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Safety of Calcium Dobesilate in Chronic Venous Disease, Diabetic Retinopathy and Haemorrhoids

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Abstract

The aim of the present review is to consider the adverse effects and the safety profile of calcium dobesilate. Calcium dobesilate (Doxium™) is a veno-tonic drug, which is widely prescribed in more than 60 countries from Europe, Latin America, Asia and the Middle East for three main indications: chronic venous disease, diabetic retinopathy and the symptoms of haemorrhoidal attack.

Data sources used for this review comprise the international literature (1970–2003), a postmarketing surveillance (PMS) report for calcium dobesilate from OM Pharma (Geneva, Switzerland) covering the period 1974–1998, and periodic safety update reports (PSUR) covering the period 1995–2003 from the French Regulatory authorities pharmacovigilance database and OM Pharma.

Data from the PMS report for 1974–1998 indicated that adverse events with calcium dobesilate did not occur very frequently and had the following distribution in terms of frequency: fever (26%), gastrointestinal disorders (12.5%), skin reactions (8.2%), arthralgia (4.3%), and agranulocytosis (4.3%). No deaths were attributed to calcium dobesilate in the PMS report. Using data on product use in the Swiss Compendium we estimated the prevalence of agranulocytosis to be 0.32 cases/million treated patients, i.e. ten times less than the calculated prevalence of agranulocytosis in the general population. Most adverse events are type B, i.e. rare and unrelated to the pharmacological properties of calcium dobesilate.

This review concludes that the risk of an adverse effect with calcium dobesilate 500–1500 mg/day is low and constant over time. The recently raised problem of agranulocytosis (a total of 13 known cases drawn from all data sources) appears to be related to methodological bias. Such a review reinforces the need for a strong international pharmacovigilance organisation using similar methods to detect and analyse the adverse effects of drugs.

Calcium dobesilate (marketed worldwide as Doxium™ [1] in more than 60 countries in Europe, Latin America, Asia and the Middle East) is calcium 2,5 dihydroxybenzene sulphonate, which is produced by chemical synthesis. It is classed in the vasculo-protector and veno-tonic category, a heterogenous group of substances comprising around 60 different drugs in the French Physicians' Desk Dictionary, Le Dictionnaire Vidal.[1-3] Calcium dobesilate has been marketed at a daily dose of 500–1500mg for some 30 years to relieve symptoms associated with venous-lymphatic insufficiency (heavy legs, pain, paraesthesia) as well as for reduced visual acuity and field defects believed to be of vascular origin (especially diabetic retinopathy). Although, in general, the safety of calcium dobesilate administration appears to be satisfactory, some recently reported serious adverse effects such as cases of agranulocytosis,[4] justify an update from the point of view of pharmacovigilance and a re-assessment of its safety. In fact, an assessment of the benefit-risk ratio of the veno-tonics is essential when one considers the high prevalence of venous pathology (over 10%) and the fact that it is such a frequent reason for consultation and drug prescription in general practice.[5-9]

Our approach for this review of the safety of calcium dobesilate is based on an analysis of data from the following sources:

- a literature search of Medline and Pascal for 1970–2003 using the terms 'calcium dobesilate', 'safety', 'pharmacovigilance', 'case reports' and 'venotonic drugs'
- a postmarketing surveillance (PMS) report for calcium dobesilate covering the period from 1974 to 1998 obtained from OM Pharma (Geneva, Switzerland)[10]
- periodic safety update reports (PSUR) covering the period 1 January 1995 to 31 January 2003 obtained from the French Regulatory authority pharmacovigilance database and OM Pharma.[11]

Individual case reports were analysed according to accepted European pharmacovigilance practice; the causal criteria used, particularly with regard to

1 The use of trade names is for identification purposes only and does not imply endorsement.

Table I. Criteria in favour of drug-induced dyscrasis[13]

