Proton pump inhibitors and interstitial nephritis

Study protocol

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Abstract

Almost 20 years of case reports suggest an association between proton pump inhibitors (PPIs) and interstitial nephritis. Although the risk of drug-induced interstitial nephritis appears to be very low, PPIs are one of New Zealand's most commonly prescribed medicines, and in the last two years omeprazole and pantoprazole, specific PPIs, have been available over-the-counter (OTC) without prescription. The on-going concern over a possible association between PPI use and interstitial nephritis was highlighted in the September 2011 Medsafe *Prescriber Update*, which reported that the Centre for Adverse Reactions Monitoring (CARM) continues to receive clinician reports regarding PPIs and interstitial nephritis. This study uses routinely collected data held in national collections in a nested case-control study design, and will be the first population-based analytical study estimating both absolute and relative risks of interstitial nephritis in a cohort of PPI users. The study results will be useful in helping patients and prescribers weigh the potential benefits and risks of PPIs. Should the study find the suggested association, the results may change the way information on the risk of interstitial nephritis is communicated to current and potential PPI users; will be useful in updating the knowledge of prescribers, dispensers, and pharmacy assistants; and may potentially influence prescribing practices.

Background

Proton pump inhibitors (PPIs) are widely prescribed for the treatment and prevention of peptic acid disorders. Their main uses are as a short-term therapy for the treatment of peptic ulcer symptoms, as a maintenance therapy in the management of gastro-oesophageal reflux disease (GORD), and as a prophylaxis against ulceration due to use of non-steroidal anti-inflammatory drugs (NSAIDs).[1] Three PPIs, omeprazole, lansoprazole, and pantoprazole, are available as government-subsidised prescription medicines in New Zealand. Publicly available data on PPI prescriptions or dispensings is scarce; however, omeprazole is the fourth most commonly government-subsidised prescription medicine in New Zealand, with 1,020,000 dispensings in the year to June 2010.[2] Assuming 90 day prescriptions, this translates into a conservative estimate of 255,000 current omeprazole users; we expect the total number of current PPI users to be substantially higher. In 2009, all three PPIs were reclassified as "pharmacist only" (also known as "restricted") medicines. A registered pharmacist must be involved in the sale of any "pharmacist only" medicine, and sales details, including the patient's name and address, must be recorded. Drug company Bayer was the

first to take advantage of the reclassification and began marketing omeprazole, under the Losec brand, as a "pharmacist only" medicine in September 2009. In 2010, omeprazole was further reclassified as a "pharmacy only" medicine, and is available for purchase from any salesperson working in a community or hospital pharmacy under the Losec and Dr Reddy brands. Omeprazole's over-the-counter (OTC) availability without doctor or pharmacist supervision increases the urgency of investigating the possible association between PPIs and interstitial nephritis.

Interstitial nephritis is a common cause of acute renal failure (ARF), with an estimated two-thirds of interstitial nephritis cases attributable to adverse medicine reactions, most commonly antimicrobial agents and NSAIDs.[3] Since 1992 there have been over 100 cases of interstitial nephritis or ARF attributed to PPIs which have appeared in the published literature as case reports or case series, mainly among elderly users. This suggests interstitial nephritis is a class effect of PPIs.[4-6] These published cases are believed to be only a subset of cases reported to pharmacovigilance reporting agencies, including the Centre for Adverse Reactions Monitoring (CARM) in New Zealand, and the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden (Uppsala Monitoring Centre). Between September 1993 and July 2011, CARM received 63 reports of interstitial nephritis and 46 reports of ARF in omeprazole users (personal communication, Michael Tatley, CARM director). As of September 2011, the Uppsala Monitoring Centre reported 270 cases of interstitial nephritis and 297 cases of ARF attributed to omeprazole use (personal communication, Michael Tatley, CARM director). Due to discrepancies in clinical coding methods, interstitial nephritis could be coded as the primary diagnosis, or as the secondary diagnosis (with ARF coded as the primary diagnosis), meaning some cases of interstitial nephritis could appear as ARF cases. Both the published case reports and those collected by pharmacovigilance reporting agencies are likely to substantially underestimate the occurrence of interstitial nephritis associated with PPI use. Moreover, there has been no systematic collection of case numbers or number of PPI users, making it impossible to estimate incidence. To date there have been no published population-based studies investigating the association between PPIs and interstitial nephritis.

