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Frequency of Interstitial Nephritis in Patients Taking Proton Pump Inhibitor

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ABSTRACT

Background: Acute interstitial nephritis (AIN), a major cause of drug-induced acute kidney injury (AKI) and possible chronic kidney disease (CKD) is linked to extended PPI use. Proton pump inhibitors (PPIs) are frequently recommended for acid-related gastrointestinal illnesses. At a tertiary care hospital in Quetta, Pakistan, this study examines the incidence and clinical consequences of PPI-induced interstitial nephritis in patients on long-term PPI therapy. **Methods:** One hundred individuals with a clinical and laboratory diagnosis of interstitial nephritis who had been using PPIs for at least six months were included in this qualitative analysis. Reviews of medical records, reports from kidney biopsies, and semi-structured interviews with patients and nephrologists were used to gather data. Laboratory parameters, histopathological results, demographics, and symptoms were all examined using descriptive statistics. **Results:** Of the participants, 80% had been taking PPIs for more than a year, and 40% had been taking them for more than three years. AKI (60%), decreased urine production (55%), and weariness (70%), were common symptoms. Laboratory results showed a lower estimated glomerular filtration rate (eGFR) (45 ± 12 mL/min/1.73m²) and an increased serum creatinine (2.1 ± 0.5 mg/dL). The diagnosis of AIN was supported by renal biopsies, which showed eosinophilic infiltration in 60% of cases and tubulointerstitial inflammation in 85% of cases. Fibrosis was observed in 30% of cases, indicating CKD progression risk. **Conclusion:** This study emphasizes the significance of routine renal function monitoring by demonstrating a substantial association between long-term PPI usage and interstitial nephritis. Renal outcomes can be improved and the risk of CKD decreased with early identification and prompt PPI discontinuation. Safer prescribing procedures should be used by medical professionals to lessen nephrotoxic consequences.

INTRODUCTION

Proton pump inhibitors which are known as PPIs function as widely utilized medication across the globe. PPIs advanced to become the second best-selling drug category in 2005 United States after distributing 95.3 million prescriptions which exceeded 2004 sales and generated $12.9 billion revenue. Various studies show that these drugs successfully treat acid reflux conditions by blocking stomach acid production according to (IMS Health ;2007). The treatment safety of PPIs remains at 3% and people generally demonstrate positive drug tolerance when using these medications. The treatment side effects consist mainly of headaches and lightheadedness with diarrhea and constipation and skin responses. The ingestion of PPI medications results in hepatic dysfunction as well as vertigo-based disorientation and unusual blood cell developments which represent rare side effects (Mearin F & Ponce J ;2005). Short-term and unusual negative effects from PPI drugs include interstitial nephritis and pancreatitis as well as Stevens-Johnson Syndrome and multiform erythema. (Simpson IJ, Marshall M, Pilmore H, et al., 2006)

The proton pump (hydrogen-potassium ATPase) inhibitors (PPIs) effectively manage acid-related dyspeptic conditions and peptic ulcers most notably when Helicobacter pylori exists and gastro-oesophageal reflux along with gastro-duodenal lesions caused by non-steroidal anti-inflammatory drugs. New Zealand patients can easily access proton pump inhibitors due to the pharmaceutical subsidy which provides subsidized access. The use of these drugs for extended periods of time continues to increase in modern times.

The usual adverse effects from treatment result in head pain alongside gastrointestinal troubles and diarrhea symptoms among most patients. Hepatic dysfunction occurs less frequently than skin rashes and vertigo while lightheadedness and disorientation together with

hematological complications appear only sporadically among patients. PPIs produce infrequent idiosyncratic adverse reactions that produce pancreatitis along with erythema multiforme, acute interstitial nephritis and AIN, or Stevens Johnston syndrome.

AIN, or acute interstitial nephritis, and Stevens Johnston syndrome. (Simpson ET AL., 2006)

Inflamed cells that infiltrate through the kidney interstitial tissue region represent the fundamental characteristic of acute interstitial nephritis (AIN). Acute renal failure develops due to AIN and leads to this complication in 15 percent of individuals admitted to hospitals with acute renal failure (Kodner, C. M., & Kudrimoti, A; 2003). Acute renal failure with AIN features oliguria as the main characteristic in addition to anorexia, nausea and vomiting and patient lethargy. The diagnosis of AIN depends most strongly upon renal biopsy testing yet additional tests can offer supportive evidence (Michel, D. M., & Kelly, C. J.,1998) (Kodner, C. M., & Kudrimoti, A; 2003) Laboratory tests do not confirm AIN diagnosis.