Severe neutropenia	Number of polynuclear neutrophils <500/mm^3
Agranulocytosis	Severe neutropenia + clinical signs (fever, alteration of general state, bucco-pharyngeal and/or perineal ulcerations)
Thrombopenia	Number of thrombocytes <100 000/mm^3
Bicytopenia or pancytopenia	2 or 3 blood lineages affected, either a neutropenia, a thrombopenia and an anaemia defined as haemoglobin <10g/100mL, in the absence of information about the marrow
Probable medullary aplasia	Cytopenia, hypocellularity, absence of infiltration of the medullary puncture?
Medullary aplasia	Cytopenia, hypocellularity, absence of infiltration and of fibrosis on medullary biopsy

drug-induced blood dyscrasias (table I), are those described in international consensus meetings[12-14] or long-term pharmacoepidemiological studies.[15-22] The available clinical studies are examined from the point of view of safety with a particular emphasis on fever and agranulocytosis. Adverse effects are reported with consumption figures (available in the PSUR) and their geographic distribution is also taken into account.

1. Pharmacology of Calcium Dobesilate

1.1 Presentation/Formulation

Calcium dobesilate is available in two formulations: a tablet containing 250mg of calcium dobesilate and an antioxidant (sulphite in some countries) as well as other excipients and a capsule containing 500mg of calcium dobesilate as well as magnesium stearate and maize starch as inactive ingredients.

1.2 Experimental Pharmacology

1.2.1 Effect on the Capillaries

Calcium dobesilate inhibits capillary permeability induced by vaso-active substances such as serotonin, bradykinin and histamine.[23] It has a scavenging effect on free radicals (reactive oxygen species) and possesses antioxidant properties.[24] Furthermore, it influences the synthesis and release of nitric oxide and reduces endothelial cell desquamation.[25]

1.2.2 Effect on the Microcirculation

Partial and dose-dependent inhibition of 6-oxo-prostaglandin (PG) $F_{1\alpha}$, $PGF_{2\alpha}$, PGF_2 and of thromboxane B_2 synthesis by calcium dobesilate contributes to a reduction in platelet aggregation.[26] Similarly, calcium dobesilate reduces erythrocyte aggregation and their suspension viscosity.[27]

1.2.3 Effect on Platelet Hyperactivity

Calcium dobesilate inhibits thrombus formation and counters platelet deposition on vascular grafts.[28] Furthermore, the product antagonises the release of serotonin from platelets induced by thrombin and collagen, which would explain its ability to reduce capillary hyperpermeability.[29]

1.2.4 Effect on Lymphatic Drainage

Calcium dobesilate reduces experimental lympho-edema in the rat.[30] It reduces intra-lymphatic pressure, thus encouraging fluid entry.[31] According to Piller,[32] calcium dobesilate at a dose of 200 mg/kg increases lymphatic flow at thoracic level in the guinea pig, an effect that persists for 3 hours after its administration.

1.2.5 Summary

Calcium dobesilate possesses haemorheological effects, it regulates microvascular permeability and reduces oedema by activating lymphatic drainage. These pharmacological properties lead logically to consideration of clinical indications involving the pathology of both the microcirculation and the venous system,[33] even if their physiopathology remains complex and subject to differing interpretations.[34,35] No animal toxicity has been seen, apart from the potential toxicity of the sulphites, which are present as the product's antioxidant in some countries.[36-38]

1.3 Clinical Pharmacology

1.3.1 Phase I and II Clinical Trials

The antioxidant and free-radical scavenging effects of calcium dobesilate have been demonstrated using mononuclear cells taken from the peripheral blood of healthy volunteers.[39,40] Similarly, in a controlled study versus placebo, involving 25 subjects presenting with a peripheral vascular pathology, 4 weeks' treatment with calcium dobesilate 2000 mg/day lowered the number of circulating endothelial cells from 4.9 cells/μL of plasma to 2 cells/μL ($p < 0.0004$).[41] In another study involving 50 patients presenting with a chronic vascular pathology, 14 days' treatment with calcium dobesilate 1500 mg/day significantly reduced the visco-elasticity of whole blood in the capillaries of the finger pad and the haematocrit ($p < 0.001$), also increasing capillary microcirculation in the fingers.[42] Reduction of erythrocyte aggregation and improvement in erythrocyte flexibility have also been demonstrated in patients,[43,44] as well as an increased supply of oxygen to the ischaemic areas (intermittent claudication) in ten patients treated with calcium dobesilate 1500 mg/day.[45] The anti-aggregation effect on platelets was demonstrated in 52 patients at daily doses of 500mg, 1000mg and 1500mg.[46] This result was also found by Pfliegler et al.[47] who administered calcium dobesilate 750 mg/day for 1 week to 20 diabetic subjects. In addition, intravenous calcium dobesilate 500mg activated fibrinolysis by increasing the release of tissue plasminogen activator.[43,48]