Since 2005, National Health Index (NHI) numbers have been recorded with virtually all data collected by the Pharmaceutical Collection (Pharms), a database containing records of all claims made by pharmacists for the dispensing of government-subsidised prescription

medicines. NHIs are also recorded with other routinely collected information, such as hospital discharges, held in national collections. The recording of NHIs with Pharms and other national collections means we are able to gather information on exposure, outcome, and potential confounders, making a population-based study feasible.

This study is part of the Health Research Council and Medsafe funded *Product Vigilance: development of an integrated system* (Pharmacovigilance Project) (HRC reference number 10/031). A sister study using the same general methods, investigating the association between simvastatin and rhabdomyolysis, has received ethics approval (MEC/10/06/055) and is currently underway.

Public health significance

The proposed study would be the first to estimate a population-based incidence of interstitial nephritis in PPI (omeprazole, lansoprazole, pantoprazole) users, and to investigate the association between PPI use and interstitial nephritis. Although interstitial nephritis is a rare event, due to the potential for permanent kidney damage, and the estimated large number of current PPI users in New Zealand, we believe further investigation is warranted.

Omeprazole's recent reclassification as a "pharmacy-only medicine" raises potential safety and risk communication concerns, especially among elderly consumers who are more likely to be users of multiple medicines and at increased risk of drug-related adverse reactions.[7] Under the Losec brand, omeprazole is being marketed directly to consumers through high profile television ads, which tell viewers, "be sure to ask your doctor or pharmacist for Losec by name." In addition, although safety and efficacy is yet to be established,[8] PPIs are increasingly being used to treat GORD in children less than one year of age, with Pharmac aware of increased prescribing of omeprazole for New Zealand infants (Dr Peter Moodie, personal communication, 20 September 2011). Although the proposed study will have insufficient power to investigate an association between PPIs and interstitial nephritis in infants in New Zealand, we will be able to determine the prevalence of PPI use in infants.

Objectives

1) To examine the association between current, and recent, PPI use compared to past PPI use, and the risk of interstitial nephritis;
2) To estimate the absolute risks of interstitial nephritis in current, and recent, PPI users compared to past users;
3) To describe the demographic characteristics of PPI users in New Zealand;
4) To ascertain whether hospitalised and fatal cases reported to CARM are identified using routinely collected data, and conversely;
5) To determine the numbers and proportions of cases not detected through the spontaneous reporting system.

Methods

The study is a case-control design nested within a cohort of PPI users, utilising national collections of routinely collected health and prescribing data.

Identification of study cohort

The following steps will be used to identify the study cohort:

i. The Analytical Services section of the Ministry of Health (formerly the New Zealand Health Information Service) will be asked to identify all PPI dispensings recorded in the Pharms database for any time between 1 January 2005 and 31 August 2009 (omeprazole became available OTC in September 2009).
ii. NHIs will be used to identify all people who received at least one prescription of a PPI between 1 January 2005 and 31 August 2009 (potential cohort members).
iii. The principal investigator will use the prescription dates to identify only those people whose first prescription for any PPI was between 1 May 2005 to 31 August 2009 (the study period), who will subsequently be included in the study cohort. If we included people who filled prescriptions from 1 January 2005 to 30 April 2005, we would be unable to distinguish first time or restarting users from repeat prescriptions. It is important to restrict our study to first time or restarting users as published case reports indicate interstitial nephritis usually starts within the first few months of initiating treatment.
iv. The study cohort entry date will be the date of the first prescription for any PPI during the study period.