Medical professionals indicate medication-induced acute interstitial nephritis as a known acute renal failure cause yet patients recover better when their provider identifies it early to eliminate the substance during the first week. When patients remain exposed to triggering substances or healthcare providers fail to identify the causative agent the outcome becomes unfavorable even leading to possible need for kidney transplant surgery. (Sierra, F et al., 2007)

Research indicates that acute interstitial nephritis produces 6–8% of all cases that lead to acute renal failure. Urine analyses show no proteinuria or hematuria among patients with renal failure who most commonly receive this diagnosis of acute interstitial nephritis according to (Torpey N, Barker T, Ross C ;2004) (Davison AM, Jones CH ;2000) This medical condition appears in 27% of such patients. Research shows that renal biopsies function to evaluate proteinuria or haematuria lead to acute interstitial nephritis in 1% of cases. (Farrington K, Levison DA, Greenwood RN, et al., 1989) Acute interstitial nephritis primarily develops from drug exposure according to medical reports (Kodner CM, Kudrimoti A; 2003), yet the condition also stems from infections, tubulointerstitial nephritis, uveitis syndrome, sarcoidosis or arises spontaneously (more than two-thirds of cases) (Kodner CM, Kudrimoti A; 2003). (Michel DM, Kelly CJ; 1989) (Baker RJ, Pusey CD; 2004). The list of frequently implicated medications includes antibiotics together with diuretics PPIs and non-steroidal anti-inflammatory drugs (NSAIDs).

A large number of PPI-induced acute interstitial nephritis research including case reports, case studies, and commentaries have been documented in literature since PPI use expanded. The prevalence of PPIs as a drug-induced cause of reversible acute renal failure now ranks them among the leading pharmaceuticals responsible for this renal side effect according to Baker RJ and Pusey CD. (2004).

LITERATURE REVIEW

Proton pump inhibitors (PPIs) are among the most often given drugs for treating acid-related gastrointestinal conditions such as peptic ulcers, Zollinger–Ellison syndrome and gastroesophageal reflux disease (GERD) (Strand et al., 2017). Although thought to be safe, PPIs are known to have both long-term side effects [including] an increased risk of acute interstitial nephritis (AIN) (Lazarus et al. 2016). Moledina and Perazella (2016) said taking acute kidney injury (AIN) as an immune-mediated kidney injury can lead to severe renal impairment and may transform to chronic kidney disease (CKD), if not treated.

Pathophysiology of PPI-Induced Interstitial Nephritis

As reported by Muriithi et al. (2017), AIN is usually a drug induced hypersensitivity reaction leading to renal dysfunction due to the infiltration of inflammatory cells to the renal interstation. Because PPIs can elicit an immunological response which leads to T cell mediated inflammation, they are also known to be a leading factor of drug induced AIN (Perazella, 2019). The precise mechanism in which PPIs act as haptens by altering kidney antigens and causing an immune mediated reaction, currently is not elucidated (Fernández-Juárez et al., 2018).

Epidemiology and Frequency of PPI-Associated AIN

There are a number of epidemiological research on the use of PPI and AIN. Retrospective cohort research by Blank et al. (2014) found that PPI induced AIN constituted about 14 % of all drug induced AIN. Additional work has been done by Muriithi et al (2017) wherein cases of AIN due to pharmaceuticals accounted for as much as 70% and PPI were responsible for the bulk of the cases. According to Moledina and Perazella (2016), the rising trend in PPI associated nephritis is associated with wide use of PPIs in inpatient and outpatient settings.

Xie et al. (2017) were able to present results from a population-based cohort study that was showing that PPI use was associated with a much increasingly more increased incidence of acute kidney injury (AKI) in patients on long term PPI therapy that often would then go onto chronic kidney disease (CKD) and end stage renal disease (ESRD) according to their findings. Moreover, Linder et al. (2020) meta analyze also demonstrated that AIN played a huge role in why there is such a high association between using PPI for long periods of time with renal problems.

Risk Factors for PPI-Induced AIN

Multiple risk factors have been linked to the onset of

AIN in people on PPI therapy. Age is a major risk factor for drug induced nephrotoxicity as elderly patients are more vulnerable to damaging drug effects because renal function deteriorates with age (Lazarus et al., 2016). Moledina and Perazella (2016) determined that immune response variability or genetic predisposition can also increase the risk of AIN. Other risk factors include long term use of PPI, simultaneous use of nephrotoxic medications (e.g. antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs); Muriithi et al., 2017).