1.3.2 Phase III and IV Clinical Trials

Calcium dobesilate has also been tested in numerous controlled clinical studies involving more than 5000 exposed patients.[41,43,46,49-65] These have demonstrated the expected therapeutic benefits, mainly in venous pathology, and above all, have confirmed the safety of calcium dobesilate.

Calcium dobesilate given at dosages of 750–2000 mg/day produces, after usually less than 2 weeks' treatment, relief of the pain associated with chronic venous disease and significantly reduces the following symptoms: a feeling of heavy legs, cramps, tingling in the legs, paraesthesia, oedema of the lower limbs.[49-53,66] The beneficial effects obtained with the product persisted for 1 month after stopping administration. Further data providing evidence of the efficacy of calcium dobesilate in chronic venous diseases are available from a large scale open study by Schmid and Haase[67] involving 3058 patients with venous pathology of varying severity. Several clinical trials have looked specifically at the effect of calcium dobesilate in diabetic retinopathy.[43,54,55] Confirmation of the safety of calcium dobesilate use can also be found in different clinical trials in chronic venous disease,[56,68,69] haemorrhoidal attacks[57,58] and in a pilot study of arterial blood hypertension during pregnancy.[59] The efficacy outcomes of the recently published studies are summarised in table II.

1.4 Pharmacokinetics

After oral administration of calcium dobesilate 500mg, maximum plasma drug concentration (C_{max}) was 8 μg/mL on average 6 hours later.[70,71] Protein binding was 20–25%. Plasma half-life was 5 hours and the elimination half-life varied between 2.5 and 15 hours. Eight per cent of the product administered orally was absorbed within the first 8 hours. Urinary elimination reached 50% of the dose administered 24 hours after absorption; 10% was eliminated in the form of metabolites in 24-hour urine output. Calcium dobesilate did not pass into the cerebrospinal fluid and did not cross the placenta. It appeared in very low concentration in maternal milk. No pharmacokinetic interactions have been reported in the literature.

2. Safety Profile

2.1 Postmarketing Surveillance (PMS) Report Data

The cumulative PMS report provided information on the adverse effects spontaneously communicated to the pharmaceutical company OM Pharma via spontaneous reports from prescribers and practitioners in the countries where calcium dobesilate is marketed, between 1974 and the beginning of

Table II. Summary of recent clinical trials with calcium dobesilate (CD) in chronic venous disease (CVI), haemorrhoids and diabetic retinopathy (DR)

