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Case Report

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Inadequate drug prescription and the rise in drug-induced acute tubulointerstitial nephritis incidence

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Abstract

Drugs are a frequent cause of acute tubulointerstitial nephritis (ATIN). Antibiotics, non-steroidal anti-inflammatory drugs and recently proton pump inhibitors stand among the most commonly responsible ones. However, their respective responsibility is not well known. This study reports 33 cases of drug-induced ATIN (DI-ATIN), the most frequent ones being metamizole and omeprazole. Clinicians often fail to diagnose DI-ATIN because its signs and symptoms are non-specific and differ from the now classic form observed with methicillin. Furthermore, drugs causing ATIN are too often prescribed unnecessarily. This study shows that in more than one-fifth of our cases, ATIN complicated prescription of a drug that was not justified by an adequate clinical indication. The consequences were noxious for the patients and costly in terms of public health expenses.

Keywords: acute tubulointerstitial nephritis; incidence; NSAIDs; proton pump inhibitors

Introduction

About 15% of biopsies for acute renal failure (ARF) show that it is caused by drug-induced acute interstitial nephritis (DI-ATIN) [1], mostly immunoallergic [2]. This study reviews the cases of DI-ATIN reported to the Adverse Drug Reaction Monitoring by our Nephrology Service (January 2000–October 2008) located in a hospital with a catchment population of 300 000. The incidence of this subset of ARF was estimated by taking into account patients who were diagnosed as DI-ATIN at admission (excluding those occurring during hospitalization) and patients exposed to NSAIDs, analgesics, and proton pump inhibitors (PPIs). The number of cases was divided by the number of subjects exposed to each drug, as estimated by their consumption charged to the Public Health System (covering 99% of the population). This consumption was converted into the defined daily doses (DDD) and the number of patients exposed by assuming that each patient was treated for 3 months (result extrapolated to 1 year) with NSAIDs or non-opioid analgesics and 12 months with PPIs. It was also assumed that the exposed population was numerous and the number of cases was small [3]; therefore, the estimate of DI-ATIN would have a Poisson distribution, and the confidence intervals (95% CI) should be exact binomials with Poisson approximation [4].

Cases

A total of 33 cases of DI-ATIN were included (25 were admission by DI-ATIN, and 8 occurred during hospitalization).

The clinical characteristics of the patients are summarized in Table 1. One patient had the ‘classic triad’ (fever, rash and eosinophilia), two patients had two symptoms (rash and eosinophilia), 12 patients had one symptom (7 eosinophilia, 5 fever and 0 rash) and 18 patients had none. Twenty-three patients (68%) fully recovered their renal function, but in 10 (30.3%), including the one who required haemodialysis and was the most clinically affected, the recovery was incomplete (serum creatinine at 7 months >25% of baseline). The diagnosis was confirmed by renal biopsy in 14 (42%) of the 33 cases.

The drugs responsible of ATIN were: non-opioid analgesics [n = 12 cases, metamizole (10), propyphenazone (1) and paracetamol (1)]; NSAIDs [n = 14 cases, ibuprofen (5), acetylsalicylic acid (3), aceclofenac (2), diclofenac (2), naproxen (1) and ketoprofen (1)]; antibiotics [n = 9 cases, ciprofloxacin (3), co-amoxiclav (1), clarithromycin (1), cloxacillin (1), benzylpenicillin (1) and co-trimoxazole (1)]; PPIs [n = 11 cases, omeprazole (10) and pantoprazole (1)]; and others (n = 4 cases, allopurinol, citalopram, clodronate and chlortalidone—one case each). Twenty patients took only one suspect drug, 10 patients took 2 and three patients took 3 (of whom, one took paracetamol and ibuprofen occasionally, and diclofenac daily during

Table 1. Clinical characteristics of the patients

Age (years) (mean ± SD)	68.7 ± 16.9
Gender (M/F)	22/11
Fever	6 (18%)
Skin rash	3 (9%)
Eosinophilia (>500 eosinophils/mm^3)	10 (30%)
Oliguria	2 (6%)
Proteinuria	18 (55%)
Microhaematuria	23 (70%)
Leukocyturia	23 (70%)
Serum creatinine (mg/dL)* (mean ± SD)	
Baseline	1.1 ± 0.3
Highest (range 1.4 – 10.4)	3.9 ± 2.2
At 7 months	1.4 ± 0.5
Kidney biopsy	14 (42%)
Corticosteroid treatment	11 (33%)

M, male; F, female.
*To convert to μmol/L, multiply by 88.4.

6 months). Eleven patients (33%) were treated with corticosteroids (of whom, five recovered completely).

Among the 25 patients admitted for DI-ATIN, in three cases (metamizole and omeprazole for fever; metamizole for dysuria—both cases self-medicated; and pantoprazole for unknown reasons), drugs were considered as unnecessary. Moreover, in four cases (propifenazone for headache—self-medicated, omeprazole for dyspepsia, omeprazole for epigastralgia and metamizole for back pain), the appropriate drug should have been different. In eight cases that occurred during hospitalization, the prescription of the drug causing ATIN was considered as appropriate. Thus, preventability would have been possible in a substantial number [7 (21.2%)] of our cases.

