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Sulfasalazine associated agranulocytosis in Sweden 1972–1989

Clinical features, and estimation of its incidence

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Summary. During the 18 year period 1972–1989 a total of 62 cases of agranulocytosis associated with the use of sulphasalazine were reported to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC).

The median age of the patients was 52 y and median duration of sulphasalazine treatment was 43 days. The fatality rate was 6.5 %, and among patients who recovered the median recovery time was 10 days. Twelve patients were treated concomitantly with other drugs generally suspected to induce agranulocytosis. From sales and prescription data the average incidence of agranulocytosis during sulphasalazine therapy was estimated to be 1/1750 patient years of exposure. From an ongoing Prescription Monitoring Project in a Swedish county it was possible to calculate the proportion of patients receiving sulphasalazine for different periods of time. The incidence of agranulocytosis during the first 30 days was estimated to be 1/2400 patients, while it was 1/700 between Days 31–90 and 1/11200 during Days 91–365.

The risk of developing agranulocytosis during sulphasalazine treatment is considerable during the first three months of treatment, and the traditional way of expressing the risk (1/1750 patient years) underestimates the risk for the individual patient.

Key words: Agranulocytosis, Sulphasalazine; adverse reactions, survey methods

Sulphasalazine has been widely used in the treatment of inflammatory bowel disease (IBD), since its development and introduction in Sweden 1945. In the recent past it has also been shown to have a useful role as a second line agent in patients with rheumatoid arthritis (RA) [1].

Cases of agranulocytosis have previously been described in patients treated with sulphasalazine for IBD [2, 3] and for RA [4, 5]. As far as is known only one previous publication on a series of cases with agranulocytosis associated that condition with sulphasalazine therapy [6].

During the period 1972–1989 the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) received reports about 374 patients with suspected adverse reactions to sulphasalazine, of which haematological reactions constituted one fourth. The present study comprises an analysis of the cases of agranulocytosis reported to SADRAC during this period, and estimates the incidence of agranulocytosis connected with sulphasalazine treatment from sales data, and data from an ongoing prescription monitoring study in the county of Jämtland.

Methods and subjects

The Swedish Drug Monitoring System

Reporting of suspected adverse drug reactions to SADRAC started in 1965 and has been compulsory since 1975 for fatal, other serious and new reactions. Each report is scrutinized for completeness by a medical officer. For all fatal cases and most of the other serious cases the complete medical records are requested. The relationship to drugs is then classified as "*P*" (possible or probable) or "N" (remote or not assessable), after which the reports are discussed by the full committee.

Reports regarding sulphasalazine

During the period of 1972 to 1989 a total of 118 reports was received concerning blood cell dyscrasias of which 117 were considered to have a possible or probable causal connection with sulphasalazine. Of the 117 there were 9 cases of thrombocytopenia, 9 cases of pancytopenia/aplastic anaemia, 18 cases of anaemia (11 of megaloblastic type), and 81 cases of leukopenia.

Definition of agranulocytosis

Agranulocytosis was defined as the occurrence in the peripheral blood of 0.5×10^9/l neutrophil granulocytes or less. In order to be included in the study the platelet counts had to be at least $100 \times 10^9 \cdot l^{-1}$. A bone marrow examination or information on recovery of the white blood count was required if there was only one low granulocyte count. Patients with malignant haematological conditions, and those who were undergoing chemotherapy or radiation therapy were excluded.

Since 1972 total sales of drugs in Sweden have been computerized and the data have been available as so-called defined daily

Table 1. Characteristics of 62 patients with sulphasalazine-associated agranulocytosis

Disease	No.	Age (y) median (range)	Sex % female	Dose (g) median (range)	Treatment time[a] (days) median (range)
IBD	32	45 (10–79)	47	3 (1–4)	31 (9–82)
R.A.	17	60 (39–73)	59	2 (1.5–3)	49 (22–124)
Other	13	41 (18–82)	54	3 (1.5–4)	31 (19–76)

[a] These figures are based on the 52 patients in whom the exact length of treatment was known

doses (DDD). One DDD of sulphasalazine is 2 g. Furthermore, since 1974 the National Corporation of Swedish Pharmacies has a continuous record of a random sample of all prescriptions, of the ages and sexes of patients, and the name, amount and prescribed doses of the drugs [7]. Based on this series, the average prescribed daily dose of sulphasalazine (so called PDD) was 2.6 g. During the period studied sales of sulphasalazine increased from 2.8 million DDD in 1972 to 4.3 million DDD in 1989. The total number of DDDs sold during the period 1972–1989 was 51.1×10^6.

