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A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use

Mei-Ling Blank[1], Lianne Parkin[1], Charlotte Paul[1] and Peter Herbison[1]

[1]*Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand*

The magnitude of the suspected increase in risk of acute interstitial nephritis among proton pump inhibitor users is uncertain. Here, we conducted a nested case-control study using routinely collected national health and drug dispensing data in New Zealand to estimate the relative and absolute risks of acute interstitial nephritis resulting in hospitalization or death in users of proton pump inhibitors. The cohort included 572,661 patients without a history of interstitial nephritis or other renal diseases who started a new episode of proton pump inhibitor use between 2005 and 2009. Cases had a first diagnosis after cohort entry of acute interstitial nephritis confirmed by hospital discharge letter or death record, and renal histology (definite, 46 patients), or discharge letter or death record only (probable, 26 patients). Ten controls, matched by birth year and sex, were randomly selected for each case. In the case-control analysis based on definite cases and their controls, the unadjusted matched odds ratio (95% confidence interval) for current versus past use of proton pump inhibitors was 5.16 (2.21–12.05). The estimate was similar when all cases (definite and probable) and their corresponding controls were analyzed, and when potential confounders were added to the models. The crude incidence rates and confidence intervals per 100,000 person-years were 11.98 (9.11–15.47) and 1.68 (0.91–2.86) for current and past use, respectively. Thus, current use of a proton pump inhibitor was associated with a significantly increased risk of acute interstitial nephritis, relative to past use.

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Correspondence: *Lianne Parkin, Department of Preventive and Social Medicine, Dunedin School of Medicine, PO Box 913, University of Otago, Dunedin 9054, New Zealand. E-mail: lianne.parkin@otago.ac.nz*

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Concern about a possible increased risk of acute interstitial nephritis among omeprazole users was first raised in 1992.[1] Subsequently, several published case reports and case series suggested a class effect of proton pump inhibitors (PPIs) (including omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole) on the occurrence of acute interstitial nephritis.[2–6] Anecdotal case reports received by national drug safety authorities prompted regulators in several countries to urge caution when prescribing PPIs[7–12]; however, despite these warnings, several studies have shown concerning and continuing levels of inappropriate prescribing of PPIs in both hospital and primary care settings.[13–16]

Surprisingly, however, only one study has formally explored the risk of acute interstitial nephritis in PPI users. This study comparing the use of omeprazole on the index date with nonuse reported an odds ratio of 3.20; however, the diagnoses were not histologically validated and chance could not be ruled out as a possible explanation (95% confidence interval (95% CI) 0.80–12.79).[17] Other research has suggested that the absolute risk is very low, but has relied on unsystematic case identification methods and imprecise estimates of PPI exposure.[9,18] We did a population-based case-control study nested in a cohort of New Zealand users of omeprazole, pantoprazole, or lansoprazole (the PPIs available in New Zealand) to estimate the relative and absolute risks of acute interstitial nephritis resulting in hospitalization or death in current and recent users of these drugs compared with past users.

RESULTS

From 1 January 2005 to 31 August 2009, the Ministry of Health identified 794,230 patients from the Pharmaceutical Collection who had been dispensed at least one course of PPI treatment (Figure 1). The study cohort comprised 572,661 patients who had correctly linked health and dispensing data, begun an episode of PPI use between 1 May 2005 and 31 August 2009, and did not have a history of renal disease (including interstitial nephritis) before cohort entry. From the study cohort, we identified 1164 patients as potential cases. We excluded 529 patients whose additional diagnoses indicated an infection of the kidney or urinary tract, and requested hospital discharge letters, postmortem reports, and

