Agranulocytosis associated with calcium dobesilate
Clinical course and risk estimation with the case-control and the case-population approaches

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Abstract Objective: Calcium dobesilate is used in the treatment of diabetic retinopathy, chronic venous insufficiency, haemorrhoids and other ill-defined vascular conditions. It has been associated with agranulocytosis in anecdotal reports. We describe the clinical course of a series of patients who developed agranulocytosis while taking this drug, and we estimate the risk by means of both a case-control and a case-population strategy.

Methods: All cases of agranulocytosis meeting strict predefined diagnostic criteria in an area of 3.3 to 3.9 × 10^6 inhabitants in the period 1980–1998 were identified. Cases and age-, gender- and hospital-matched controls were interviewed with a structured questionnaire including a detailed drug history. Each case was reviewed and confirmed by a haematologist, who was blind with respect to drug exposures. Consumption data were used to estimate the risk of agranulocytosis associated with calcium dobesilate using a case-population approach in which the incidence of agranulocytosis among users of calcium dobesilate was compared with that among the non-exposed population.

Results: After a follow up of 68.55 × 10^6 person-years, 345 cases of agranulocytosis (242 community cases) were assembled. Reliable information was obtained from 216 cases. Two patients exhibited positive rechallenge. Twelve cases (5.6%) and 5 of 1380 controls (0.4%) had taken calcium dobesilate in the week before. With the case-control approach, the odds ratio was 23.66 [95% confidence interval (CI), 7.54–74.24], the attributable risk was 5.3% (95% CI, 3.0–9.4), and the number of cases attributable to dobesilate in the study area during the study period was 12.8. The case-population estimates were an incidence of 121.03 cases per 10^6 patient-years, a relative risk of 39.55 (95% CI, 17.96–77.49), an attributable risk of 6.73% (CI 3.4–12.9), and 16.30 cases attributable to dobesilate in the study area during the study period.

Discussion: This study adds to evidence indicating that the case-population method is adequate for the study of rare type B adverse drug reactions. An additional advantage of this approach is that the incidence of the disease of interest among those exposed to the drug can be estimated. The risk of agranulocytosis associated with calcium dobesilate should be considered in relation to poor evidence of its clinical efficacy.

Key words Agranulocytosis · Calcium dobesilate · Risk estimation · Case population

Introduction

Calcium dobesilate (2,5-dihydroxybenzene sulfonate) is claimed to decrease capillary permeability, platelet aggregation and blood viscosity [1, 2]. It also increases endothelium-dependent relaxation through an increase in nitric oxide synthesis [2]. It has been used for the treatment of diabetic retinopathy, chronic venous insufficiency, haemorrhoids and other ill-defined vascular conditions, at usual systemic doses of 500–1000 mg daily, and both systemically and locally for haemorrhoids [1]. It is currently known to be marketed in Austria, France, Germany, Greece, Italy, Portugal, Spain, Switzerland and several Latin American countries.

Reported side effects associated with its use include gastrointestinal disturbances, drug fever [3, 4] and agranulocytosis [5, 6, 7]. This has been described in anecdotal reports, but the magnitude of this risk is unknown.

Different methods can be used for estimating the risk of rare adverse reactions. In this paper, we present a...
series of patients who developed agranulocytosis while receiving treatment with calcium dobesilate. We use both the case-control method and the case-population approach to estimate the risk of agranulocytosis associated with calcium dobesilate, and we discuss the use of these epidemiological strategies in the assessment of the risk of rare diseases.

Patients and methods

From 1980 to 1986, data collection was part of the International Agranulocytosis and Aplastic Anemia Study (IAAAS), a multicentre case-control study carried out in several European countries to assess the risk of these blood dyscrasias associated with the use of drugs [8]. Although the IAAAS ended in 1986, in our centre the surveillance scheme was maintained. The present data refer to the period January 1980 to December 1998.

Briefly, in order to detect all cases of agranulocytosis in the study region, our centre maintains regular contact with all hospitals in the metropolitan area of Barcelona (3.3–3.9 \times 10^6 inhabitants) through weekly visits or telephone calls to a designated contact person (see Acknowledgements). Potential cases were patients with a granulocyte count of 500 × mm^-3 or less, or a total white count of 3000 × mm^-3 or less at two different counts, with a haemoglobin level of 10 g × dl^-1 or higher, and a platelet count of 100,000 × mm^-3 or higher. Patients on cancer chemotherapy, radiotherapy or immunosuppressive therapy and those with hypersplenism, systemic diseases such as systemic lupus erythematosus (SLE), leukæmia and lymphomas, megaloblastic anaemia and acquired immunodeficiency syndrome (AIDS) were excluded. Asymptomatic cases, i.e., those discovered by chance on the occasion of a white blood cell (WBC) count and differential, and those under 2 years of age (in which a proportion of cases of neutropenia are due to viral infection) were also excluded. A bone marrow aspirate or biopsy was usually required, but it was not compulsory if all the other diagnostic criteria were met and if the neutrophil count became normal within 30 days.