Study	Study design	No. of patients	Indications	Treatment protocol	Efficacy outcomes	Safety outcomes (no.of pts with drug-related AEs [no. of withdrawals])
Widmer et al.[50]	Double-blind, PL-controlled	225	CVI early stages	1.5 g/d for 28d	Improvement in all clinical parameters (pain, cramps, heavy legs, restless legs, paraesthesias, $p < 0.05$–0.001) and reduction in leg volume ($p < 0.005$)	18 (6) out of 114 CD pts and 23 (3) out of 111 PL pts, mostly GI disorders
Pecchi et al.[53]	Double-blind, PL-controlled	40	CVI early stages	1.0 g/d for 28d	Improvement in all clinical parameters (oedema, pain, cramps, heavy legs, itching, paraesthesia, $p < 0.05$–0.001)	0 (0) out of 20 CD pts and 0 (0) out of 20 PL pts
Angehrn[68]	Open-label	375	CVI early stages	1.5 g/d for 28d	Improvement in all clinical parameters (pain, cramps, heavy legs, restless legs, paraesthesias, $p < 0.001$) and reduction in leg volume ($p < 0.001$)	22 (7) out of 375 CD pts, mostly GI disorders and skin reactions
Jaeger[56]	Double-blind, PL-controlled	217	CVI early stages	1.5 g/d for 28d	Improvement in all clinical parameters (pain, cramps, heavy and tired legs, itching, discomfort; NS), and reduction in leg volume ($p = 0.02$)	9 (3) out of 128 CD pts and 8 (2) out of 125 PL pts, mostly GI disorders and skin reactions
Arceo et al.[69]	Open-label	352	CVI early stages	2 g/d for 63d	Improvement in all clinical parameters (pain, cramps, heavy legs, paraesthesias, $p < 0.001$) and reduction in leg volume ($p < 0.001$)	63 (1) out of 352 CD pts, mostly GI disorders and headache
Mentes et al.[57]	Controlled (vs fibre-rich diet without CD)	45	Haemorrhoids (grades 1 and 2)	1.5 g/d for 7d then 1 g/d for for 7d + fibre-rich diet	Improvement in all clinical parameters (rectal bleeding, anal pain, pruritus, pressure and discomfort, tenesmus, constipation, $p < 0.001$)	1 (0) out of 29 CD pts and 0 (0) out of 16 control pts, GI disorder
Sarabia et al.[58]	Double-blind, double dummy CD vs diosminum	51	Haemorrhoids, acute crisis	2 g/d for 28d	Improvement in all clinical parameters (anal pain, discharge, bleeding, oedema, inflammation, pruritus and pressure)	3 (0) out of 25 CD pts and 2 (0) out of 26 PL pts, mostly GI disorders and vertigo
Leite et al.[54]	Double-blind, PL-controlled	41	DR stages I, II	2 g/d for 360d	Improvement of penetration ratio and posterior vitreous values ($p < 0.05$) but not of microaneurysms or capillary closure gradings	0 (0) out of 21 CD pts and 0 (0) out of 20 PL pts
Vojnikovic[55]	Double-blind, PL-controlled	79	DR with glaucoma, stages I, II	1.5 g/d for 180d	Improvement in all parameters (retinal haemorrhages, visual defects, visual acuity, intraocular pressure, blood hyperviscosity, $p < 0.001$)	11 (0) out of 41 CD pts and 1 (0) out of 38 PL pts, mostly GI disorders

d = day(s); **GI** = gastrointestinal; **NS** = not significant; **PL** = placebo; **pts** = patients.

1998.[10] Data on 113 cases corresponding to 186 adverse events were summarised in the report and are presented in table III. The cases mainly originated from Germany, France, Switzerland, Spain and

Table III. Adverse events profile of calcium dobesilate from postmarketing surveillance data (1974–1998). 186 events were recorded in 133 cases[11]

Adverse events	Number of events (%)
Fever	48 (25.8)
Agranulocytosis	9 (4.3)
Arthralgia	8 (4.3)
Nausea	7 (3.8)
Erythematous rash	7 (3.8)
Vomiting	7 (3.8)
Diarrhoea	5 (2.7)
Headache	5 (2.7)
Malaise/ill-feeling	5 (2.7)
Myalgia	5 (2.7)
Asthenia	4 (2.2)
Urticaria	4 (2.2)
Abnormal vision	4 (2.2)
Arrhythmia	3 (1.6)
Euphoria	3 (1.6)
Oedema	3 (1.6)
Rigors	3 (1.6)
Weight increase	3 (1.6)
Abdominal pain	2 (1.1)
Angina pectoris	2 (1.1)
Haematuria	2 (1.1)
Influenza-like symptoms	2 (1.1)
Acute liver injury	2 (1.1)
Maculo-papular rash	2 (1.1)
Pustular rash	2 (1.1)
Somnolence	2 (1.1)
Tachycardia	2 (1.1)
Taste disturbance	2 (1.1)
Vertigo	2 (1.1)
Varia	32 (17.2)
Total	**186 (100%)**

Portugal. Seventy-six percent of all notifications can be grouped under six headings: (i) cutaneous-mucosal manifestations; (ii) gastrointestinal effects; (iii) musculoskeletal effects; (iv) effects on haemopoietic lineage (including agranulocytosis at 4.3% [9 events in eight patients]); (v) neurological effects; and (vi) a general syndrome (of which fever accounted for 26% of all notifications).