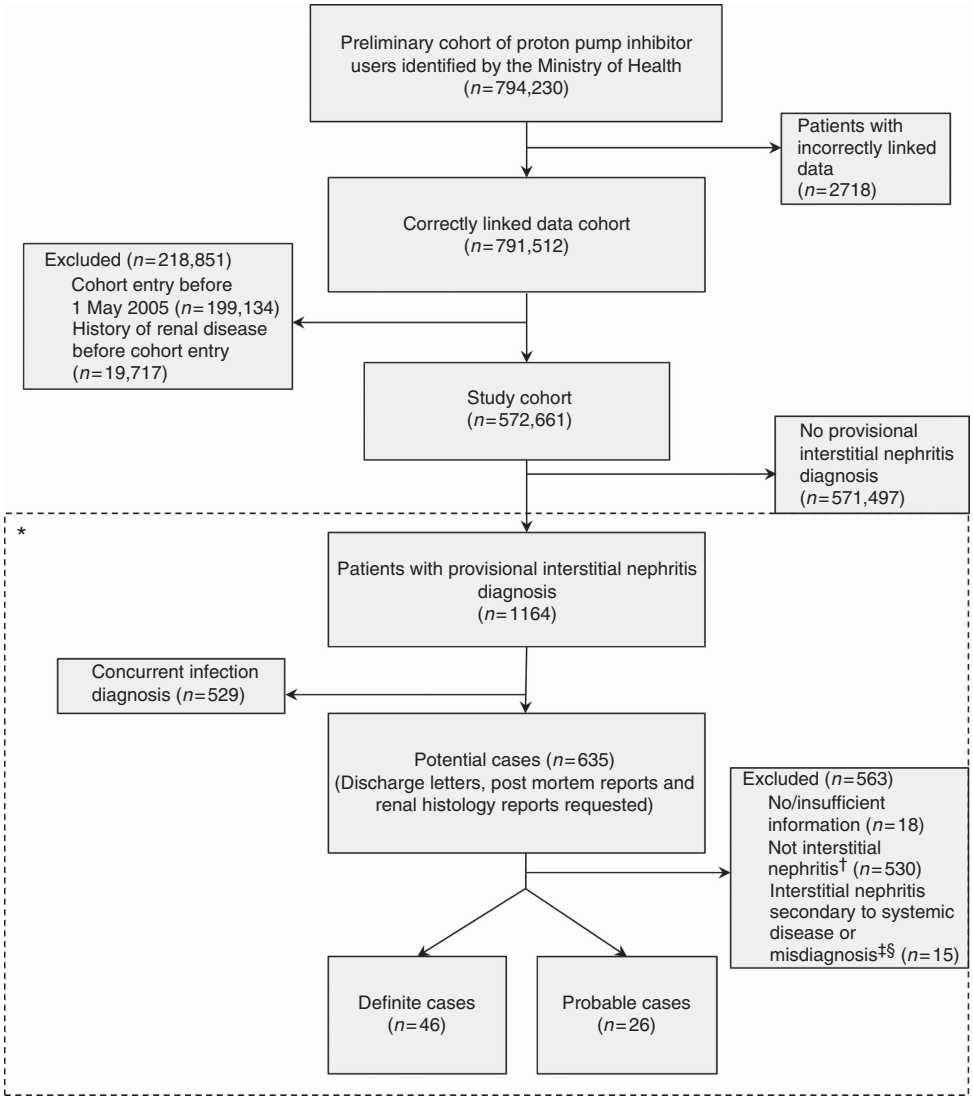

Figure 1 | Study flow diagram. *The dashed line indicates that this part of the figure only describes the case identification process. †Determined after reviewing patients' hospital discharge information. ‡Chronic interstitial nephritis with early amyloid disease ($n=1$); focal segmental glomerulosclerosis ($n=1$); glomerulonephritis ($n=1$); light chain cast nephropathy ($n=3$); minimal change disease with nephrotic syndrome ($n=1$); multiple myeloma ($n=2$); systemic lupus erythematosus ($n=1$); vasculitis ($n=1$); acute tubular necrosis ($n=2$); nonsteroidal anti-inflammatory drug nephropathy in context of dehydration ($n=1$); 'interstitial nephritis on USS (ultrasound)' ($n=1$). §Determined after consultation with a renal physician.

renal histology reports for the remaining 635 potentially eligible cases, receiving information for 617 patients (97.2%). On the basis of this information, an additional 545 patients were excluded (most had pyelonephritis). The case-control study therefore included 72 validated cases who presented acutely with interstitial nephritis (46 definite, histologically confirmed; 26 probable, discharge letter confirmed) and 719 matched controls (460 definite and 259 probable). There were no fatal cases. Owing to a data management oversight, only nine controls were selected for one case.

Table 1 shows the characteristics of the cases and controls. Cases (definite and all) were more likely than controls to be of European ethnicity, to be current users of drugs other than PPIs associated with increased risk of acute interstitial nephritis, to have been hospitalized in the previous year for any reason, and to live in the most deprived socioeconomic areas (Supplementary Table S1 online). Omeprazole was the most commonly dispensed PPI at the last dispensing before the index date, and almost two-thirds of cases and controls who were current users were dispensed a 'standard' daily dose at the last dispensing before the index date (Supplementary Table S2 online).

The results of the main analysis are shown in Table 2. In the matched analysis confined to definite cases and controls, the unadjusted odds ratio was 5.16 (95% CI 2.21–12.05; $P<0.001$) for current use of any study PPI compared with