Cases and controls were interviewed during hospital stay with a structured questionnaire by trained interviewers. Detailed information about drug use in the 6 months before admission was obtained by means of an open question about previous use of drugs and a list of common symptoms often prompting drug use. Clinical and laboratory data were collected. A haematologist confirmed the diagnosis, by examining the clinical and laboratory data, and established the index day, i.e., the day when the first symptom attributable to agranulocytosis occurred. This review was carried out without knowledge of previous drug use.

Initially, for each episode of agranulocytosis or aplastic anaemia, up to four controls admitted to the participating hospitals within 3 months of the index case were selected according to a list of admission diagnoses judged to be independent from the reason for use of most groups of drugs (e.g., acute traumatic injuries, non-symptomatic conditions leading to surgery, acute infections). However, in order to increase statistical power, all controls for both series of patients (agranulocytosis and aplastic anaemia) were included in the present analysis.

Drug exposures during the week before the index day were considered, regardless of the duration of previous use. This definition of drug exposure was chosen taking into account that for most cases of agranulocytosis the time elapsed between the injury to the bone marrow or to peripheral neutrophils and the initial symptoms of infection is usually less than 7 days.

In the case-control study, the odds ratio was calculated by applying a multiple logistic regression model with the following additional terms: age, gender, interviewer and one term for each of the following exposures: acetylsalicylic acid, metamizole, propyphenazone, paracetamol, indomethacin, other nonsteroidal anti-inflammatory drugs (NSAIDs), cotrimoxazole, antithyroid drugs, ticlopidine and a group of drugs with a relatively low consumption which are known causes of agranulocytosis (allopurinol, apirinide, phenytoin, carbamazepine, gold salts, chloramphenicol, cinzapide, clozapine and pyridylidone). Population attributable risk was estimated from the odds ratio, with the formula \( AR = P_a \times (OR - 1)/OR \), in which AR is the attributable risk, \( P_a \) the proportion of exposed cases and OR the odds ratio.

In order to estimate the incidence of agranulocytosis among users of calcium dobesilate with a case-population approach, consumption data within the National Health System, specific for the study area and for Spain, were used. Consumption was expressed in defined daily doses (DDD) per 1000 inhabitants and per day; as the DDD of calcium dobesilate has not been established [9], a DDD of 1 g, which is the recommended dose for the most prescribed (greater than 90%) pharmaceutical speciality containing calcium dobesilate, was assumed. Consumption data were only available for the period 1989–1998.

Results

During a follow-up period of 68.55 \times 10^6 person-years, 345 cases of agranulocytosis (242 community cases and 103 in hospital cases) were identified, giving an incidence of 5.03 per 10^6 inhabitants and per year (95% confidence interval, CI, 4.52–5.59). The incidence of community-acquired agranulocytosis was 3.53 per 10^6 inhabitants and per year (95% CI, 3.10–4.00). For 216 community cases, reliable information on previous drug exposures was obtained, and they were compared with 1380 controls. There were 12 cases (5.6%) and 5 controls (0.4%) exposed to calcium dobesilate in the week before the index day (OR = 23.66, 95% CI, 7.54–74.24). Restriction of the analysis to the controls specifically matched by age, gender and hospital to the cases of agranulocytosis (n = 515), gave an OR of 47.43 (95% CI, 5.80–388.62), with only one control exposed. Two patients exhibited a second episode of agranulocytosis on rechallenge with the drug.

Table 1 shows detailed information on the 12 episodes of agranulocytosis. All patients recovered in 5–14 days after withdrawal of calcium dobesilate. Eight were female. All were using other drugs concomitantly, but only one was also taking a drug for which a risk of agranulocytosis has been established (allopurinol, patient number 2). The induction period for the first episode ranged from 7 days to several years, with one patient developing agranulocytosis after 7 days of treatment, one between 8 days and 28 days, four between 29 days and 90 days, and four after more than 3 months. The induction periods in the two patients with positive rechallenge were 30 days and 55 days.

Population attributable risk calculated from the odds ratio estimate was 5.3% (95% CI, 3.0–9.4). This would translate into 12.8 cases in the study area during the study period, and 7.41 cases per year in the whole country, assuming an uniform incidence of community-acquired agranulocytosis of 3.53 per 10^6 inhabitants.

Consumption data were available only for the period 1989 to 1998 in the study area and for 1993–1998 in the whole country. During these periods, there were