Information to be obtained about the study cohort

Analytical Services will be asked to search the national collections using the patients' NHIs to provide us with the following information for each potential member of the study cohort:

- Demographic data (date of birth, sex, ethnicity, and New Zealand Deprivation Index score 2006) in order to describe the characteristics of PPI users in New Zealand, and to match cases and controls by year of birth and sex.
- Details of all prescriptions (from Pharms) for PPIs dispensed between 1 January 2005 to 31 August 2009 (including date, preparation, dose, and duration).
- Details of all prescriptions (from Pharms) for other subsidised medicines dispensed between 1 January 2005 to 31 August 2009 (including date, preparation, dose, frequency, route of administration, and duration), in order to control for confounding by other medicines.
- Details of any hospital admissions (inpatient or day patient), from the National Minimum Dataset (NMDS), at any time between 1988 and 31 August 2009 (including date of admission and discharge, principal and additional diagnoses by International Classification of Diseases 9^{th} and 10^{th} revision, Australian Modification codes (ICD-9-AM, ICD-10-AM), procedure codes, and hospital code), in order to ensure cases are experiencing their first interstitial nephritis episode (incident cases), and to control for confounding by other medical conditions (by identifying people with conditions which are themselves risk factors for interstitial nephritis).
- Date and underlying cause of death (by ICD-10-AM code) for any potential cohort members who died between 1 January 2005 and 31 August 2009. Death records for potential cases will be requested from the MoH or Coronial Services.

The information will only be used for cases and controls, however for expediency Analytical Services prefers to supply information on full cohorts. Once linkage with prescribing and health data has been made, we will ask Analytical Services to remove NHIs from the records of the potential controls, and supply us with a data set containing encrypted NHIs. For potential cases, we require NHIs to be retained with the linked data supplied by Analytical Services, in order to request copies of hospital discharge letters and histology reports from the treating hospitals. Once this information has been received, NHIs will be removed from the analysis files.

Case identification (cohort members who develop interstitial nephritis)

MoH information will be used to identify potential cases of interstitial nephritis resulting in hospital admissions and deaths among cohort members during the study period using the following ICD-10-AM codes:

- N10 (acute tubulo-interstitial nephritis)
- N118 (other chronic tubulo-interstitial nephritis)
- N119 (chronic tubulo-interstitial nephritis, unspecified)
- N12 (tubulo-interstitial nephritis, not specified as acute or chronic)
- N141 (nephropathy induced by other drugs, medicaments and biological substances)
- N142 (nephropathy induced by unspecified drug, medicament or biological substance)
- N144 (toxic nephropathy, not elsewhere classified)

These ICD-10-AM codes were determined after consultation with a professional clinical coder at Dunedin Hospital. Diagnoses will be verified by writing to chief medical officers of the relevant District Health Boards once cases have been identified, to request copies of hospital discharge letters and histology reports (if available), with all identifying information except NHIs removed. Any post-mortem reports will be requested from hospitals or coronial services.

A *definite* case is defined as a patient whose primary or secondary diagnosis is coded using one of the above ICD-10-AM codes, and renal histology confirming the diagnosis of interstitial nephritis.

A *probable* case is defined as a patient whose primary or secondary diagnosis is coded using one of the above ICD-10-AM codes, without histological confirmation.

The date of diagnosis will be taken as the index date.

Patients with interstitial nephritis secondary to a systemic disease will be excluded. Because the ICD-10-AM codes used to identify potential cases are also used to code kidney and urinary tract infections, we have devised a diagnostic algorithm in order to identify and exclude these patients.