Clinical Presentation and Diagnosis of PPI-Induced AIN

The symptoms of PPI induced AIN (Perazella, 2019) include fever, rash, eosinophilia and malaise. Some patients present with acute kidney injury (AKI), defined as increase in serum creatinine in a short time, and all will develop chronic interstitial nephritis and progressively chronic kidney damage (Fernández-Juárez et al., 2018).

According to Muriithi et al. (2017), however, despite all this, only a renal biopsy is left to be the gold standard for the diagnosis of AIN since it shows interstitial inflammation in conjunction with lymphocytic and eosinophilic infiltration. If used, the treatment is invasive and doctors use imaging examinations, laboratory results (such as rise in serum creatinine or eosinophilia), and clinical history (Perazella 2019). However, according to Xie et al (2017) study, early withdrawal of PPI therapy is associated with the opportunity of a partial or full renal recovery that attests the importance of early diagnosis.

Management and Outcomes of PPI-Induced AIN

In fact, the primary treatment for PPI induced AIN is to discontinue the offending agent as rapidly as possible and usually leads to impressive recovery of renal function (Moledina & Perazella, 2016). Studies have demonstrated that corticosteroid therapy reduces inflammation and promotes renal outcomes in patients of severe renal impairment (Fernández-Juárez et al., 2018). A retrospective study of Linder et al. (2020) has shown that patients who discontinued using PPI medication in a timely fashion, had a higher rate of renal recovery, compared to the patient who continued taking PPI. However, even after stopping, a small number of patients continued to develop chronic kidney disease (CKD), so close monitoring and follow up are still needed (Blank et al., 2014).

Research Objective

The intent of this study is to find out how often interstitial nephritis occurs in people who take proton pump inhibitors (PPIs). However, surprisingly, PPIs are commonly prescribed for acid-related conditions, and long-term use of PPIs has been linked to negative renal outcome, including interstitial nephritis. This was a study to determine the risk variables associated with this disorder and evaluate the prevalence for PPI users. Using clinical data, health testing of kidneys and histopathological findings, this study will evaluate the effect of PPIs on renal health. These results will serve to help the prescription of safer, to prevent the kidney related problems, in exposed populations, the early diagnosis of interstitial nephritis, and the identification of the potential risk of PPI use for prolonged periods.

METHODOLOGY

Qualitative research design was used in this study to examine the frequency and experience of interstitial nephritis in patients using proton pump inhibitor (PPI). The study included a purposive sample technique of 100 patients in use with PPI for more than six months and diagnosed on clinico - laboratory basis with interstitial nephritis in tertiary care hospital Quetta Pakistan. In order to get thorough insights, in depth interviews and reviews were made of medical records. Data was gathered reviewed and medical records, kidney biopsy reports and laboratory component were identified and used; semi structured interviews with patients and nephrologists were also used. Important factors were serum creatinine levels, eGFR, outcomes of urine analyses and length of PPI administration. Thematic analysis was used to assess the use of PPIs and symptoms of interstitial nephritis and qualitative data was generated. Descriptive statistics like frequency and percentages, participants' demographic and clinical characteristics were displayed.

RESULTS

Table 1

Demographic Characteristics of Patients

Characteristic	Frequency (n=100)	Percentage (%)
Gender	Male	55
	Female	45
Age	30-40	25
	41-50	35
	51-60	30
	>60	10

Figure 1

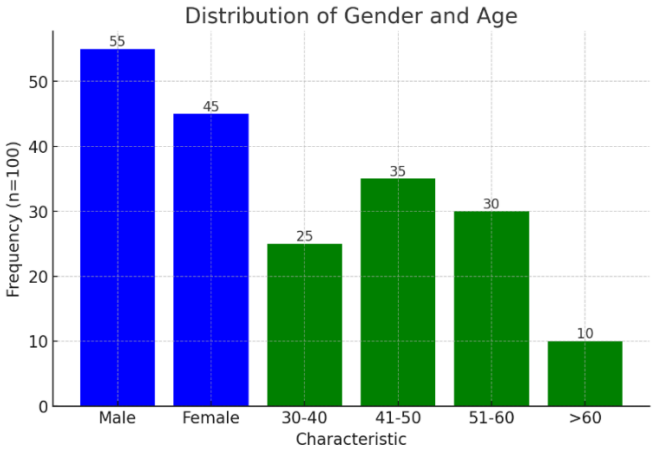


Table 2

Duration of Proton Pump Inhibitor Use

Duration of PPI Use	Frequency (n=100)	Percentage (%)
6 months – 1 year	20	20%
1 – 3 years	40	40%
>3 years	40	40%