According to the WHO classification, 40 of the 186 adverse events (21.5%) were classed as serious (occurring in 20 of the 113 cases). These serious events were considered either 'possibly' or 'probably' related to calcium dobesilate therapy in seven cases and 'certainly' related in three cases (two cases of agranulocytosis and one case of granulomatous hepatitis and fever in a 71-year-old). In one additional case of hepatitis causality could not be established, while five other cases were mentioned but *a posteriori* firmly considered as not drug related. In another four cases causality could not be established because of lack of information. These four cases were reported from Spain and the elderly patients, aged 64–93 years, had developed agranulocytosis (two other case reports from Spain of agranulocytosis in patients receiving calcium dobesilate were reported in the literature[72,73]). No deaths were found to relate to the medicine during the period of the PMS report. All of the adverse events notified regressed *ad integrum* after stopping treatment.

During the period of the PMS report, there was significant variation in the types of events reported to the pharmaceutical company from different countries. For example, there were eight notifications of adverse events from Spain, of which six were cases of agranulocytosis (four from the PMS report[10] and two reports from the literature[72,73]).There were 32 reports from France and the most frequently reported adverse events were arrhythmias or 'a feeling of malaise'. There were 13 adverse event reports from Germany and fever was the most common event (five patients).

During the time period from 1974 to the beginning of 1998 covered by the PMS report there were eight patients who developed agranulocytosis in association with the use of calcium dobesilate. Data from OM Pharma indicate that since its market introduction in 1970 about 25 million patients have been treated with calcium dobesilate for periods varying from 30 to 300 days. Using these two figures we estimate that the prevalence of development of a severe reaction (i.e. agranulocytosis) seems slight (i.e. one case for 6 million treatments).

2.2 Periodic Safety Update Report (PSUR) Data

Health authorities require pharmaceutical companies to provide them with a regular update on the

safety of marketed compounds. This is achieved using the PSUR, which is a standardised document that follows guidelines devised by the International Conference on Harmonisation.[74] Any adverse events should be included regardless of causality, but the quality of PSURs will vary depending on the level of the data-mining conduced by the drug company. In our present analysis, it was important to consider different sources of information to eventually detect discrepancies or errors in reporting. PSURs are supposed to include the data obtained from PMS reports, clinical trials and the international literature and to eliminate duplicate reports.

Analysis of the PSURs from the period of 1 January 1995 to 31 January 2003 partially confirms the data discussed in section 2.1 from the PMS report. Only data from the first PSUR for the period 1995–2000 will be analysed in detail, as the PSUR covering the next period up to 2003 provides no additional data as far as safety or adverse effects are concerned.

2.2.1 Patient Exposure Data

Data on patients exposure are presented in the last edited PSUR and show that the available worldwide sales for the reference period covered in the PSUR from 1 January 1998 to 31 January 2003 can be estimated to be approximately 401 274 338 tablets for calcium dobesilate 250mg and 683 340 364 capsules for calcium dobesilate 500mg (2002 was estimated on the basis of the sales in 2001, a decrease of 7%). Considering that for the indication of chronic venous disease the average dosage is 1 g/day for 30 days/year and for the indication of diabetic retinopathy, the average dosage is 1 g/day for 300 days/year, it can be estimated that 668 790 patients were treated with calcium dobesilate 250mg and 2 277 801 with calcium dobesilate 500mg for chronic venous disease or 66 879 patients were treated with calcium dobesilate 250mg and 227 780 with calcium dobesilate 500mg for diabetic retinopathy.

2.2.2 Adverse Event Data

Notifications of 19 cases corresponding to 46 events were collected directly by the company for the period covered by the 1995–2000 PSUR. Fourteen cases (32 events) were considered as not serious or not severe (vertigo, abnormal vision, insomnia, ventricular extra-systoles). Five cases (14 events) were classed as serious: one case with exanthema; one case with vomiting, diarrhoea and choreathetosis; one case with fever, rigors and haematuria; one case with fever, diarrhoea and haematuria; and one case with anorexia, taste anomaly, cough and nausea.

Of the 19 cases, the drug-adverse effect relationship was judged as 'certain' for five cases, of which four involved fever with urticaria. For 13 cases, relationship of the events to calcium dobesilate was judged as 'probable' or 'possible', whereas for one case the causality was considered 'improbable'.

