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Prescriptions for mesalazine and sulphasalazine: a prevalence estimate of patients treated for inflammatory bowel disease in Rome

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SUMMARY

Background: Sulphasalazine and 5-amino salicyclic acid drugs are specifically indicated for the treatment of inflammatory bowel disease.
Aim: To use drug consumption by a given population as a marker to estimate the number of patients with inflammatory bowel disease.
Methods: Prescriptions for sulphasalazine and mesalazine were identified for the 133000 inhabitants of a local health unit in Rome. Other prescriptions received by the patients, who were users of sulphasalazine or mesalazine, were also studied.
Results: 99465 patients received at least one prescription for any drug in 1991. Three hundred and seventy-six patients were prescribed sulphasalazine and/or mesalazine, an average of 3.8 prescriptions per patient. These patients were exposed more frequently than the general population to other drugs often used in inflammatory bowel disease treatment, for example, corticosteroids, anti-diarrhoeal drugs and intestinal anti-infectives. We identified that 258 of 100000 inhabitants were prescribed either sulphasalazine or mesalazine; 127 of 100000 inhabitants received full-dose treatment for at least 30 days, and 42.8 of 100000 inhabitants received prescriptions of either drug, also associated with systemic corticosteroids.
Conclusion: The consumption of drugs used specifically for inflammatory bowel disease may act as a marker for the prevalence of the condition in a community.

INTRODUCTION

The inflammatory bowel diseases, ulcerative colitis or Crohn's disease, are among the most serious conditions of the gastrointestinal tract. The medical therapy of choice for inflammatory bowel disease is similar for ulcerative colitis and Crohn's disease.[1] Corticosteroids are useful for patients with moderate to severe ulcerative colitis or Crohn's disease.[2] Sulphasalazine and the new preparations of 5-amino salicyclic acid (mesalazine) are used in ulcerative colitis, when Crohn's disease involves the large bowel,[3–5] in patients with isolated Crohn's ileitis[6] (although less frequently) and to prevent ulcerative colitis relapse.[7–9] Treatment with these drugs must be for at least 3–4 weeks before the induction of remission.

Estimates of the incidence and prevalence of inflammatory bowel disease are usually based on data derived mainly from hospital surveys.[10–13] In the present study we analysed the consumption of sulphasalazine and mesalazine (the latter available in Italy since 1991) in the population of a local health unit in Rome. Since these drugs are specifically indicated for the treatment of inflammatory bowel disease, we used prescription data for these substances as markers for an estimate of the number of presumed inflammatory bowel disease patients. Since other drugs are used routinely as supportive therapy, we also studied the overall prescriptions received by the patients who were identified as users of sulphasalazine or mesalazine.

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METHODS

All Italian citizens are enrolled in local health units, which depend upon the National Health Service. Prescriptions issued by general practitioners or specialists are

dispensed, either free of charge or with a co-payment, through private and public pharmacies. A computerized database has been operating in Rome since 1986, which contains data relevant to all prescriptions issued to outpatients who are covered by the National Health Service.[14] We recorded all the prescriptions issued in Rome (3.8 million inhabitants) throughout 1991. We selected a local health unit (133000 inhabitants) to follow the prescription history of patients receiving either sulphasalazine or mesalazine. From the data recorded on each prescription form we selected the individual code number of the patient, the drugs dispensed and the number of packages per prescription. Demographic data were not required, therefore ensuring anonymity.

All patients receiving at least one prescription (any pharmaceutical formulation) of sulphasalazine or mesalazine were identified. Other drugs, if any, that these patients received during the same year were identified through individual code numbers. To describe the overall prescription patterns, we grouped the prescriptions in therapeutic categories according to the Anatomical Therapeutic Chemical Classification System.[15]

The defined daily doses for each package were used to calculate the duration of treatment. This is the average dose per day of a given drug used for its main indication as maintenance therapy in adults. The defined daily doses adopted from sulphasalazine and mesalazine in this study were 2 and 1.8 g, respectively.

