5-Aminosalicylic Acids and the Risk of Renal Disease: A Large British Epidemiologic Study

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Background & Aims: This study was performed to quantify the risk of renal disease in patients using aminosalicylates (5-ASA). *Methods:* Data from the United Kingdom General Practice Research Database were used to estimate the incidence of renal disease in adult patients with inflammatory bowel disease (IBD) or prescription for 5-ASA and in patients without IBD. In a nested case-control analysis, each case of renal disease was matched to 5 controls. *Results:* Among the 19,025 5-ASA users with IBD, 130 patients developed renal disease (incidence rate of 0.17 cases per 100 patients per year). The incidence among patients with IBD but without 5-ASA use was 0.25 and among patients without IBD was 0.08. In the case-control analysis, the crude odds ratio (OR) for renal disease in current 5-ASA users was 1.60 (95% confidence interval [95% CI]: 1.14–2.26); the adjusted OR was 0.86 (95% CI: 0.53–1.41). For recent users, the crude OR was 4.18 (95% CI: 2.59–6.76) and adjusted OR 2.48 (95% CI: 1.33–4.61); for past users (last prescription more than 12 months before), 1.71 (95% CI: 1.09–2.70) and 0.99 (95% CI: 0.55–1.76), respectively. Although the numbers were small, mesalazine and sulfasalazine users had comparable risks (crude OR for current and recent users of OR 2.08 [95% CI: 1.44–3.01] and 1.84 [95% CI: 1.20–2.82], respectively). In only a few records was renal disease attributed to interstitial nephritis or 5-ASA use. *Conclusions:* Users of 5-ASA have an increased risk of renal disease that may be partly attributable to the underlying disease. Although renal disease is a recognized adverse effect of 5-ASA, the incidence appears to be low and does not appear to be related to either the dose or type of 5-ASA used.

There have been many case reports of renal disease associated with 5-aminosalicylic acids (5-ASA), specifically interstitial nephritis and nephrotic syndrome,[1–21] and, in a recent analysis of reports of suspected adverse drugs reactions submitted to the United Kingdom regulatory authority, interstitial nephritis was reported more frequently for mesalazine than for sulfasalazine.[22] Because adverse reactions are not always recognized or reported to the regulatory authorities by physicians, these reports do not allow an accurate calculation of the incidence of an adverse drug reaction. Also, under reporting is usually not random but selective, which may introduce serious bias when comparing different drugs.[23] The aim of the present study was to quantify the incidence of renal disease in patients using 5-ASA for the treatment of IBD and to compare the risks of different 5-ASA types.

Materials and Methods

Data Source

In the United Kingdom, health care delivery is centered on general practitioners (GPs) whose responsibilities include primary health care and specialist referrals. The information for this study was obtained from the General Practice Research Database (GPRD), which contains the computerized medical records of general practices across the United Kingdom.[24] Approximately 6% of the total registered population of England and Wales is represented in the database, and it includes a cumulative total of about 5 million adult patients. The age and sex distribution of patients enrolled is representative of the general English and Welsh populations. The data accrued in the GPRD include demographic information (including patient's sex and year of birth), prescription details, clinical events, preventive care, referrals to specialist care, and hospital admissions and their major outcomes. The data quality of each entry into GPRD is measured against specific targets, developed by comparisons with external statistics, to ensure that research standards are met. Only data from practices that pass this quality control are compiled to form the GPRD database. Data collection for the GPRD began in 1987 and, for this study, ended in 2001. Previous studies of GPRD data have reported a high level of data validity.[25–27] A valida-

tion study of IBD reported a high level of accuracy of IBD recording.[27] Also, the estimated prevalence of Crohn's disease (CD) and ulcerative colitis (UC) in the GPRD population[27] was found to be comparable with those reported in another United Kingdom study.[28]

