

Proton pump inhibitor-induced acute interstitial nephritis

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What is already known about this subject

- In several case reports the use of omeprazole has been associated with interstitial nephritis.
- Recently there have been reports linking other proton pump inhibitors (PPIs) with interstitial nephritis.

What this study adds

- We present supplementary cases received by the Netherlands Pharmacovigilance Centre Lareb, concerning interstitial nephritis in users of PPIs including omeprazole, pantoprazole and rabeprazole.
- In this case series seven patients are presented. In six cases they recovered spontaneously after cessation of the PPI, in one case the patient recovered after treatment with a corticosteroid.
- Further support for this association comes from the worldwide adverse drug reaction database of the World Health Organization.
- This report shows that interstitial nephritis can occur with all PPIs. Health professionals should be aware of this potential serious adverse drug reaction.

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Aim

To investigate the association between the use of proton pump inhibitors (PPIs) and acute interstitial nephritis (AIN).

Methods

The Netherlands Pharmacovigilance Centre Lareb received seven case reports of AIN induced by various PPIs. In five of the reports it was mentioned that the diagnosis was confirmed by a renal biopsy.

Results

The time to onset varied between hours to 4 months. In all cases but one the patient spontaneously recovered after withdrawal of the offending agent. In one case the patient received treatment with prednisolone and recovered. In one patient a rechallenge was done 9 days after the initial event. Within 12 h of re-exposure the patient developed symptoms of AIN.

Conclusions

The mechanism of drug-induced AIN is unknown, but an immunological mechanism is suspected. Our reports show no relation between dosage, latency, time to recovery, age or gender, supporting the hypothesis that the aetiology of AIN is immunological. Lareb has received reports of AIN with the use of omeprazole, pantoprazole and rabeprazole. This shows that AIN is a complication associated with the whole group of PPIs and not only omeprazole. It is important for health professionals to be aware of this adverse drug reaction, because an accurate and timely diagnosis and withdrawal of the offending drug can prevent potentially life-threatening renal failure.

Introduction

Acute interstitial nephritis (AIN) is characterized by the presence of an inflammatory cell infiltrate in the interstitium of the kidney. AIN can lead to acute renal failure and it is estimated that AIN may be the cause in up to 15% of patients hospitalized for acute renal failure [1]. Patients with AIN typically present with nonspecific symptoms of acute renal failure, including oliguria, malaise, anorexia, nausea and vomiting. Although clinical and laboratory findings can be suggestive for AIN, there is no laboratory test available that can confirm the diagnosis; renal biopsy remains the golden standard [1, 2].

According to Michel and Kelly, causes of AIN can be classified into five general categories: drug hypersensitivity reactions, infections, kidney-limited or systemic autoimmune processes, idiopathic reactions and glomerular diseases. A biopsy specimen taken from a patient with glomerulonephritis often shows interstitial nephritis; however, this does not typically contribute to the classification of the glomerular lesion. Deterioration of renal function correlates more closely with interstitial pathology than with the extent of glomerular pathology and therefore Michel and Kelly believe that glomerulonephritis should be included as a cause of interstitial nephritis [2]. Drug-induced AIN was first described in 1968 with the use of methicillin [3]. Since then, the list of drugs causing AIN has grown to include several antimicrobial agents, nonsteroidal anti-inflammatory drugs, anticonvulsants and diuretics [4]. In 1992 the first case of omeprazole-induced AIN was published [5].

Case reports

We report a series of cases where AIN has occurred with the use of various proton pump inhibitors (PPIs). These reports were received from health professionals between 1 January 1998 and 1 December 2005 via the voluntary adverse drug reaction reporting system in the Netherlands. All reports except case A were submitted by specialists in internal medicine; case A was submitted by a hospital pharmacist. In cases F and G it was not reported if a biopsy had been performed, verifying the diagnosis of AIN. We assume that when a specialist in internal medicine reports an adverse drug reaction, they have accurately diagnosed the adverse drug reaction being reported. All seven cases are presented in Table 1. Two of these are discussed below in further detail.