Table 3

Clinical Presentation of Interstitial Nephritis

Symptoms	Frequency (n=100)	Percentage (%)
Fatigue	70	70%
Decreased urine output	55	55%
Hematuria	45	45%
Proteinuria	50	50%
Acute kidney injury	60	60%

Table 4

Laboratory Findings in Affected Patients

Laboratory Parameter	Mean ± SD	Range
Serum Creatinine (mg/dL)	2.1 ± 0.5	1.5 – 3.2
eGFR (mL/min/1.73m²)	45 ± 12	25 – 60
Urinary Protein (mg/day)	400 ± 150	200 – 700

Figure 2

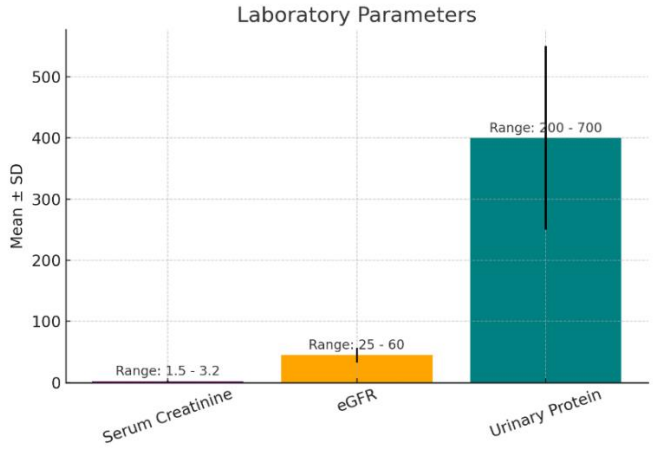
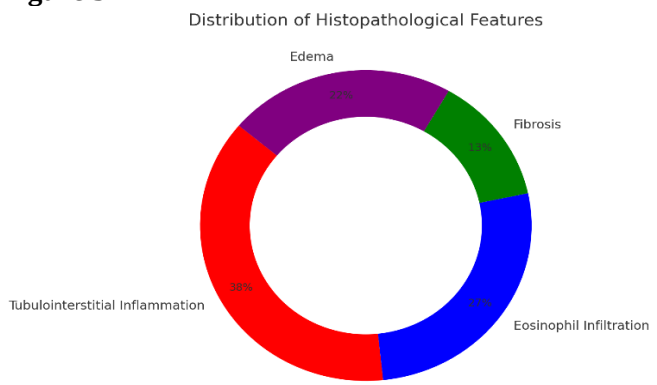


Table 5

Renal Biopsy Findings

Histopathological Feature	Frequency (n=100)	Percentage (%)
Tubulointerstitial inflammation	85	85%
Eosinophil infiltration	60	60%
Fibrosis	30	30%
Edema	50	50%

Figure 3



DISCUSSION

This study sought to assess the frequency of interstitial nephritis among patients with the use of proton pump inhibitors (PPIs) in quack fair hospital of Quetta, Pakistan. Thus, findings support a strong association with long-term PPI use and interstitial nephritis and therefore highlight the need for monitoring of renal function in those taking prolonged PPI therapy.

The population of the research was demographic, with 55% of patients being men and 45% being women, but with only 55% male predominance. This matches up with other research that suggests it might be the case that men commonly have kidney-related illnesses because of lifestyle choices or genetic predispositions. According to the age distribution, 35% of the patients were between 41 and 50 and 30% between 51 and 60, indicating that interstitial nephritis is more developed in the elderly predisposed people who use PPI medication. As age increases, so does renal impairment, which is known to be enhanced by long periods of use of a drug.

In our research, 40 per cent of patients were on PPIs for more than three years and 80 per cent on PPIs for more than a year. Thus, use of PPI for a long time can lead to increased risks of interstitial nephritis. According to previous study, anyone using PPI for long term may develop acute interstitial nephritis (AIN) and chronic kidney disease (CKD). It is our results that point to the need for the routine checking of kidney function in chronic PPI users, as these medications are given for long periods of time without routine renal function monitoring.