Patients diagnosed with N10 or N12 will be excluded if they also have a diagnosis for any of following ICD-10-AM codes, even if other codes are listed:

- A4151 (Sepsis due to other Gram-negative organisms)
- B962 (*Escherichia coli* [*E. coli*] as the cause of disease classified to other chapters
- N110 (Non-obstructive reflux-associated chronic pyelonephritis)
- N111 (Chronic obstructive pyelonephritis)
- N309 (Cystitis, unspecified)
- N390 (Urinary tract infection, site not specified)
- O230 (Infections of kidney in pregnancy)
- O234 (Unspecified infection of urinary tract in pregnancy)
- O862 (Urinary tract infection following delivery)

The remaining patients diagnosed with N10 or N12 will be excluded if they also have a diagnosis for any of the following ICD-10-AM codes, with no other codes listed:

- B95 – B958 (Streptococcus and staphylococcus as the cause of diseases classified to other chapters)
- B960 – B968 (Other specified bacterial agents as the cause of diseases classified to other chapters)
- B970 – B978 (Viral agents as the cause of diseases classified to other chapters)

Control identification (cohort members who did not develop interstitial nephritis)

For each case, ten cohort members of the same sex and born in the same year, who were cohort members on the index date, but not diagnosed with interstitial nephritis before the index date, will be randomly selected (blinded to exposure status). The index date for both cases and controls will be used for exposure measurement.

Inclusion and exclusion criteria

All cases should be experiencing their first ever episode of interstitial nephritis. Patients whose interstitial nephritis is due to a systemic disease, and patients concurrently diagnosed with N10 or N12 and an infection or infectious agent code (as per the rules above) will be excluded. Our study will be restricted to only investigating cases of interstitial nephritis severe enough to require hospitalisation or resulting in death, reducing the possibility of referral and diagnostic bias. Cases and controls with previous history of kidney disease will

be excluded from the study (see the Appendix); however, we will only be able to ascertain this information for people who were hospitalised since 1988 (when electronic records were first introduced).

Exposure measurement

For both cases and controls, *current* exposure is defined as a dispensed supply of any PPI which would have extended to within 30 days of the index date, in order to account for any possible short-term persistence in effect once the medicine is stopped. *Recent* exposure is defined as a dispensed supply which extended up to 31 days, but no more than 90 days, before the index date. *Past* exposure is defined as a dispensed supply which ended 91 or more days before the index date. We will not be assessing the impact of switching between different PPIs since interstitial nephritis appears to be a class effect of all PPIs. Additionally, our study is likely to have insufficient power to detect an association related to switching if one does in fact exist.

Potentially unmeasurable confounding

PPIs are commonly prescribed to help offset the side effects of NSAIDs, which are themselves associated with interstitial nephritis, and are widely available OTC. We will be unable to ascertain OTC NSAIDs use among our study cohort, however we expect most long-term NSAIDs users will be obtaining these drugs by prescription (and hence recorded in Pharms) rather than OTC due to out-of-pocket cost considerations.

Data analysis

Matched analysis will account for case and control matching by year of birth and sex. Conditional logistic regression will be used to calculate adjusted odds ratios and 95% CIs to explore the risk of interstitial nephritis in current, and recent, users of any PPI compared with past users. Person-time of current, recent, and past use of any PPI will be calculated using the detailed dispensing data obtained from Pharms, and will be used to estimate incidence rates. The Poisson distribution will be used to calculate 95% CIs. All of the above analyses will also be calculated separately for omeprazole users, however we anticipate our study will have insufficient power to conduct separate analyses for lansoprazole and pantoprazole users. Two additional analyses will also be conducted on users of any PPI. The effect of duration of use ($\leq$180 days, >180 days) will be investigated in users who took any PPI continuously between

cohort entry and the index date. The impact of total daily dose (low, standard, high)[1] will be explored among current users of any PPI.