RESULTS

During 1991, the 133000 inhabitants of the local health unit involved in this study received a total of 1814000 drug packages: 99465 subjects (74.8%) received at least one prescription, with an average of 13.6 per enrolled patient. The pattern of ethical drug use is similar to that of the population of Rome, both for the frequency of prescriptions of mesalazine and sulphasalazine (Table 1) and for general prescriptions (Table 2). The number of packages of sulphasalazine or mesalazine per 100 inhabitants was 1.81 in the study population, and 2.15 in the population of Rome. Three hundred and seventy-six patients received at least one prescription of either tracer drug (mean 3.8 prescriptions per patient), mesalazine being the most frequent (Table 3); 39.6% of the patients received three or more prescriptions of either drug. For these patients, the duration of treatment was 71 days according to the defined daily dose.

Table 1. Prescriptions for drugs used as tracers of inflammatory bowel disease in Rome 1991

	Rome (3800000 inhabitants)		Local health unit sample (133000 inhabitants)	
Drugs	% packages	rank	% packages	rank
Mesalazine	0.11	267	0.10	265
Sulphasalazine	0.02	629	0.03	562

When compared with patients who were not receiving either mesalazine or sulphasalazine, presumed inflammatory bowel disease patients received more prescriptions—at least twice as many—of drugs belonging to the following therapeutic groups: systemic corticosteroids, anti-diarrhoeal drugs and micro-organisms, vitamin B_{12} and folic acid, intestinal anti-infectives, anti-spasmodics and psycholeptics.

The relative frequency of prescriptions of corticosteroids for systemic use in this patient group was 5.6 vs. 1.3% for the general population (Table 2). In particular, the proportion of subjects exposed to methyl prednisolone and prednisone (the most frequently prescribed corticosteroids for general use) was 10-fold higher in the patients identified by use of sulphasalazine or mesalazine (12%) than in the general population of the local health unit (1.2%). Anti-diarrhoeal therapy with loperamide or diphenoxolate was associated with the markers in 26 patients. Two patients used cholestyramine and 28 patients used anti-diarrhoeal micro-organisms. None of our subjects used metronidazole, the only anti-microbial shown to be efficacious in inflammatory bowel disease controlled trials. Although the efficacy of multi-vitamins as standard therapy in inflammatory bowel disease is doubtful, 54 patients were prescribed folic acid and 14 were prescribed iron.

Thirty-two patients (of whom 26 received only one prescription of sulphasalazine or mesalazine) also received lactulose, and they were excluded from the analyses because diarrhoea is the most common symptom in inflammatory bowel disease. The remaining 344 patients give an overall estimated prevalence of 258 patients with inflammatory bowel disease per 100000 inhabitants. Focusing the analysis on those receiving three or more prescriptions in a year, this gives an estimated prevalence of inflammatory bowel disease of 127 patients in 100000 inhabitants. The estimated prevalence of patients prescribed either sulphasalazine or

Table 2. Prescriptions issued to patients treated with mesalazine or sulphasalazine (presumed inflammatory bowel disease patients) and to the general population (local health unit inhabitants vs. total Roman population)

Therapeutic groups*	Local health unit		% packages
	Presumed inflammatory bowel disease patients	133 000 inhabitants	Rome 3 800 000 inhabitants
Drugs for peptic ulcer	6.3	3.4	3.1
Corticosteroids for systemic use	5.6	1.2	1.3
Nonsteroidal anti-inflammatory drugs	4.4	4.0	4.3
Antidiarrhoeal drugs	3.3	1.2	1.4
Cephalosporins	2.6	2.3	3.8
Myocardial therapy	2.5	3.0	2.5
Vitamin B_{12} and folic acid	2.5	1.2	0.5
Capillary stabilizing agents	2.4	2.3	2.0
Other analgesics and antipyretics	2.4	2.7	3.3
Peripheral vasodilators	2.3	2.9	1.9
Antidepressants†	2.0	1.4	0.9
Other CNS drugs	1.8	1.6	0.3
ACE inhibitors	1.7	2.8	2.1
Other ophthalmologicals	1.7	1.3	0.8
Antithrombotic agents	1.6	2.3	1.3
Calcitonin preparations	1.6	1.7	1.1
Intestinal antiinfectives	1.4	0.4	0.4
Serum lipid reducing agents	1.4	1.9	1.7
Immunostimulating agents	1.4	1.3	1.0
Antispasmodics and psycholeptics	1.3	0.5	0.6

* The single substances are grouped in therapeutic categories.
† Data on anxiolytics are not available, since in Italy these drugs are not reimbursed by the National Health Service.