The majority of the 46 events can be grouped into four classes using organ- or system-targets: general disorders (26.1%), gastrointestinal disorders (19.6%), central and peripheral nervous system disorders (17.4%) and skin and appendages disorders (8.7%). The most frequent single reactions were fever (17.4%), headache (8.7%), rigors (8.7%), vertigo (6.5%), diarrhoea (6.5%) and vomiting (6.5%).

In addition, seven cases of agranulocytosis were reported in the PSUR – five from Spain and two in France – but in all the cases, patients were taking concomitant medications that were suspected to be the cause of the agranulocytosis. As an example, the most recent case of agranulocytosis reported in the last PSUR described from Spain, involved an 88 year-old man treated with calcium dobesilate 1000 mg/day for 1 month. In spite of a positive rechallenge, in the file the causality remains as 'not assessable' due to the age and the continuation of comedication during the rechallenge which is known to be associated with agranulocytosis.

2.3 Summary of PMS/PSUR Data

Due to overlap between the data from the PMS report (eight cases of agranulocytosis)[10] and the PSUR (seven cases of agranulocytosis)[11] these data sources provided information on a total of 13 cases (nine from Spain, two from France, one from Germany and one from Switzerland) occurring from 1985 to 2001. Overall, the safety profile of calcium

Table IV. Data on calcium dobsilate-induced agranulocytosis published in the literature (1970–2003)

Author	Year of publication	Number of cases (gender, age)	Dosage in mg/day (indication)	Treatment duration (wk)
Kulessa et al.[72] (case report)	1992	1 (female; 64y)	1000 (retinopathy)	15
Cladera Serra et al.[73] (case report)	1995	1 (female; 70y)	1000 (haemorrhoids)	36
Garcia Benayas et al.[75] (case report)	1997	1 (male; 64y)	1500 (retinopathy)	8
Ibanez et al.[4] (case-control/case-population study)	2000	12		7d to ≥1y

dobesilate seems stable, with a question mark over the Spanish agranulocytosis cases (e.g. nine of the 13), fever induction and arthralgias. All of these serious events feature clearly in the summary of product characteristics for calcium dobesilate despite their very low incidence.

2.4 Data from the Published Literature

2.4.1 Agranulocytosis

Three cases of agranulocytosis (table IV) have been published in the international literature since 1992;[72,73,75] two of these cases came from Spain. The three cases involved patients aged >64 years of age in a context of polytherapy with the agranulocytosis occurring at the earliest after 2 months of treatment. All these cases were also reported in either the PMS report and/or the PSUR. These three published cases of agranulocytosis linked to calcium dobesilate use lead to a case-control and case-population study being carried out.[4] The study involved follow-up of 68.55×10^6 person-years and 345 cases of agranulocytosis. In the study population, 12 cases (5.6%) were patients exposed to calcium dobesilate (with exposure lasting from 7 days to ≥1 year). The agranulocytosis regressed between 5 and 14 days after stopping therapy. The authors concluded that the risk of agranulocytosis with calcium dobesilate was 25 times greater than that of a non-exposed population, a similar figure whether it was calculated using a case-control approach or case-population approach and in spite of the low calculated incidence (1 for 10 000 years of treatment) and a relative risk of 39.55 (95% CI 17.96, 77.49). The authors extrapolated that 121 cases or agranulocytosis would occur per million exposures per year [4] contrasting with the few spontaneous reports made during the same period of time, and our estimation based on the calculation of the number of potentially treated patients or the one issued by the Swiss Compendium, the Swiss Physician's Desk Reference (0.32 cases per million treated patients).[76]

2.4.2 Other Adverse Events

Fever (39–40°C) attributed to calcium dobesilate was described in two subjects both aged 56 years, treated with calcium dobesilate 500 mg/day.[77] This fever (never described as being linked to blood dyscrasias) in one case was associated with erythematous rash and arthralgias, and in the other with facial oedema, generalised erythema and buccal ulceration (disseminated erythematous lupus context).[77] A skin prick test was negative indicating that it was not a pure allergic reaction. Another case of drug-induced fever was reported by Puyana et al.[78]

A case of anaphylaxis was published by Royo et al.[79] The female patient, aged 50 developed erythema, papular exanthema, angioedema of the hands, the feet and the face, dysphonia, dysphagia, abdominal pain and diarrhoea, several hours after first taking calcium dobesilate. A skin prick test was positive supporting but not proving that it was a pure allergic reaction.