Study Population

We screened the GPRD for all permanently registered adults aged 18 years or older who were either prescribed a 5-ASA formulation or pro-drug or who had a record of IBD. The 5-ASA drugs included balsalazide sodium, mesalazine, olsalazine sodium, and sulfasalazine. The approved indications in the United Kingdom for balsalazide sodium, mesalazine, and olsalazine sodium are treatment of mild to moderate UC and maintenance of remission; for approved indications for sulfasalazine, these are treatment of mild to moderate ulcerative colitis, maintenance of remission, active CD, and, also, active rheumatoid arthritis (RA).[29] Given these different indications, patients who only used sulfasalazine were classified according to the presence or absence of IBD in the medical records. The study population was divided into 3 cohorts. The first cohort, referred to as "5-ASA/IBD," included either patients who received a prescription during the period of data collection for balsalazide, mesalazine, or olsalazine, or included patients who received sulfasalazine and who had a record indicating the presence of IBD. The second cohort ("IBD/no 5-ASA") consisted of patients who had a history of IBD but no 5-ASA prescribed during the period of data collection. The third cohort ("sulfasalazine RA") included the remaining sulfasalazine users. A reference cohort was selected consisting of patients without a history of IBD or prescription for 5-ASA, who were matched by age (within 5 years), sex, and medical practice. They were also matched by calendar time (i.e., they had to be registered at the practice at the date of the first record of IBD or first 5-ASA prescription of their matched patient). In the event of no eligible control patient within 5 years of age, an age- and sex-matched control patient was selected from another practice.

Cohort Analysis

In the cohort analysis, the rates of incident renal events during follow-up were estimated. The 5-ASA/IBD cohort was followed from the first 5-ASA prescription during the period of data collection up to the end of data collection. For the IBD/no ASA cohort, follow-up started at the first record of IBD during the period of data collection. The renal events included acute glomerulonephritis (International Classification of Diseases 9th Revision [ICD-9], 580); nephrotic syndrome (581); chronic glomerulonephritis (582); other nephritis or nephropathy (583); and acute, chronic, or unspecified renal failure (584 to 586).

Nested Case-Control Analysis

To evaluate the effect of the exposure patterns on the risk of renal events, we used a nested case-control analysis. This analysis was conducted in the patients from the 5-ASA/IBD cohort, patients from the IBD/no 5-ASA cohort, and the matched reference patients for these 2 cohorts. In these cohorts of patients, all those with a first record of renal disease during follow-up were identified ("cases"); the index date was the date of the first record of renal disease. Each case was then randomly matched to 5 patients without renal disease ("controls") by age, sex, and calendar time. For the age matching, cases and controls were matched by year of birth. If control was found, this age-matching criterion was expanded, stepwise, by 1 year of age, to a maximum of 5 years. The exposure to 5-ASA was based on the prescription information prior to the index date. Current users were patients who had received their last 5-ASA prescription in the 3 months preceding the index date; recent users, within 3 to 12 months; and past users, more than 12 months before the index date. The daily dose of 5-ASA was obtained from the written dosage instructions for the last prescription prior to the index date and the strength of the tablet. History of IBD and the type of IBD (UC or CD) was measured; duration of IBD was based on the time between the index date and the first record of IBD or 5-ASA prescription, whichever date came first.

As part of this study, the GPs were requested to reply to a questionnaire and provide discharge summaries or diagnostic reports on the renal disease. The questionnaire requested details on the renal disease (acute or chronic renal failure and type of renal disease) and the cause of the renal disease. Patients who died or left the practice were excluded because their medical notes were no longer present at the practice. Also, validation was restricted to practices that were still registered with GPRD. We also requested anonymous free-text information from the computerized GPRD medical records. GPs can enter uncoded free-text information into the records, but this information is not routinely provided to researchers for reasons of patient confidentiality. All free-text information as recorded by the GP on the date of the renal event was reviewed for mention of interstitial nephritis.

Statistical Analysis

In the cohort analysis, incidence rates of renal events were calculated by dividing the number of cases by the total number of person-years of follow-up. Age- and sex-adjusted relative rates (RR) were estimated using Poisson regression models. In the case-control analysis, the odds ratio (OR) of incident renal events was calculated by comparing patients with and without a renal event. Conditional logistic regression models included current, recent, and past use of 5-ASA. The analysis was controlled for clinical variables and drug use that have been associated with risk of renal failure. These included a history of diabetes mellitus (ICD-9, 250), heart disease (393–398, 410–414, 420–429), hypertensive disease (401–405), malignancy (140–208, 235–238) and other diseases of urinary system: renal sclerosis, small kidney, and disorders from impaired renal function (587–599). Prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, angiotensin-converting enzyme (ACE) inhibitors, diuretics, β-adrenoceptor-blocking drugs and other antihypertensives,