Case A

Patient A is a man aged 51 years with a medical history of unspecified blood coagulation defects. He received treatment for leukaemia with cytostatics and several

adjuvant drugs including paracetamol, ciprofloxacin, fluconazole, furosemide, amphotericin B lipid complex, gentamicin and vancomycin (indication not provided). Pantoprazole therapy 40 mg once daily was initiated, indication not provided. Three weeks after initiation of pantoprazole all other drugs except piperacillin were withdrawn. One week later, the patient was admitted to hospital. On admission, C-reactive protein was elevated (52 mg l^{-1}) as well as serum creatinine ($108 \text{ } \mu\text{mol l}^{-1}$, baseline value $53\text{--}75 \text{ } \mu\text{mol l}^{-1}$). Treatment with piperacillin was started. Renal function deteriorated over the next few days, serum creatinine rising to a maximum of $395 \text{ } \mu\text{mol l}^{-1}$. Piperacillin, an agent known to cause AIN, was first withdrawn, but no improvement in renal function was seen. Two days later pantoprazole therapy was stopped and serum creatinine began to normalize. Renal biopsy showed 'widespread acute tubulo-interstitial nephritis with granuloma'. One month after pantoprazole withdrawal renal function had normalized, with a serum creatinine of $61 \text{ } \mu\text{mol l}^{-1}$.

Case B

Patient B is a man aged 57 years with a medical history of diverticulosis, oesophageal reflux due to a diaphragmatic hernia, and eczema. The reflux oesophagitis was initially treated with ranitidine, but was at a later stage changed to rabeprazole 20 mg daily. The patient was admitted to hospital after 3 weeks of daily temperature peaks up to 38.7°C , chills, increased micturation frequency and headache. On admission he had an arterial blood pressure of 164/101 mmHg, heart rate 98 bpm, no signs of icterus or oedema. Further physical examination revealed no abnormalities. Laboratory results showed increased erythrocyte sedimentation rate (67 mm h^{-1}), blood sodium (146 mmol l^{-1}) and serum creatinine ($307 \text{ } \mu\text{mol l}^{-1}$). Abdominal ultrasound showed no abnormalities. Renal biopsy revealed 'interstitial nephritis with unspecified minor to moderate glomerular sclerosis with predominantly interstitial changes. Signs of active glomerulonephritis were absent and immunofluorescence showed no abnormalities. Previous episodes of glomerulonephritis could not be excluded'. The patient's condition improved after withdrawal of rabeprazole. After 18 months the creatinine was $150 \text{ } \mu\text{mol l}^{-1}$ (value before the event $112 \text{ } \mu\text{mol l}^{-1}$) and the creatinine clearance was 55 ml min^{-1} according to the Cockcroft–Gault formula. Treatment was continued with ranitidine 300 mg daily.

Other cases

Patient F was given pantoprazole intravenously. The onset of events varied from hours to 4 months after initiation of PPI treatment. In all but one case an increase

Table 1
Reports of acute interstitial nephritis associated with the use of proton pump inhibitors

Patient, sex, age	Drug	Concomitant medication	Suspected adverse drug reaction	GFR ml min ⁻¹ per 1.73 m ² before AIN	GFR ml min ⁻¹ per 1.73 m ² during AIN	Biopsy	Time to onset, outcome
A, M, 51	Pantoprazole 40 mg od	Piperacillin*	Interstitial nephritis	>60	15	Yes	4 weeks, spontaneous recovery after withdrawal
B, M, 57	Rabeprazole 20 mg od	Coal tar/menthol shampoo, hydrocortison cream	Interstitial nephritis	Not reported	20	Yes	2 months, spontaneous recovery after withdrawal
C, M, 73	Omeprazole 40 mg od	Norflloxacin*	Interstitial nephritis	>60	8	Yes	4 months, spontaneous recovery after withdrawal
D, M, 70	Omeprazole 40 mg od	None	Interstitial nephritis	>60	7	Yes	12 days, spontaneous recovery after withdrawal
E, F, 76	Omeprazole 20 mg od solifenacine 5 mg od	Didlofenac*	Interstitial nephritis	Not reported	12	Yes	3 months (omeprazole), 3 days (solifenacine), drugs withdrawn, treatment with prednisolon, recovered
F, F, 18	Pantoprazole 40 mg, i.v.	Metoclopramide, paracetamol*	Abnormal renal function	>60	21	Not reported	Hours, spontaneous recovery within days after withdrawal
G, M, 69	Pantoprazole 20 mg	Nifedipine and paroxetine	Interstitial nephritis	Not reported	Not reported	Not reported	1 day, spontaneous recovery after withdrawal, positive re-challenge

*The glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula. *Drugs which have also been associated with acute interstitial nephritis. †Has been published elsewhere by the reporting physician [13].*

in serum creatinine was reported. Table 1 shows the glomerular filtration rate calculated using the abbreviated Modification of Diet in Renal Disease formula [6]. In five cases it was reported that the diagnosis of AIN was verified by renal biopsy. In six cases spontaneous recovery occurred after withdrawal of the offending agent. Patient E was treated with prednisolone and recovered. Patient G had a positive rechallenge 9 days after the first episode of AIN. Within 12 h of re-exposure the patient developed symptoms of AIN.