Table 3. Patients exposed to inflammatory bowel disease tracer drugs among the local health unit sample

Substances	Patients		Prescriptions per patient	Packages per patient mean (%)	Median duration of treatment (days)
	(*n*)	(%)			
Mesalazine	272	72.3	3.6	6.2	22
Sulphasalazine	74	19.7	2.7	4.5	50
Mesalazine + sulphasalazine	30	8.0	7.9	13.2	187
Overall	376	100	3.8	6.4	31

mesalazine plus corticosteroids gives an estimated prevalence of 42.8 patients per 100 000 inhabitants.

DISCUSSION

Sulphasalazine and mesalazine appear to be significant tracers for the identification of an inflammatory bowel disease patient, as the associated pattern of prescriptions is consistent with treatment for ulcerative colitis or Crohn's disease. The patients on sulphasalazine and mesalazine received a significantly higher number of prescriptions for drugs consistent with the management of inflammatory bowel disease (Table 2). Apart from the corticosteroids, the action of these drugs is not aimed directly at the inflammatory process, even though they are used for symptomatic relief for the management of associated pathologies.[16–21]

In the Italian National Formulary, mesalazine is listed only for the treatment of inflammatory bowel disease, whereas sulphasalazine is also listed, as a second choice

drug, for the treatment of rheumatoid arthritis. Therefore, the specificity of sulphasalazine as an indicator for inflammatory bowel disease is questionable. Recently, in a prescription-monitoring study of adverse reactions to sulphasalazine, 52% of patients have been treated for inflammatory bowel disease, and only 27% for arthritis.[22] In our study, 25 of 344 subjects received an isolated prescription for sulphasalazine, but one patient also received penicillamine—a drug specifically indicated for the treatment of rheumatoid arthritis. Unpublished market statistics provided by Marketing Information Service–Medical Prescription Service (IMS/SPM) (data for 600 physicians in Italy) indicated that 90% of out-patients diagnosed as having inflammatory bowel disease receive at least one prescription for sulphasalazine or mesalazine (sensitivity estimate) and that 86% of physical examinations which end with a prescription of sulphasalazine or mesalazine are related to inflammatory bowel disease (positive predictive value, that is, the probability of having the disease).

Most studies suggest that the combined prevalence of ulcerative colitis and Crohn's disease lies within the range 90–150 per 100000,[23–25] with a lower frequency in eastern and southern European countries.[26–30] Recently the population studies, particularly those from Scandinavia, have produced higher prevalence figures.[23–25, 31] Recent Italian studies reported figures similar to those found in some parts of northern Europe.[32–34] In the present study, the prevalence found when considering any prescription of either trace of drug was relatively high (250 per 100000), although higher values have been reported.[31, 35, 36] Possible biases in our analysis may result from the inclusion of patients who have had a short period of treatment, because either the beginning or the end of their therapy was outside the 1-year interval of observation, and the inclusion of patients who had a short duration of treatment related to the non-specific use of either mesalazine or sulphasalazine for infectious diarrhoea.

By restricting the analysis of the patients receiving three or more prescriptions of the tracer drugs, the prevalence estimate (127 per 100000) gets close to the figures reported by most papers in the literature. However, Mayberry *et al.* reported that the inclusion of well-defined symptomatic cases may underestimate the prevalence by at least 30%, and that milder forms of inflammatory bowel disease tend to go unrecognized.[37]

Given the wide spectrum of severity in inflammatory bowel disease, we probably trace most of the median-to-moderate forms of symptomatic disease. Recent multicentre trials show that oral mesalazine is effective in preventing or delaying clinical relapse in Crohn's disease, especially in milder cases and also in those with ileal involvement.[38–40] In addition, since our study refers to a 1-year period only, there must certainly be patients with inflammatory bowel disease in remission who were not detected in the survey and some other patients going through a severe phase of inflammatory bowel disease who received corticosteroids alone. In our study, the association of either sulphasalazine or mesalazine with corticosteroids was found in 57 patients, yielding a prevalence value of 42.8 per 100000. Although this combination is very specific for inflammatory bowel disease, it probably recognizes only the most severely ill out-patients.