Finally, a case of erythematous pustulosis was described by Perez et al.[80]

2.5 Clinical Studies In Progress

Three clinical studies of calcium dobesilate in diabetic retinopathy, which involve 240, 51 and 24 subjects, are undergoing analysis. Only two cases of severe adverse effects of a cerebrovascular nature have been recorded but these were unrelated to calcium dobesilate administration.[81]

3. Discussion

Calcium dobesilate at dosages varying between 500–1500 mg/day have shown therapeutic efficacy in venous pathologies such as chronic venous disease[50] and haemorrhoids,[57] as well as in diabetic retinopathy.[55] Taking into account its very wide use (>10 million patients treated with calcium dobesilate annually in 60 countries), the risk of adverse outcomes with this medication must be considered as minimal, of minor gravity and mainly consisting of general syndromes (fever, arthralgias, cutaneous-mucosal signs, allergies). Only the agranulocytosis cases (13), and for the most part emanating from Spain, merit discussion. The prevalence of calcium dobesilate-induced agranulocytosis that we estimated as 0.32 cases per million treated patients,[76] is ten times lower than that found in the general population if one refers to the figures of 2.6 per 10^6 for Switzerland,[82] 3.3 per 10^6 for France[22] and 3.4 per 10^6 for the population recruited in the International Agranulocytosis and Aplastic Anaemia Study[16] and recently discussed by Kaufman et al.[15]

Let us recall that the risk of agranulocytosis due to dipyrone (also known as metamizole and noramidopyrine) was found to be 1 per 2000 prescriptions in one survey[83] and in two other reports[20,84] the risk was found to be 0.58 cases per 10^6 treatment days or 5.03 cases per 10^6 inhabitants/year. The increased risk indicated by Ibanez et al.[4] with its occurrence apparently localised to Spain are difficult to explain (associated with concomitant medication, or to some pharmacogenetic effect?) but seem above all questionable if one believes the recent treatment of the problem by the authors Zapater Hernandez et al.,[85] who conclude that from 1985 to 2000, the risk of agranulocytosis associated with calcium dobesilate was no higher than the maximum number of predicted cases in the general population. According to several teams and as reported by Varonos et al.[86] it is the calculation of agranulocytosis risk based on daily doses and treatment length that may be biased. According to Zapater et al.,[87] who used a Poisson-based methodology, the discrepancy between the calculated dobesilate-associated agranulocytosis risk and the number of noted spontaneous reports in the Ibanez study[4] becomes more and more unrealistic in terms of calculated risk that can be explained by at least three different factors: under-reporting which is rather significantly decreasing nowadays, duration of treatment and age of patients which were not taken into account in the Ibanez's study.

The explanation of the adverse effects induced by calcium dobesilate, which appear to be all type B in the absence of an evident link between the reported events and the pharmacological effects of the drug, could be immunological (drug-induced antibodies). Alternatively they could be due to direct toxicity particularly after suppression of cell production in the bone marrow;[88] the hypothesis concerning the role of the sulphites, although not systematically studied, and of their toxicity, can not be excluded.[89]

4. Conclusion

The present review of the safety of calcium dobesilate shows that the safety profile of this agent is favourable and that the risk of adverse effects appears constant over time. The incidence of adverse effects is low and, apart from the occurrence of agranulocytosis in Spain, it has no geographical peculiarity. Fever, arthralgias and gastrointestinal effects dominate the safety profile whereas rare cases of agranulocytosis, because of their potential gravity, have been described but rarely have they been firmly related to calcium dobesilate intake.

Finally, in view of the benefit/risk ratio and, taking into consideration the wide international use of calcium dobesilate, these updated data are reassuring.[90,91] The almost exclusively Spanish origin of the reported cases of agranulocytosis remain obscure especially when one takes into account the fact that consumption of calcium dobesilate in that country is not higher than in other countries where it is available, and that the pharmacovigilance organisation in Spain is similar to that of other Western countries.

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