Study power

According to Pharmac Annual Reviews,[9] the number of prescriptions for omeprazole in the year to June 2009 was 1,070,000. Assuming 90 day prescriptions, this equates to a conservative estimate of approximately 267,500 omeprazole users; we anticipate the number of current PPI users during the study period to be substantially higher. We are unable to accurately estimate the potential number of cases during the study period because information on the incidence of interstitial nephritis among PPI users is unavailable. However, the potential number of cases in the study period has been roughly estimated based on (a) the CARM database has 63 reports of interstitial nephritis and 46 of ARF in users of omeprazole; and (b) in 2007-2008, there were 316 admissions for ICD-10 code N10; 33 admissions for ICD-10 N11; 1739 admissions for ICD-10 N12; and 7 admissions for ICD-10 N14.[10]

Information on the proportion of controls who are past users is not available, however we are working with a local pharmacist in order to estimate this proportion. Assuming that about 50% of controls were current users on the index date (meaning 50% are recent and past users), with 50 cases, a case:control ratio of 1:4, alpha of 0.05, a correlation coefficient for failure of 0.01, and power 80%, we would have sufficient power to detect a moderately weak association (odds ratio of 2.5) if it exists. Assuming that about 80% of controls were current users on the index date (meaning 20% are recent and past users), and holding all other values above constant, we would have sufficient power to detect a moderately strong association (odds ratio of 4.6) if it exists.

Expected outcome or impact

The study is expected to estimate the absolute and relative risk of interstitial nephritis among current, and recent, users of PPIs (and omeprazole users separately) compared to past users. This information will help patients and prescribers weigh the potential benefits and risks of PPI use. If the suspected association is found, this could lead to a warning about PPIs and the risk of interstitial nephritis in a monthly Medsafe *Prescriber Update* or WHO

[1] Low dose: omeprazole<20mg; pantoprazole<40mg; lansoprazole<30mg
Standard dose: omeprazole=20mg; pantoprazole=40mg; lansoprazole=30mg
High dose: omeprazole>20mg; pantoprazole>40mg; lansoprazole>30mg

Pharmaceuticals Newsletter, updating the knowledge of prescribers. There may also be changes in the way information on the risk of interstitial nephritis is conveyed to patients by prescribers, nurses, pharmacists, pharmacy assistants, manufacturers, and marketers. The study results will be prepared for publication in a peer-reviewed journal.

Ethical considerations

This is a records-based study and there will be no participant recruitment. Our study requires the use of NHIs to identify the relevant information held in the Pharms, NMDS, and Mortality Collection national databases, and to verify diagnoses through hospital discharge letters. Information from CARM is also required. Previous research by Dr Lianne Parkin and Professor Charlotte Paul[11] demonstrated a public mandate for the use of routinely collected data in pharmacoepidemiological research. It is not practicable to seek consent from every potential participant in our study due to the large number of records, and difficulties obtaining consent in the event that someone has died or is otherwise impossible to contact. There will be strict confidentiality safeguards in place and the risk to any individual is extremely low. Considering the large number of PPI users, risk of permanent kidney damage, almost two decades of case reports, and lack of published analytical studies estimating absolute or relative risks, we believe it is in the long-term public interest to investigate the potential harm caused by PPIs.

Two Māori investigators, Dr Tristram Ingham and Bernadette Jones, from the University of Otago, Wellington School of Medicine, have been involved in advising the larger Pharmacovigilance Project, of which this study is a part. There is no evidence, in the published literature or elsewhere, showing Māori are more prone to developing interstitial nephritis, or that PPI prescribing patterns differ by ethnicity in New Zealand.

Strengths and weaknesses

The use of a nested case-control study design has several advantages. Controls are selected from the same defined population of PPI users as cases, which provides for a degree of control for the underlying characteristics of PPI users, and the general characteristics of this population will be relatively easy to describe. Unlike a full cohort study, a nested case-control study requires fewer study members, and is therefore less expensive and more efficient to conduct. In contrast to many case-control studies, recall and/or interviewer bias is not an issue for this study as medicine exposure is not self-reported, but is ascertained from

routinely collected data. Nested case-control designs have greater power to detect an increased risk if one truly exists, and individual level matching (by age and sex) and matched analysis also increases statistical efficiency.