Prescription monitoring project

The prescription monitoring Project in the county of Jämtland, Sweden started in 1970. To day it comprises about 17000 individuals (born on the same four days each month). Data on gender and year of birth of the patients, trade name, quantity and dosage of all drugs prescribed for these patients have been stored [8]. There were 173 patients who had received at least one prescription for sulphasalazine in the register. In 28 of them the number of PDDs was for up to 1 month, in 32 it was for up to 3 months, in 64 it was up to 12 months, in 16 patients the number of PDDs received was for 24 months, and 33 patients had received sulphasalazine for a longer period.

The total number of PDDs received by these 173 patients was 80367. The PDD in Jämtland during this period was 2.7 g.

Results

During the study period 62 patients were reported to have developed neutropenia fulfilling the criteria for agranulocytosis given above. Sixty of the patients had agranulocytosis when admitted to hospital, and 2 patients developed agranulocytosis 36 and 50 days after admission to hospital.

The series comprised 29 men and 33 women, aged 10 to 86 y (median age 52 y). Thirty-two patients (52%) had been treated for inflammatory bowel disease, mainly ulcerative colitis, and 17 patients (27%) for arthritis. Other diseases were stated as the indication in 13 patients (21%). In the latter group 10 patients had been treated for unspecified colitis (Table 1).

In 52 of the patients it was possible to determine the exact number of days from the start of sulphasalazine treatment up to the diagnosis of agranulocytosis median treatment time was 43 days (range 9–124 d).

In 52 patients (84%) symptoms like fever and sore throat occurred some days before sulphasalazine was withdrawn. In 10 cases (16%) agranulocytosis was detected through laboratory results. Eight out of the latter patients were identified on routine check-up, and two were in hospital for other reasons; 1 for inflammatory bowel disease and 1 for a broken leg.

Fifty patients (81%) had not taken any other drug which had previously been associated with agranulocytosis, while 12 patients (19%) had taken other such medicines [9]. All those drugs were stopped simultaneously with sulphasalazine. Eight patients had taken one other drug (indomethacin 5 patients, ketoprofen 1 patient, naproxen 1 patient, and acetazolamide 1 patient). Three patients had been on 2 other drugs (1 each had taken combinations of piroxicam and bendroflumetiazide, indomethacin and tetracycline, indomethacin and furosemide). The combination of naproxen, furosemide and piroxicam had been taken by 1 patient together with sulphasalazine.

Twelve patients suffered from skin reactions, and three from liver reactions concomitantly with the agranulocytosis.

Bone marrow examination was carried out in 28 patients (45%) 1–17 days after the diagnosis of agranulocytosis was made. Granulocytopoiesis was absent to sparse in 14 of the bone marrow specimens, and different stages of "maturation arrest" were present in 14 cases. There was no description of megaloblastic change in the myelopoiesis, but in 3 patients the erythropoiesis was megaloblastic.

In 44 patients (71%) it was possible to assess the recovery time of the granulocytes in the peripheral blood. The median time elapsed from stopping treatment to recovery was 10 days (Fig. 1).

Four of the patients (6.5%) died. Three of them had been treated for colitis for 21, 31 and 50 days respectively, and one had been treated for 49 days for arthritis. All four patients died because of severe infections and in three of them there was no sign of recovery of granulocytes in the peripheral blood when they died.

The patients were in hospital for a median of 12 days (1–120 d) in connection with their agranulocytosis.

