samples (0-3, 3–8, 8–24 hours) will be collected to determine the renal clearances of metformin, urate, creatinine, and gentamicin.

The renal clearance mechanisms will be quantified using a population pharmacokinetic analysis and compared between groups.

Subjects will be followed-up by research staff one week after the study day to enquire about any adverse effects or other problems associated with the study.

PROTOCOL – IN DETAIL

Screening/ recruitment

All subjects will either be referred by one of the Nephrologists or will contact the study co-ordinator as a volunteer (from print ads etc).

Refer to the ***screening form*** to ensure that the patient is eligible for inclusion.

Provide the subject with the information sheet and a consent form. Explain all aspects of the study- including risks and time commitments.

Once the patient has been enrolled;

1. Assign the next consecutive study number.
2. Arrange an appointment for the patient to come to Dunedin Hospital for the study day.
3. Record the study date on the appropriate study forms (e.g. timeline documents, patient blood forms, data entry sheet)
4. Provide the subject with the following;
    - **Study Day Instructions** – please fill in all the agreed dates for the study
    - **Petrol vouchers**
    - **Morning tea and lunch vouchers**
5. Reminders for the patient;
    - Do not eat breakfast on the study day

Study Day (see investigator time sheet attached)

1. Confirm that the patient has not had yet had a morning meal. Tea, coffee and/or water are acceptable. If they have already taken a morning meal– refer to the contingency instructions below

> *Contingency*
>
> *If the patient has had a morning meal (apart from tea, coffee and/or water) please arrange another study day.*

2. Record demographic/ clinical information on the **data entry sheet**.

3. Ask subject to empty his/her bladder prior to the study initiation

4. Dosing and blood sampling

> *Labelling of blood tubes*
>
> *Please ensure that blood tubes and SLC form are clearly labelled with the study ID, date, and the time*
>
> *Recording sample times*
>
> *Record the exact time of each blood sample (nearest minute) on the **data entry sheet***

   a. Withdraw;

      i. Baseline blood samples for; urate, creatinine, cystatin C (1 x 4mL heparin tube)

      ii. Blood sample for genotyping (1 x 4mL EDTA – to be sent to Assoc Prof Tony Merriman, Department of Biochemistry

   b. The subject will take metformin 500mg orally with at least 250mL of water and will be given 40mg gentamicin by IV bolus. *Record the time of drug administration to the nearest minute on the **data entry sheet***

   c. Withdraw blood samples after the dose of metformin at the following times;

      - 15-30 minutes,
      - 30-60 minutes,
      - 90-120 minutes,

- At approximately 4 hours,
- At approximately 6 hours,
- At approximately 24 hours

Record the blood sampling time to the nearest minute.

Morning tea/ lunch: Note that the subject will be free to eat after the second blood sample (30-60 minutes). Provide the patient with a morning tea and a lunch voucher.

5. Urine samples

   - All urine must be collected for the full 24 hour study period in three intervals; 0-3hours, 3-6 hours and 6-24 hours.
   - At each completed interval record the urine volume on the **data entry sheet** and remove 4 aliquots for sampling. Label with study ID, date, urine collection interval and time. Once completed the urine can be discarded.
   - Provide the subject with three urine collection containers. These must be clearly labelled with study ID, date and the time interval. The 0-3 and 3-6 hour samples will be collected while the subject is attending the study clinic.
   - The 6-24 hour container must be supplied to the subject to take home (fully labelled – including the time to STOP collecting urine)

6. Patient reminders;

   - Return to the research clinic on the following day for the final (24 hour) blood sample
   - Collect all urine until 24 hours has been reached in the container provided. Return the urine container to the research clinic.

7. Follow-up/ adverse events

   - Record all adverse events on the data entry sheet
   - Follow-up in 1 week and in 4 weeks with each subject for reporting of adverse effects or problems associated with the study.

	Study Day/ time									
	Screening	**Study day** baseline	**Time 0**	**15-30 mins**	**30-60 mins**	**90-120 mins**	**~3 hours**	**~4 hours**	**~6 hours**	**~24 hours**
Date:										
Demographics:	**X**									
Consent form signed	**X**									
Petrol and coffee voucher numbers	**X**									
Drug administration										
Metformin 500mg tablet with 250mL			**X**							
Gentamicin 80mg IV			**X**							
Blood sampling										
Urate, creatinine, cystatin C		**1x 4mL Hep tube**								
Plasma metformin			**1x 4mL plain tube**	**1x 4mL plain tube**	**1x 4mL plain tube**	**1x 4mL plain tube**	**1x 4mL plain tube**	**1x 4mL plain tube**	**1x 4mL plain tube**	**1x 4mL plain tube**
Plasma Gentamicin			**1x 4.5mL lith-hep**	**1x 4.5mL lith-hep**	**1x 4.5mL lith-hep**	**1x 4.5mL lith-hep**	**1x 4.5mL lith-hep**	**1x 4.5mL lith-hep**	**1x 4.5mL lith-hep**	**1x 4.5mL lith-hep**
Urine collection										
Urine metformin							**X**		**X**	**X**

	Study Day/ time									
	Screening	**Study day** baseline	**Time 0**	**15-30 mins**	**30-60 mins**	**90-120 mins**	**~3 hours**	**~4 hours**	**~6 hours**	**~24 hours**
Date:										
Urine creatinine							**X**		**X**	**X**
Urine urate							**X**		**X**	**X**
Urine gentamicin							**X**		**X**	**X**

Follow-up: 1 week. Date_____