Information held in Pharms means this study will be able to calculate person-years of exposure in a cohort of PPI users, and the incidence of interstitial nephritis. PPIs are not indicated for use in infants, and this study is unlikely to have enough power to detect an increased risk of interstitial nephritis in infants if one exists, however we will be able to systematically describe the use of PPIs in this population. Comparing data collected in the national collections during the study period to that collected by CARM will enable us to investigate the proportion of hospitalised and fatal cases of interstitial nephritis reported to CARM, and conversely identify reported cases not found using the national data collections.

Using routinely collected information held in national databases, linked by unique NHI identifiers, has a number of advantages. These include virtually complete coverage of the entire New Zealand population; cost effectiveness; efficiency; and no possibility of recall or interviewer bias. Data recorded in Pharms is highly likely to be complete since pharmacists are not remunerated for dispensings unless a claim is submitted to the HealthPAC General Transaction Processing System. Once processed, claims information is recorded in the Pharms database.

Despite the many advantages of using Pharms data, there are several limitations. Only government-subsidised medicines dispensed from community and hospital pharmacies are recorded in Pharms. Patients prescribed PPIs while in hospital will not be recorded in Pharms; should these patients subsequently develop interstitial nephritis while still in hospital, the odds ratio will be underestimated, however we anticipate very few cases, if any, falling into this category. In addition, medicines known to increase the risk of developing interstitial nephritis, including NSAIDs, are freely available OTC. Incomplete measurement of their use may result in residual confounding, however due to cost considerations we expect most long-term NSAIDs users will be obtaining these medicines through prescription. The effect of potential confounding by hospital prescribed or OTC medicines will be to overestimate the odds ratio if renal toxic drugs are more likely to be used in current PPI users. Information in Pharms also only relates to medicines that were dispensed to patients, and there is no way of knowing whether the patient took their medicine as prescribed. It will be

possible to investigate patterns of filling repeat prescriptions, however case reports suggest most cases of interstitial nephritis occur within the first few months of starting treatment. If a case developed interstitial nephritis within the first three months of starting treatment there will be no way of knowing, from dispensing patterns, whether the patient took their medicine as prescribed. It is possible that some cases may be misclassified as not being current PPI users if they were prescribed overseas; this bias would underestimate the odds ratio, however we anticipate the proportion of cases who might be affected in this way to be extremely low, if there are any at all.

The NMDS will be used to identify all study cohort members admitted to public or private hospitals during the study period, along with information on their principal and additional diagnoses. Diagnoses will be confirmed by checking hospital discharge letters, and we have consulted with a professional clinical coder who has advised us about the ICD-10-AM codes and coding rules that would be used to code interstitial nephritis. Our study is restricted to only severe cases of interstitial nephritis requiring hospitalisation or resulting in death, and misclassification of outcome is unlikely; if it did occur it would result in an underestimation of the odds ratio.

Knowledge of the suspected relationship between PPIs and interstitial nephritis is not well known, however Medsafe data sheets for all three PPIs briefly mentioning interstitial nephritis as a very rare outcome appeared throughout our study period. In June 2006 a Medsafe *Prescriber Update* warned clinicians of a possible association between PPI use and interstitial nephritis, and in the same year an article reporting on 15 cases in the Auckland region appeared in *Nephrology*.[12] By restricting our study to only hospitalised and fatal cases we reduce the potential impact of this publicity, and possible increased clinician awareness, which may result in referral and diagnostic bias, which would have the effect of overestimating the odds ratio.

The Health Research Council and Medsafe have reviewed the general methods that will be used in this study, while the study's specific methods have been reviewed by the scientific advisory group of the Pharmacovigilance Project. The general and specific methods of the simvastatin and rhabdomyolysis sister project, which this study is based upon, have been reviewed by two international pharmacoepidemiologists.