Estimates of incidence

The incidence of agranulocytosis based on the 62 reported cases was 1.2/million DDD for the period 1972–89. The incidence figure does not change if the incidence is only calculated on the 60 out-patients and with the out-patient sales figures, 1.1/million DDD. If all patients who had taken other suspected drugs (see Materials and Methods section) are excluded, the incidence is 0.9/million DDD.

Using the average prescribed daily dose (PDD) and all 62 patients who contracted agranulocytosis while on sulphasalazine treatment during the actual period, the incidence was estimated to one case of agranulocytosis in 1750 treatment years.

Provided that the distribution of treatment times concerning sulphasalazine in Jämtland does not differ from that in the rest of Sweden, it is possible to calculate the actual number of patients for whom the total of 51.1×10^6 DDDs had been prescribed. The 173 individuals who had been prescribed 66973 PDDs of 2.7 g correspond to 34500 patients with a PDD of 2.6 g in the whole of Sweden. The corresponding number of patients receiving sulphasalazine for different periods can also be calculated. The num-

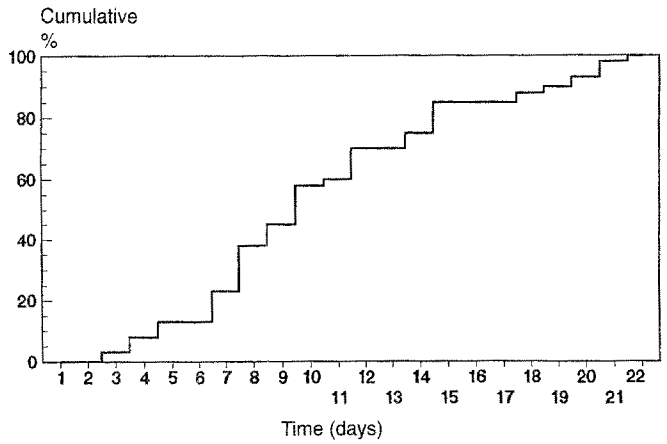

Fig. 1. Recovery pattern of 44 patients with agranulocytosis that developed during sulphasalazine treatment

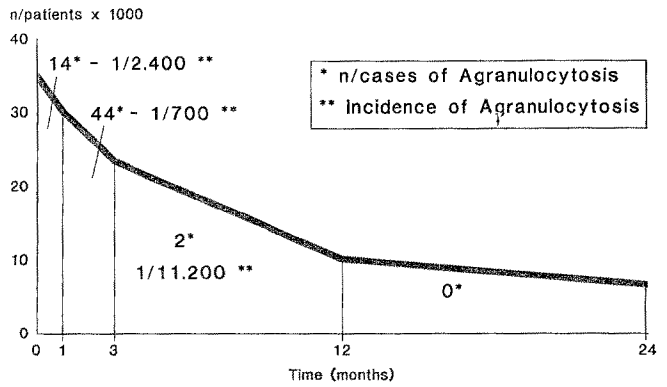

Fig. 2. Distribution of the estimated length of sulphasalazine treatment in 34 500 patients, and the duration of treatment up to the diagnosis of agranulocytosis in 60 patients

ber of cases and the risk of agranulocytosis during different time intervals are depicted in Fig. 2. Based on these data the reported cases indicate that 1/2400 patients will develop agranulocytosis while on sulphasalazine treatment for up to 1 months. The corresponding estimate for patients during 1–3 months of treatment and 3–12 months of treatment is 1/700 patients and 1/11200 patients, respectively. In the present study there were no patients who developed agranulocytosis after more than 12 months of treatment.

Discussion

Agranulocytosis during sulphasalazine treatment is a well known idiosyncratic adverse drug reaction. The present report appears, however, to be the first occasion that the clinical characteristics in so many patients have been described at the same time, and it also provides one of the first defined estimate of the risk of developing agranulocytosis during sulphasalazine treatment.

Sulphasalazine today is mainly used in two different categories of patients, those suffering from IBD and those with RA. From the present series it was not possible to determine if the risk of developing agranulocytosis differed between the two diseases because the Jämtland series is still too small to extrapolate the proportions of sulphasalazine used for each disease (sulphasalazine has only been approved for RA since 1987).