Table 1. Incidence Rates of Renal Events in the Different Study Cohorts

	5-ASA IBD cohort			IBD/no 5-ASA cohort			Sulfasalazine RA cohort			Reference cohort (no 5-ASA use or IBD)		
Characteristic	No. of cases	Rate[a]	Age- and sex-adjusted RR (95% CI)	No. of cases	Rate[a]	Age- and sex-adjusted RR (95% CI)	No. of cases	Rate[a]	Age- and sex-adjusted RR (95% CI)	No. of cases	Rate[a]	Age- and sex-adjusted RR (95% CI)
Overall	130	0.17	2.29 (1.78–2.94)	33	0.25	3.58 (2.43–5.27)	166	0.29	3.33 (2.62–4.22)	115	0.08	Reference
Age (yr)												
18–34	12	0.06		1	0.03		2	0.03		3	0.01	
35–49	20	0.08		5	0.13		19	0.13		8	0.02	
50–64	27	0.15		8	0.26		64	0.32		28	0.07	
65–79	57	0.44		18	0.88		74	0.52		57	0.19	
80+	14	0.62		1	0.21		7	0.42		19	0.40	
Women	48	0.12		19	0.24		107	0.29		55	0.07	
Men	82	0.22		14	0.26		59	0.29		60	0.10	

[a]Number of cases per 100 person-years.

and antibacterial drugs in the 12 months prior to the index date were also ascertained. Furthermore, the analysis was adjusted for indicators of underlying disease severity, including history of IBD, hospitalization for a gastrointestinal disorder (GI) in the previous 12 to 24 months, and prescriptions for oral and rectal glucocorticoids and disease-modifying agents (azathioprine, methotrexate, or cyclosporine) in the 3 months prior to the index date. Severity of IBD was assessed by considering the number of GP visits for symptoms (previous history of GP visits for diarrhea, abnormal pain, anemia, rectal bleeding, or weight loss) in the year prior to the index date. Final regression models were determined by backward elimination using a significance level of 0.25.

Results

A total of 37,984 patients in the GPRD population had a record of IBD or a prescription for 5-ASA; 19,025 were assigned to the 5-ASA/IBD cohort. The mean age of these patients was 48 years, and 53.0% were women. They were followed for an average of 6 years. Their mean number of 5-ASA prescriptions during follow-up was 19.4 (median 10): The mean duration of each prescription was 1 month. The distribution of the type of prescribed 5-ASA in the 5-ASA/IBD cohort was as follows in these patients: mesalazine (57.9%), sulfasalazine (37.2%), olsalazine (4.6%), and balsalazide (0.4%). Information was available on the formulation for about 43% of the mesalazine prescriptions (of those, 88.3% of the prescriptions were for Asacol, 11.3% Pentasa, and 0.4% Salofalk). There were 4079 patients with a history of IBD but without use of 5-ASA. The sulfasalazine/RA cohort consisted of 14,880 patients.

A total of 130 patients out of the 19,025 patients in the 5-ASA/IBD cohort developed renal disease during follow-up, giving an incidence of 0.17 cases per 100 patients per year in this cohort (Table 1). In comparison, the rate in the reference cohort (i.e., patients without IBD and 5-ASA use) was 0.08, whereas the rate in the IBD/no 5-ASA cohort was 0.25.

There were 230 cases of incident renal disease in the 2 IBD cohorts and their reference patients. The most frequent diagnostic codes recorded were renal failure (198 patients), followed by nephritis or nephropathy (16) and nephrotic syndrome (14). These cases were matched by age and sex to 1150 controls. Table 2 shows the characteristics of those cases and controls; the majority of cases (84.8%) had a history of conditions that are risk factors for renal disease.