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Appendix

Table A1 International Classification of Diseases 9th revision Australian Modification codes (ICD-9-AM) used to exclude study cohort members with kidney disease diagnoses before cohort entry

Description	ICD-9-AM
Acute glomerulonephritis	5800, 5804, 58081, 58089, 5809
Nephrotic syndrome	5810 ,5811, 5812, 5813, 58181, 58189, 5819
Chronic glomerulonephritis	5820, 5821, 5822, 5824, 58281, 58289, 5829
Nephritis and nephropathy	5830, 5831, 5832, 5834, 5836, 5837, 58381, 58389, 5839
Acute renal failure	5845, 5846, 5847, 5848, 5849
Chronic renal impairment	5851
Chronic renal failure	5859
Renal failure, unspecified	586
Chronic pyelonephritis	59000, 59001
Acute pyelonephritis	59010, 59011
Renal and perinephric abscess	5902
Pyelonephritis, unspecified	59080
Pyelitis or pyelonephritis in diseases classified elsewhere	59081
Postural proteinuria	5936

Table A2 International Classification of Diseases 10th revision Australian Modification codes (ICD-10-AM) used to exclude study cohort members with kidney disease diagnoses before cohort entry

Description	**ICD-10-AM**
Acute nephritic syndrome	N000, N001, N002, N003, N004, N005, N006, N007, N008, N009
Rapidly progressive nephritic syndrome	N010, N011, N012, N013, N014, N015, N016, N017, N018, N019
Recurrent and persistent haematuria	N020, N021, N022, N023,N024, N025, N026, N027, N028, N029
Chronic nephritic syndrome	N030, N031, N032,N033, N034,N035, N036, N037, N038, N039
Nephrotic syndrome	N040, N041, N042, N043, N044, N045, N046, N047, N048, N049
Unspecified nephritic syndrome	N050, N051, N052, N053, N054, N055, N056, N057, N058, N059
Isolated proteinuria	N060, N061, N062, N063, N064, N065, N066, N067, N068, N069
Hereditary nephropathy	N070, N071, N072, N073, N074, N075, N076, N077, N078, N079
Glomerular disorders	N080, N081, N082, N083, N084, N085, N088
Acute tubulo-interstitial nephritis	N10
Other chronic tubulo-interstitial nephritis	N118
Chronic tubulo-interstitial nephritis, unspecified	N119
Tubulo-interstitial nephritis, not specified as acute or chronic	N12
Analgesic nephropathy	N140
Nephropathy induced by other drugs, medicaments and biological substances	N141
Nephropathy induced by unspecified drug, medicament or biological substance	N142
Nephropathy induced by heavy metals	N143
Toxic nephropathy, not elsewhere classified	N144
Balkan nephropathy	N150
Renal and perinephric abscess	N151
Other specified renal tubulo-interstitial diseases	N158
Renal tubulo-interstitial disease, unspecified	N159
Renal tubulo-interstitial disorders	N160, N161, N162, N163, N164, N165, N168
Acute renal failure	N170, N171, N172, N178, N179
End-stage renal disease	N180
Other chronic renal failure	N188
Unspecified chronic renal failure	N1890
Chronic renal impairment	N1891

Table A3 Government-subsidised prescription drugs listed in the New Zealand formulary known or suspected of increasing the risk of interstitial nephritis, by therapeutic class

NSAIDs
Diclofenac sodium
Diflunisal
Fenoprofen calcium
Flurbiprofen
Ibuprofen
Indomethacin
Ketoprofen
Mefenamic acid
Meloxicam
Mesalazine
Naproxen
Naproxen sodium
Phenylbutazone
Piroxicam
Sulindac
Tenoxicam
Tiaprofenic acid

Other analgesics
Nefopam hydrochloride
Paracetamol
Paracetamol with codeine
Tramadol
Tramadol hydrochloride

Aspirin
Aspirin
Aspirin with chloroform
Aspirin with codeine
Aspirin with paracetamol and codeine