The incidence of ATIN (admissions) for NSAIDs ranged from 0.6 cases per 10 000 patient-year for diclofenac to 26.84 for ketoprofen. With non-opioid analgesics, there were 0.32 cases per 10 000 patient-year for paracetamol and 10.48 for metamizole, whereas for PPIs, there were 1.06 cases per 10 000 patient-year for pantoprazole and 1.07 for omeprazole (Table 2).

Discussion

Numerous drugs have been associated with ATIN (penicillins, cephalosporins, sulphonamides, NSAIDs [5,6] and PPIs [7]). In our study, the most frequent drugs that cause DI-ATIN were NSAIDs, non-opioid analgesics and PPIs.

Paracetamol might be considered as a disputable cause of DI-ATIN. In one case, we attributed the causality only to diclofenac; however, the offending role of paracetamol, although minor, cannot be excluded. In the Spanish Adverse Drug Reaction Monitoring database (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS), there are 3204 reports of adverse reactions associated with paracetamol; of which, six only are ATIN (this case included), and in all of them, there was another drug suspected. In the Medicines and Healthcare Products Regulatory Agency database (MHRA, the UK agency), there are 4072 reports of adverse reactions associated with paracetamol; of which, only three are ATIN (in one case, the only suspected drug was paracetamol, and in the other two, there were also other drugs considered as causative) [8].

In clinical practice, it is not easy to identify the drug responsible for DI-ATIN, especially in elderly patients taking several medications. This study included 33 cases (49 suspected drugs).

The clinical signs of DI-ATIN vary depending on the drug and the patient's response [5]. The classic triad described in methicillin-associated ATIN is now identified in <5% [2]. In this study, only one patient presented the triad.

Table 2. Incidence of acute tubulointerstitial nephritis associated with NSAIDs, non-opioid analgesics and proton pump inhibitors (admissions for ATIN only)

Drug	ATIN cases	Number of DDDs	Number of patients	Incidence rate per 10 000 patient-year (95% CI)
NSAIDs				
Aceclofenac	2	1 771 777	19 686	4.08 (0.48–14.68)
Diclofenac	1	5 896 045	65 512	0.60 (0.01–3.40)
Ketoprofen	1	134 074	1490	26.84 (0.68–149.56)
Ibuprofen	4	11 902 922	132 255	1.20 (0.32–3.08)
Naproxen	1	2 752 554	30 584	1.32 (0.04–7.28)
ASA* analgesic dose	1	1 834 649	20 385	1.96 (0.04–10.92)
ASA* antiplatelet dose	2	23 482 820	64 292	1.24 (0.16–4.48)
Non-opioid analgesics				
Metamizole	5	1 714 474	19 050	10.48 (3.40–24.52)
Paracetamol	1	10 964 176	121 824	0.32 (0.00–1.84)
Proton pump inhibitors				
Esomeprazole	0	887 138	2429	
Lansoprazole	0	2 099 860	5749	
Omeprazole	9	30 707 768	84 073	1.07 (0.49–2.03)
Pantoprazole	1	3 441 144	9421	1.06 (0.03–5.91)
Rabeprazole	0	609 112	1668	

ASA, acetylsalicylic acid; ATIN, acute tubulointerstitial nephritis; DDDs, defined daily doses.

Treatment consists of withdrawing the medication to improve renal function.

However, 40% of patients with DI-ATIN may have persistently high creatinine levels, indicating irreversible kidney damage [2]. Treatment with steroids has been advocated in cases confirmed by biopsy that do not improve with withdrawal of the offending drug as, if begun early, this may speed up recovery of the renal function by delaying the transformation of interstitial infiltrate into fibrotic areas, the histological basis of chronic kidney failure [1].

The incidence found for ketoprofen and metamizole was higher than that described for NSAIDs [9]. The incidence for PPIs was similar to that described in the literature [10]. In any case, they were low compared with methicillin [10].

This study has limitations: (i) the assumption that the patients took the drugs as prescribed, and therefore, in the event of a low compliance, the incidence would be greater; (ii) the unduly low reporting of severe adverse reactions in Spain [11]; (iii) it was assumed that all patients with DI-ATIN attended their referral hospital as there were no other hospitals in the region; and (iv) the lack of a biopsy in all patients, as we considered it unethical to perform a kidney biopsy in cases with a rapid improvement of renal function when the drug is withdrawn.

In conclusion, the incidence of DI-ATINs changes along with inappropriate drug prescription trends. DI-ATIN is an increasingly common cause of ARF. Clearly, drugs such as PPIs, non-opioid analgesics and NSAIDs are too often prescribed without sound reasons to do it, and this is especially true of metamizole and omeprazole.

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