Even though our results may be regarded as representative of the population of Rome, the study of a larger population sample during a longer period would provide a more accurate estimate of the prevalence of inflammatory bowel disease. Clearly, the investigation of patients identified in this manner should be used as a further validation of the method. Nevertheless, the methods used in this study appear to provide a fast and simple tool to estimate the prevalence of inflammatory bowel disease in different communities.

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REFERENCES

1 Carpani de Kaski M, Hodgson HJF. Rolling review: inflammatory bowel diseases. Aliment Pharmacol Ther 1993; 7: 567–79.
2 Meyers S. Oral and parenteral corticoids. In: Peppercorn MA, ed. Therapy of Inflammatory Bowel Disease. New Medical and Surgical Approaches. New York: Marcel Dekker, 1990: 3–34.
3 Jarnerot G. Newer 5-aminosalicylic acid based drugs in chronic inflammatory bowel disease. Drugs 1989; 37: 73–86.
4 Hanauer SB. Topical and oral aminosalicylates. In: Peppercorn MA, ed. Therapy of Inflammatory Bowel Disease. New Medical and Surgical Approaches. New York: Marcel Dekker, 1990: 65–91.
5 Singleton JW, Hanauer SB, Gitnick GL, *et al.* Mesalamine capsules for the treatment of active Crohn's disease: Results of a 16-week trial. Gastroenterology 1993; 104: 1293–1301.