Discussion

In 1992 Ruffenach *et al.* were the first to report a case of omeprazole-induced AIN [5]. Since then, several cases of AIN due to omeprazole have been published. The first case report of pantoprazole-induced AIN was published in 2004 [7] and the first case of rabeprazole-induced AIN in 2005 [8]. Two cases of lansoprazole-induced AIN are mentioned in a study of drug-induced tubulo-interstitial nephritis secondary to PPIs in a renal unit in the UK [9].

Our reports show that AIN can be induced by various PPIs. This assumption is supported by data from the World Health Organization Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, where PPI-induced AIN is disproportionately present in the database. The reporting odds ratios are presented in Table 2. This databank contains more than 3.7 million spontaneous reports of adverse drug reactions from more than 80 countries worldwide. About 150 of these concern PPI-induced AIN, showing that this is a relatively rare condition.

Recently, Simpson *et al.* published a paper analysing 15 cases of AIN, which were identified in renal services in Auckland, New Zealand. Their calculations show that AIN occurred at eight per 10 000 patient-years in these centres [10].

Geevasinga *et al.* have published a study where the magnitude of PPI-induced AIN was investigated in Australia. A review of potential cases in two teaching hospitals revealed 18 cases of biopsy-proven PPI-induced AIN [11]. In a study by Torpey *et al.*, eight cases were identified in a single hospital in the UK [9].

A possible explanation for the discrepancy between the number of cases found in retrospective studies and those reported via the spontaneous reporting schemes might be that medical doctors are not aware that PPIs can cause AIN.

Patient A used piperacillin, which can also cause AIN. Piperacillin was started upon admission when renal function was already impaired and was first withdrawn without effect on renal function. Only when pantoprazole was withdrawn 2 days later normalization of the renal function was observed.

Patient C was using norfloxacin, which is also known to cause AIN. However, the patient had used omeprazole earlier and suffered from flank pain, malaise and a dry mouth. Omeprazole was then temporarily stopped. When omeprazole was restarted the same symptoms reappeared. The treating physician prescribed norfloxacin, suspecting the patient was having a urinary tract infection. This had no effect on the symptoms.

In case H solifenacin was also reported as the suspect drug. However, AIN due to solifenacin has not previously been described in the literature.

The mechanism of drug-induced AIN is unknown, but an immunological basis is suspected. Drugs can elicit an immune response leading to AIN in different ways. The drug can bind to a normal component of the tubular basement membrane (TBM) and act as a hapten or the drug can mimic an antigen normally present within the TBM or the interstitium and induce an immune response that will also be directed against this antigen. Other ways to evoke an immune response include the drug binding to the TBM or deposit within the interstitium and act as a planted (trapped) antigen. The drug can also elicit the production of antibodies and become deposited in the interstitium as circulating immune complexes [4].

The hypothesis that drug-induced AIN has an immunological basis is supported by our reports. The characteristics of the reports we have received are diverse, with no relation in gender, age, latency or time to recovery. Furthermore, a dose-response relationship has not been established.

Because AIN is thought to be an immune-mediated disorder, drugs that modulate the immune response, especially corticosteroids, have been used in the treatment of AIN. The effect of corticosteroid therapy on the outcome of AIN, measured as serum creatinine, has been

Table 2

Number of reports and reporting odds ratios (ROR), with a 95% confidence interval, on the association proton pump inhibitor and interstitial nephritis received by the World Health Organization Collaborating Centre for International Drug Monitoring in Uppsala, Sweden

Drug	Number of reports	ROR	95% CI
Esomeprazole	7	6.6	3.2, 13.9
Lansoprazole	18	4.9	3.1, 7.8
Omeprazole	109	9.4	7.8, 9.4
Pantoprazole	15	9.0	5.4, 15.0
Rabeprazol	10	8.8	4.7, 16.3

studied. No statistically significant difference in serum creatinine was seen between treated and nontreated groups [12]. In our reports only one patient had been treated with corticosteroids. In all other cases withdrawal of the offending agent was sufficient for recovery.

AIN is difficult to diagnose, as symptoms are nonspecific, including oliguria, malaise, anorexia, nausea and vomiting. Some symptoms of AIN might initially be confused with the illness the drug was originally prescribed for, leading to a delay in diagnosis.

Lareb has received reports of AIN with the use of omeprazole, pantoprazole and rabeprazole. This shows that AIN is a complication associated with all PPIs. It is important for health professionals to be aware of this adverse drug reaction, because accurate and timely diagnosis and withdrawal of the offending drug can prevent potentially life-threatening renal failure.

Competing interests: None declared.

The views expressed are purely those of the authors and may not in any circumstances be regarded as stating an official position of the World Health Organization.

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