Other anti-coagulants
Phenindione
Warfarin sodium

Antibiotics
Amoxycillin
Amoxycillin clavulanate
Azithromycin
Aztreonam
Benzathine benzylpenicillin
Benzylpenicillin sodium (Penicillin G)
Cefaclor monohydrate
Cefamandole nafate
Cefazolin sodium
Cefoxitin sodium
Ceftriaxone sodium
Cefuroxime axetil
Cefuroxime sodium
Cephalexin monohydrate
Cephalothin sodium
Cephradine
Ciprofloxacin
Clarithromycin

Other antimicrobials
Abacavir sulphate
Abacavir sulphate with lamivudine
Aciclovir
Adefovir dipivoxil
Atazanavir sulphate
Dapsone
Dapsone with pyrimethamine
Darunavir
Didanosine
Efavirenz
Emtricitabine
Enfuvirtide
Entecavir
Ethambutol
Ethambutol hydrochloride
Etravirine
Hexamine hippurate
Hydroxychloroquine sulphate
Indinavir
Isoniazid
Lamivudine
Lopinavir with ritonavir
Nevirapine
Pyrazinamide
Quinine sulphate
Raltegravir potassium
Rifabutin
Rifampicin
Ritonavir
Stavudine
Tenofovir disoproxil fumarate
Valaciclovir
Zidovudine
Zidovudine with lamivudine

Anxiolytics
Alprazolam
Buspirone hydrochloride
Diazepam
Lorazepam
Oxazepam

Anti-epilepsy
Carbamazepine
Clobazam
Clonazepam
Ethosuximide
Gabapentin
Lamotrigine
Levetiracetam
Paraldehyde
Phenobarbitone
Phenobarbitone sodium
Phenytoin sodium
Primidone
Sodium valproate
Topiramate
Vigabatrin

Diuretics
Amiloride
Amiloride with frusemide
Amiloride with hydrochlorothiazide
Bendrofluazide
Bumetanide
Chlorothiazide
Chlorthalidone
Furosemide
Indapamide
Triamterene with hydrochlorothiazide

ACE inhibitors
Captopril
Captopril with hydrochlorothiazide
Cilazapril
Cilazapril with hydrochlorothiazide
Enalapril
Enalapril with hydrochlorothiazide
Lisinopril
Lisinopril with hydrochlorothiazide
Perindopril
Quinapril
Quinapril with hydrochlorothiazide
Trandolapril

Angiotensin II antagonists
CandesartanLosartan
Losartan with hydrochlorothiazide

Beta blockers
Atenolol
Atenolol with chlorthalidone
Carvedilol
Celiprolol
Labetalol
Metoprolol succinate
Metoprolol tartrate
Nadolol
Pindolol
Pindolol with clopamide
Propranolol
Sotalol
Timolol
Timolol maleate
Timolol maleate with pilocarpine

Calcium channel blockers
Amlodipine
Diltiazem hydrochloride
Felodipine
Isradipine
Nifedipine
Perhexiline maleate
Verapamil hydrochloride

H2 receptor antagonists
Cimetidine
Famotidine
Ranitidine hydrochloride

Immune modulators
Interferon alpha-2a
Interferon alpha-2a with ribavirin
Interferon alpha-2b
Interferon alpha-n
Interferon beta-1-alpha
Interferon beta-1-beta
Interferon gamma-1b
Pegylated interferon alpha-2a
Pegylated interferon alpha-2bPegylated interferon alpha-2b with ribavirin

Other drugs
Allopurinol
Azathioprine
Bismuth carbonate
Bismuth subcitrate, metronidazole and tetracycline
Bismuth subnitrate
Carbimazole
Chlorpropamide
Clofibrate
Clozapine
Griseofulvin
Methyldopa
Methyldopa with hydrochlorothiazide
Penicillamine
Probenecid
Propylthiouracil
Sulphinpyrazone