Among the study patients' clinical presentations of interstitial nephritis were non-specific symptoms including fatigue (70%), decreased urine output (55%), hematuria (45%), proteinuria (50%) and acute kidney injury (60%). In reality the most frequently reported symptoms were fatigue and a diminished urine production which may be due to worsening of renal function and decreased removal of waste material from the body. The high percentage of proteinuria and hematuria is consistent with the pathogenesis of interstitial nephritis, which is renal tubulointerstitial inflammation leading to defective filtration, protein leakage and red blood cell excretion.

Acute kidney injury (AKI) in patients at 60 percent is in agreement with another research that PPI induced AIN is a major contributor to drug induced AKI. As shown in this, clinical significance of early detection of AKI (irreparable impairment of kidney) and drug cessation to ward off the vicious cycle of AKI is more than half of study population with AKI.

The laboratory results of affected patients were also interestingly abnormal, i.e. they had a lower estimated glomerular filtration rate (eGFR 45 ± 12 mL/min/1.73 m2) and elevated serum creatinine (mean 2.1 ± 0.5 mg/dL). The results show that those renal function is definitely lost and some are near certainly severe to moderately lost renal function. The continued elevation

of urine protein excretion (mean 400 ± 150 mg/day) is consistent with interstitial nephritis, as proteinuria is a hallmark of the tubulointerstitial renal diseases, and the data of Bradley et al. indeed present several other clinical features more frequently associated with tubulointerstitial diseases. Furthermore, differences in serum creatinine and eGFR levels suggesting that some patients presented with less damaging amount of renal dysfunction than others suggest that the disease is also clinically heterogeneous.

Histopathological analysis of renal samples revealed 85%, 60%, 30%, and 50% of patients with tubulointerstitial inflammation with eosinophilic infiltration, fibrosis and edema respectively. The high frequency of this diagnosis if confirmed by the most typical histological feature of interstitial nephritis, tubulointerstitial inflammation. More than half of the cases show interstitial nephritis due to the presence of eosinophilic infiltration, which are immunologic and hypersensitivity mediated.

Additionally, I was intrigued that 30 % of these patients had fibrosis, perhaps to no other end than that some of these patients were progressed to what used to be termed CKD 1 or chronic interstitial nephritis after late involvement and prolonged PPI use. PPIs are suspect in patients with suspected nephritis and the suspects should stop taking PPIs as soon as possible because irreversible renal damage is incurred.

Second, our results are consistent with the literature reports that PPIs induce an interstitial nephritis that is the main cause of AKI and CKD. Moledina and Perazella (2016) and Muriithi et al. (2017) also studied that PPIs are considerably responsible for the relative percentage of AIN mentioned by drugs. Different study populations and diagnostic criteria, however, alter incidence rates from 14% to 70%. The thing is the results we found match with the previous studies reporting that persons of age and middle aged are prone to develop renal problems due to PPI medication.

Additionally, our findings are corroborated by what Xie et al. (2017) found that chronic PPI use increases the likelihood of developing renal damage and progression of CKD. On top of that, in their research Fernández Juárez et al (2018) discovered that late PPI diagnosis and prolonged administration may lead to chronic interstitial nephritis and permanent renal scarring.

CONCLUSION

It was demonstrated in this study that PPI therapy over a long period of time is associated with significantly increased development of interstitial nephritis; consequently, PPI therapy patients are advised to be monitored for renal function. People over middle age and older are more at risk for developing interstitial nephritis unless they were on pills a year or less. Acute kidney damage (AKI), hematuria, proteinuria, tiredness and reduced urine output were the typical clinical manifestations of the affected patients. An important amount of renal impairment was indicated by laboratory data, such as increased urine protein excretion, low eGFR and raised serum creatinine. Histopathological investigation revealed a most common finding, which was tubulointerstitial inflammation in large numbers of cases with eosinophilic infiltration and fibrosis in many of them as well.

PPIs reported cases of acute kidney injury and also diagnosed cases of drug induced acute interstitial nephritis (AIN) constitute a large fraction of reported cases of acute kidney injury and when undiagnosed potentiated the development of CKD. Among patients, a fraction has fibrosis that suggests irreparable kidney injury from overuse of long-term PPI. Thus, medical professionals use PPIs so commonly there should be no prescription of them longer than a few months, and at risk patients should be carefully monitored for renal function. Early PPI withdrawal and prevention of interstitial nephritis development can prevent the development and improvement of renal outcomes.

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