Table 3 shows the ORs of incident renal events according to 5-ASA use. The unadjusted risk of incident renal events was increased in current and recent users of 5-ASA with ORs of 1.60 and 4.18, respectively. After adjustment, this excess risk disappeared in current users but not in recent users. Therefore, to include cases with a delayed diagnosis, an analysis was conducted combining current and recent 5-ASA users. The ORs were as follows: crude OR, 2.04 (95% CI: 1.50–2.78) and adjusted OR, 1.14 (95% CI: 0.73–1.80); mesalazine users crude OR, 2.08 (95% CI: 1.44–3.01) and adjusted OR, 1.10 (95% CI: 0.67–1.82); sulfasalazine users crude OR, 1.84 (95% CI: 1.20–2.82) and adjusted OR, 1.05 (95% CI: 0.58–1.90).

There was no relationship between risk of renal events and daily dose or type of 5-ASA: Users of mesalazine and sulfasalazine had comparable risks (Table 4).

Additional analyses were conducted to evaluate the robustness of the findings. Exclusion of cases or controls who were hospitalized in the 6 months before the index date (and who may have started 5-ASA treatment in the hospital) did not alter the results (crude OR for current 5-ASA use, 1.83 [95% CI: 1.15–2.93]; adjusted OR,

Table 2. Characteristics of Renal Cases and Controls

Characteristics	Cases (n = 230)	Controls (n = 1150)	Crude OR (95% CI)
Mean age, *yr*	67	67	
Female	97 (42.2%)	485 (42.2%)	
Drug use			
NSAIDs	63	213	1.65 (1.19–2.28)
Paracetamol	102	323	2.08 (1.55–2.81)
ACE inhibitors	55	88	4.38 (2.90–6.61)
Diuretics	120	256	4.82 (3.43–6.77)
Oral glucocorticoids	29	86	1.95 (1.24–3.06)
Rectal glucocorticoids	11	45	1.36 (0.69–2.70)
Disease modifying agents	18	7	2.11 (0.88–5.09)
Medical history			
Diabetes	25	64	2.11 (1.29–3.46)
Heart disease	96	251	3.06 (2.19–4.28)
Hypertension	92	254	2.61 (1.89–3.60)
Malignancy	48	119	2.36 (1.62–3.46)
Other renal disorders[a]	88	231	2.53 (1.86–3.46)
Prior hospitalization for GI disorder	14	29	2.50 (1.30–4.81)
Number of symptoms			
1	65	136	3.46 (2.42–4.94)
2+	25	23	8.06 (4.32–15.04)
Inflammatory bowel disease			
UC	74	316	1.76 (1.26–2.45)
CD	53	134	3.10 (2.11–4.56)

[a]Other diseases of urinary system: renal sclerosis, small kidney, disorders from impaired renal function.

0.84 [95% CI: 0.39–1.80]). Analysis without an indicator of IBD disease yielded an adjusted OR for current 5-ASA use of 1.16, and an analysis without indicators of IBD disease, GI symptoms, or hospitalization yielded an adjusted OR for current 5-ASA use of 1.50. A separate case-control analysis, conducted only in the 5-ASA/IBD cohort and their reference patients (and not including the patients from the IBD/no 5-ASA cohort) yielded comparable results. Medical records were also reviewed for any symptoms of renal disease prior to the index date (such as hematuria or proteinuria). Again, similar results were found when 5-ASA exposure was evaluated relative to a date of first symptoms of renal disease.

In addition to the review of diagnostic codes recorded (2 cases were coded as interstitial nephritis), we searched for cases of interstitial nephritis or renal disease possibly induced by 5 ASA in 2 other ways. First, we examined the comments of the GP in the computerized medical record. There were 3 cases with GP comments suggesting a possible role of 5-ASA treatment in the development of renal disease (2 mesalazine and 1 balsalazide users). Second, we sent a questionnaire to the GPs of 39 cases; 35 returned questionnaires were analyzed. The diagnosis of renal disease was confirmed by the GP in 91% of the cases; 70% of the confirmed cases concerned chronic renal failure. There were 5 cases with either