6 Goldstein F, Farquhar S, Thornton JJ, Abramson J. Favorable effects of sulphasalazine on small bowel Crohn's disease: a long-term study. Am J Gastroenterol 1987; 82: 848–53.
7 Summers RW, Switz DM, Session JT, Jr, *et al*. Results of drug treatment. Gastroenterology 1979; 77: 847–69.
8 Riis P, Anthonisen P, Wulff HR, *et al*. The prophylactic effect of salazosulphapyridine in ulcerative colitis during long-term treatment. A double-blind trial on patients asymptomatic for one year. Scand J Gastroenterol 1973; 8: 71–4.
9 Dissanayake AS, Trulove SC. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine. Gut 1973; 14: 923–6.
10 Evans JG, Achenson ED. An epidemiological study of ulcerative colitis and regional enteritis in the Oxford area. Gut 1965; 6: 311–24.
11 Monk M, Mendeloff AI, Siegel CI, Lilienfeld AM. An epidemiological study of ulcerative colitis and regional enteritis among adults in Baltimore. Hospital incidence and prevalence, 1960 to 1963. Gastroenterology 1967; 53: 198–210.
12 Garland CF, Lilienfeld AM, Mendeloff AI, *et al*. Incidence rate of ulcerative colitis and Crohn's disease in fifteen areas of the United States. Gastroenterology 1981; 81: 1115–24.
13 Sonnenberg A. Hospital discharges for inflammatory bowel disease. Time trends from England and the United States. Dig Dis Sci 1990; 35: 375–81.
14 Maggini M, Menniti Ippolito F, Spila Alegiani S, Traversa G, Fortini M. Drug utilization studies within the VIDEOFAR project. Ann Ist Sup Sanità 1991; 27: 201–6.
15 Nordic Statistics in Medicine. Anatomical Therapeutic Chemical Classification. Uppsala: Nordic Council on Medicines, 1987.
16 Muss AA, Carbone JV, Kressell HY. Radiologic and clinical assessment of broad-spectrum antibiotic therapy in Crohn's disease. Am J Roentgenol 1978; 131: 787–90.
17 Barrett KE, Dharmathaption K. Pharmacological aspects of therapy in inflammatory bowel diseases: anti-diarrheal agents. J Clin Gastroenterol 1988; 10: 57–63.
18 Brandt LJ. Metronidazole. In: Peppercorn MA, ed. Therapy of Inflammatory Bowel Disease. New Medical and Surgical Approaches. New York: Marcel Dekker, 1990: 93–102.
19 Fleming CR. Enteral and parenteral nutrition. In: Peppercorn MA, ed. Therapy of Inflammatory Bowel Disease. New Medical and Surgical Approaches. New York: Marcel Dekker, 1990: 145–57.
20 Elsborg L, Larsen L. Folate deficiency in chronic inflammatory bowel diseases. Scand J Gastroenterol 1979; 14: 1019–24.
21 Thompson WG, Wrathell E. The relation between ileal resection and vitamin B12 absorption. Can J Surg 1977; 20: 461–9.
22 Keisu M, Ekman E. Sulphasalazine associated agranulocytosis in Sweden 1972–1989. Clinical features, and estimation of its incidence. Eur J Clin Pharmacol 1992; 43: 215–8.
23 Devlin HB, Datta D, Dellipiani AW. The incidence and prevalence of inflammatory bowel disease in North Tees Health District. World J Surg 1980; 4: 183–93.
24 Binder V, Both H, Hansen PK, *et al*. Incidence and prevalence of ulcerative colitis and Crohn's disease in the County of Copenhagen 1962–1978. Gastroenterology 1982; 83: 563–8.
25 Gollop JH, Phillips SF, Melton LJ III, Zinsmeister AR. Epidemiologic aspects of Crohn's disease: a population based study in Olmstead County, Minnesota, 1943–1982. Gut 1988; 29: 49–56.
26 Mayberry JF, Rhodes J. Epidemiological aspects of Crohn's disease: a review of the literature. Gut 1984; 20: 602–8.
27 Mayberry JF. Some aspects of the epidemiology of ulcerative colitis. Gut 1985; 26: 968–74.
28 Ruiz V. Crohn's disease in Galicia, Spain. Scand J Gastroenterol 1989; 24 (Suppl. 170): 29–31.
29 Vucelic B, Korac B, Sentic M, *et al*. Epidemiology of Crohn's disease in Zagreb, Yugoslavia: A ten-year prospective study. Int J Epidemiol 1991; 20: 216–20.
30 Lanfranchi GA, Michelini A, Brignola C, *et al*. Uno studio epidemiologico sulle malattie infiammatorie intestinali nella provincia di Bologna. G Clin Med 1976; 57: 235–45.
31 Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population based study in Sweden. Gastroenterology 1991; 100: 350–8.
32 Trallori G, D'Albasio G, Palli D, *et al*. Epidemiology of inflammatory bowel disease over a 10-year period in Florence (1978–1987). Ital J Gastroenterol 1991; 23: 559–63.
33 Cottone M, Cipolla C, Orlando A, *et al*. Hospital incidence of Crohn's disease in the province of Palermo. Scand J Gastroenterol 1989; 24 (Suppl. 170): 27–8.
34 Amanta E, Barbara L, Biasco C, *et al*. Incidence and prevalence of Inflammatory Bowel Disease in Bologna—risk factors. Scand J Gastroenterol 1989; 24 (Suppl. 170): 63.
35 Goodman MJ, Strickland RG, Kirsner JB. Inflammatory bowel disease and lymphocitic antibody in members of the American Gastroenterological Association. Gastroenterology 1979; 76: 1140.
36 Kyle J. Crohn's disease in the Northeastern and Northern Isle of Scotland: an epidemiological review. Gastroenterology 1992; 103: 392–9.
37 Mayberry JF, Ballantyne KC, Hardcastle JD, Mangham C, Pye G. Epidemiological study of asymptomatic inflammatory bowel disease: the identification of cases during a screening programme for colorectal cancer. Gut 1989; 30: 481–3.
38 Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M and the Italian IBD Study Group. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's Disease. Gastroenterology 1992; 103: 363–8.
39 Gendre JP, Mary JY, Florent C, *et al*. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. Gastroenterology 1993; 104: 435–9.
40 Caprilli R, Andreoli A, Capurso L, *et al*. Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post operative recurrence of Crohn's disease. Aliment Pharmacol Ther 1994; 8: 35–43.