Among the cases 98 % of the patients developed agranulocytosis during the first 3 months of sulphasalazine treatment. This timing is consistent with the findings in patients who developed agranulocytosis while taking dapsone for dermatitis herpetiformis [10], and also for patients affected during thyreostatic treatment [11]. On the assumption that the distribution of the duration of sulphasalazine treatment in the county of Jämtland is representative of the whole of Sweden, the estimates show a sharp decline in the incidence of agranulocytosis if it does not appear within three months of commencing therapy. It is possible that patients developing agranulocytosis after a long time of sulphasalazine treatment will not be reported to SADRAC as a suspected reaction to sulphasalazine, and so the value might be an underestimate. The distribution of treatment times is consistent with the findings of a case-control study, in which the criteria for inclusion were based on laboratory values and not on drugs suspected of causing agranulocytosis [12].

There are cases of agranulocytosis in the literature [6] appearing after much longer exposure to sulphasalazine. Whether those patients require a much longer time to become sensitive, whether an additional factor required in them to develop agranulocytosis, or even if the agranulocytosis in fact was not caused by sulphasalazine, is not known. Further research into the mechanisms leading to agranulocytosis in individual patients is required to answer this question.

The overall mortality rate in this series was 6.5 %, and it was 7.7 % among the symptomatic cases. This is lower than the overall mortality rate in cases of agranulocytosis in the Swedish Spontaneous Reporting System over the same period (14 %), and the 11 % mortality rate in the study of Arneborn and Palmblad over the period of 1973–1978 [13]. The lower mortality rate in the present patients might be explained at least to some extent if the well known connection between sulphasalazine and agranulocytosis had made physicians react faster when patients complained of symptoms related to agranulocytosis, thus diminishing the number of patients with serious life-threatening infections.

The recovery time from agranulocytosis was within 10 days in 50 % of the patients and within 15 days in 90 % (Fig. 1).

This information on recovery time is interesting from a clinical point of view as it shows that patients will recover spontaneously if they are protected from overwhelming infections during the neutropenic phase.

The estimated incidence of agranulocytosis during sulphasalazine treatment according to the spontaneous reporting system was 1/1750 treatment years. This is the same order of magnitude as the incidence of dapsone-associated agranulocytosis (1/3000 treatment years) [10], and the incidence of agranulocytosis estimated during thyreostatic treatment [11]. Only 19 % of the patients had taken other drugs previously associated with agranulocytosis, when their blood dyscrasia was detected. Most of the patients who had been treated with other drugs had taken

them for a long time. The relative risk of developing agranulocytosis during sulphasalazine treatment [12] is so high that other drugs should play a minor role [14, 15]. Thus, this estimate is probably not materially inflated. On the other hand spontaneous reporting systems generally suffer from under reporting. The total reporting of agranulocytosis was found to be 35% in Stockholm county in 1973–1978 [13], and in the 1980's about 50% of cases are reported. However, we believe that the reporting of agranulocytosis in connection with sulphasalazine is substantially higher, as the risk estimate is similar to that in a case-control study [12].

Using the detailed information in the Jämtland register it was also possible to determine the peak incidence of agranulocytosis at 1/700 patients during the second and third months of sulphasalazine therapy. Thus, the traditional expression of risk (1/1750 patient years) underestimates the risk for the individual patient. It can be expected that, in a similar manner, the risk of developing agranulocytosis differ during different treatment periods for other drugs too. Risk should be expressed, therefore, as a function of time (hazard function) when studying idiosyncratic drug reactions.

In conclusion, the risk of developing agranulocytosis during sulphasalazine treatment is considerable during the first 3 months of therapy. Although agranulocytosis when properly treated today has a low mortality rate, sulphasalazine should only be used for the established indications, and patients should be instructed to seek immediate medical care if they develop signs of infection in the first 3 months of treatment. Risk estimates for idiosyncratic reactions should preferably be expressed as a function of time.

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