Table 3. Use of 5-ASA and Risk of Renal Events

Use of 5-ASA	No. of cases	No. of controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Non use	102	699	Reference	Reference
Current use	66	282	1.60 (1.14–2.26)	0.86 (0.53–1.41)
Number of prior prescriptions				
1–4	8	35	1.61 (0.72–3.62)	0.52 (0.20–1.35)
5–12	16	61	1.75 (0.97–3.17)	1.18 (0.57–2.45)
13+	42	186	1.55 (1.04–2.32)	0.86 (0.49–1.50)
Recent use	33	53	4.18 (2.59–6.76)	2.48 (1.33–4.61)
Number of prior prescriptions				
1–4	16	24	4.46 (2.29–8.67)	3.06 (1.32–7.11)
5–12	4	12	2.09 (0.67–6.56)	1.81 (0.53–6.22)
13+	13	17	5.62 (2.60–12.14)	2.31 (0.91–5.88)
Past use	29	116	1.71 (1.09–2.70)	0.99 (0.55–1.76)

[a]Adjusted ORs are based on multivariate logistic regression models, including diabetes mellitus, heart disease, hypertensive disease, malignancy and other renal diseases, use of ACE-inhibitors, diuretics, other antihypertensives and antibacterial drugs, history of IBD, prior hospitalization for a GI disorder, and number of GP visits for IBD symptoms in the previous 12 months.

Table 4. Daily Dose and Type of 5-ASA and Risk of Renal Events

Use of 5-ASA	Type 5-ASA	Daily dose[a]	No. of cases	No. of controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Any prior use (current, recent, or past)	Mesalazine		72	241	2.05 (1.46–2.86)	1.13 (0.71–1.78)
	Sulfasalazine		48	187	1.75 (1.19–2.56)	0.98 (0.57–1.70)
	Other types		8	23	2.63 (1.11–6.27)	1.33 (0.47–3.71)
Current use	Mesalazine		33	149	1.54 (1.00–2.37)	0.79 (0.45–1.39)
		<2 g	22	96	1.57 (0.95–2.62)	0.86 (0.47–1.59)
		≥2 g	9	40	1.54 (0.72–3.27)	0.83 (0.31–2.19)
	Sulfasalazine		30	121	1.67 (1.06–2.65)	0.94 (0.50–1.77)
		<2 g	13	33	2.63 (1.34–5.17)	1.93 (0.82–4.55)
		≥2 g	16	72	1.50 (0.82–2.74)	0.73 (0.34–1.56)
Recent use	Mesalazine		22	35	4.41 (2.48–7.86)	2.75 (1.33–5.68)
		<2 g	14	18	4.73 (2.30–9.75)	4.37 (1.87–10.25)
		≥2 g	5	7	4.34 (1.36–13.84)	1.08 (0.28–4.22)
	Sulfasalazine		7	17	2.69 (1.10–6.58)	1.48 (0.51–4.34)
		<2 g	2	3	4.38 (0.72–26.57)	2.83 (0.40–19.99)
		≥2 g	2	12	1.05 (0.23–4.75)	0.56 (0.10–3.03)

[a]Daily dose based on the last 5-ASA prescription; information missing in 62 patients.

interstitial nephritis or with drug-induced renal disease according to the GP. In total, there were 10 cases of interstitial nephritis or renal disease possibly induced by 5-ASA (5 in mesalazine users, 4 in sulfasalazine users, and 1 in a balsalazide user).

Discussion

This study found that IBD patients who were 5-ASA users had an increased risk of renal disease. However, after adjustment, the risks of 5-ASA users were comparable with controls. In only a few records was renal disease attributed to interstitial nephritis or 5-ASA use. These findings indicate that the incidence of 5-ASA-induced renal disease is rare.

We also found that both IBD patients not using 5-ASA drugs and past 5-ASA users had increased risks of renal disease. Risk of renal disease was related to indicators of IBD severity, such as prior hospitalization for GI disorders, number of IBD symptoms, and recent use of oral glucocorticoids and disease-modifying agents.

The exact mechanism for this increase is unknown, but it has been reported that the kidney is an extraintestinal target of IBD. These manifestations of IBD include acute renal failure, glomerular abnormalities, and tubular proteinuria.[30] Recently, Izzedine et al. reported on 4 patients with Crohn's disease who developed severe interstitial nephritis and were not treated with 5-ASA.[31] Other studies have found that renal tubular proteinuria was related to IBD disease activity.[32–35] Thomas et al. reported that, in a small case series, the incidence of biopsy-proven glomerulonephritis was higher in patients with ulcerative colitis.[36] These findings suggest that IBD itself may lead to an increased risk of renal disease.

An unexpected finding in this study was that recent 5-ASA users had an increased risk of renal disease com-

pared with nonusers. There was no indication in our data of greater disease severity in recent users (e.g., the use of oral glucocorticoids and prior medical history were comparable between recent and current users). But similar to the 5-ASA analysis, recent users of oral glucocorticoids and disease-modifying agents also had increased risks of renal disease (crude OR of 2.82 [95% CI: 1.71–4.63] and 3.90 [95% CI: 1.93–7.87], respectively). The reason for this increase in recent users is unknown.

On the basis of animal studies, it might be hypothesized that the development of 5-ASA-induced interstitial nephritis would be dose related. In these studies, the kidney was the principal target organ of 5-ASA toxicity, which primarily took the form of dose-related renal papillary necrosis.[37,38] In addition, 5-ASA has structural similarities to the analgesics phenacetin and salicylic acid, both known to cause renal lesions (specifically, papillary necrosis) in humans if taken in high doses for long periods of time. However, use of 5-ASA is generally not associated with renal papillary necrosis in humans,[39] whereas interstitial nephritis has been seen in patients taking low doses of 5-ASA.[4,7,17] In the current study, there was no relationship between 5-ASA dose and the risk of renal disease. These findings and the low overall incidence of renal disease during 5-ASA treatment suggest that the renal reactions may be idiosyncratic rather than dose related in nature. The information that we had on renal disease mostly concerned its presentation (i.e., renal failure), rather than the underlying renal pathology (e.g., interstitial nephritis). Our search for cases of interstitial nephritis or drug-induced renal disease yielded only a small number of cases. Although it is likely that we have not identified all cases with drug-induced renal toxicity, this low number of drug-induced cases and the comparability of the rates between 5-ASA users and

controls support other studies that reported that the incidence of renal toxicity associated with 5-ASA treatment is rare.[40–42]

Sulfasalazine is a pro-drug metabolized into free mesalazine by the bacterial flora in the colonic lumen. An analysis of reports of suspected adverse drug reactions submitted to the United Kingdom regulatory authority suggested that interstitial nephritis may occur more frequently with mesalazine than sulfasalazine.[22] One could hypothesize that this may be related to larger and higher systemic exposure of mesalazine because of a more rapid release in the intestine compared with other products. A recent systematic review of the pharmacokinetic profiles of 5-ASA-containing products found that the total systemic absorption as measured by 24-hour urinary excretion and the maximum plasma levels of 5-ASA or its metabolites were comparable between different 5-ASA formulations.[43] Although the numbers were small, there was no clear indication in this study of higher rates of renal disease with mesalazine (88% of which was Asacol) compared with sulfasalazine.

This study has several strengths and limitations. It is a large population-based study with near-complete collection of significant medical events that allows reasonable estimates on the incidence of renal disease in 5-ASA users in an unselected population in routine clinical practice. The main limitation of this study is that patients were not randomized to treatment and, therefore, interpretation as to the etiology needs to be made with caution. The IBD/no 5-ASA cohort may have included some patients who were at risk of developing renal disease and who were not therefore prescribed 5-ASA treatment. We also had relatively crude information on the disease activity of IBD, such as drug use or a recorded visit for abdominal pain, diarrhea, or rectal blood loss. Thus, it is likely that we underestimated the relationship of disease activity to the risk of renal disease because of the use of nonspecific data. Another limitation was that 5-ASA treatment may have been started in the hospital without GPRD recording of this initial exposure (chronic treatments are provided by the GP). But no differences in the results were found after exclusion of patients who had been hospitalized in the previous 6 months. There is also the possibility of ascertainment bias: Patients with active disease may be more closely monitored than patients without disease, and renal disease may be more likely diagnosed in these patients. We did not have information on the serum creatinine levels of the cases.

In conclusion, users of 5-ASA have an increased risk of renal disease. However, this increase may be partly at-tributable to the underlying disease. In only a few records was renal disease attributed to interstitial nephritis or 5-ASA use. These findings indicate that the incidence of 5-ASA-induced renal disease is rare. Although the numbers were small, there were no differences in risk of renal disease between mesalazine and sulfasalazine.

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