1.1. Nitrofurantoine and cutaneous vasculitis – an update

In 2007 the Netherlands Pharmacovigilance Centre Lareb sent an signal to the Medicines Evaluation Board (MEB) concerning four reports of cutaneous vasculitis associated with nitrofurantoin [1]. These reports were received by Lareb in the period from September 1997 to October 2006. Since then, Lareb received three additional reports of vasculitis associated with the use of nitrofurantoin.
The current observation is an update of the signal sent to the MEB in the second quarter of 2007.

Nitrofurantoin is an antibiotic indicated for first choice treatment of *acute uncomplicated lower urinary tract infections* in general practice [2]. Further indications are *short-term preventive treatment in urological interventions and long term treatment of complicated urinary tract infections when there is no alternative available*. It is available on the Dutch market since 1969 [2].

Vasculitis is an inflammatory process affecting the vessel wall and leading to its compromise or destruction and subsequent hemorrhagic and ischemic events. Vasculitis can be classified as a primary phenomenon (e.g. idiopathic cutaneous leukocytoclastic angiitis or Wegener granulomatosis) or as a secondary disorder (connective tissue disease, infection, or adverse drug eruption-associated vasculitis) [3].
The aetiopathogenesis of vasculitis is unknown, and therefore nomenclature and classification are often descriptive and based on pathological features. In general, affected vessels vary in size, type, and location in association with the specific vasculitic disorder, which may occur as a primary process or be secondary to another underlying disease [4].

Cutaneous vasculitis is mostly a self-limiting, short-lived and benign disease with palpable purpura of the lower extremities as the most frequent manifestation. Sometimes other signs and symptoms (fever, malaise, arthralgia, paraesthesia) are present and of minor severity.
The majority of cases of cutaneous vasculitis will show a neutrophilic small vessel vasculitis that can be either a primary (idiopathic) disorder (eg, cutaneous leukocytoclastic angiitis) or a secondary disorder that is associated with drugs, infection (eg, streptococcal infection, viral hepatitis), or underlying disease (eg, connective tissue disease, malignancy) [5].
Cutaneous vasculitis can be the initial presentation of more severe systemic vasculitis [3]. Histological examination of a skin biopsy most often shows neutrophilic infiltrate surrounding and disrupting small vessels (postcapillary venules) associated with fibrin deposits and nuclear debris (leukocytoclasia). Extravasated red blood cells, purpura, are found in the adjacent dermis [5].

Reports

On the 14th of February 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained seven reports of vasculitis associated with the use of nitrofuratoin. The reports are listed in table 1.

Table 1. reports of vasculitis associated with the use of nitrofurantoin

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 18977 F, 51 – 60 years general practitioner	nitrofurantoin 2 dd 50 mg urinary tract infection	zopiclone	vasculitis both lower legs	>1 year discontinued recovered
B 36056 F, 71 years and older specialist doctor	nitrofurantoin 4 dd 100 mg urinary tract infection	insulin acenocoumarol amitryptilin magnesiumoxide paracetamol codein midazolam	vasculitis	7 days recovered
C 47603 F, 31 – 40 years specialist doctor	nitrofurantoin 1 dd 100 mg urinary tract infection		petechiae vasculitis	1 hour recovered
D 59737 F, 71 years and older general practitioner	nitrofurantoin 50 mg cystitis acenocoumarol according to INR indication not reported	fentanyl bisoprolol bumetanide perindopril hydrokinine nitroglycerin	vasculitis purpura vascular haematoma INR increased drug interaction	5 days recovered
E 65329 F, 71 years and older general practitioner	nitrofurantoin 50mg 4dd urinary tract infection	sotalol	vasculitis, liver function disorder, fever	2 day discontinued recovered
F 125066 F, 61 – 70 years specialist doctor	nitrofurantoin 50mg cystitis	atorvastatin nifedipine carbasalate calcium triamterene/ hydrochloro-thiazide	leukocytoclastic vasculitis	14 days discontinued recovered
G 128557 F, 71 years and older pharmacist	nitrofurantoin 100mg 2 dd urinary tract infection calcium carbonate with cholecalciferol 500mg/800ie osteoporosis, simvastatin 40mg cerebrovascular accident, dipyridamole 150mg cerebrovascular accident	salmeterol/ fluticasone acetylsalicylic acid ipratropium	vasculitis, dyspnoea	3 day discontinued recovered

Some characteristics of the reports are described below. Case A to D are described in detail in the Quarterly Report 2007-2.

In case A (18977) the patient developed vasculitis on both lower legs with a latency of more than one year. After eight more months, nitrofurantoin was withdrawn and she was treated with bandages and recovered.

In case B (36056), the patient developed redness of the left leg, with additional multiple purpura of the right leg and the arms, seven days after start of

nitrofurantoin 4 dd 100 mg for urinary tract infection. The diagnosis vasculitis was confirmed by a dermatologist, no biopsy was done. Laboratory tests revealed increased ESR 30 mm/hour, CRP 75 mg/l, thrombocytes 212*10^9/l and slight blood eosinophilia 0,8*10^9/l. After withdrawal the patient recovered completely. She had a medical history of diabetes mellitus, venous thrombosis of the leg with pulmonary embolism, hip and knee prosthesis, hemicolectomy for coloncarcinoma without metastases and TIA from the basilary artery. Concomitant medication was continued.

In case C (47603), the patient developed an acute petechial reaction on both feet within one hour after administration of 100 mg nitrofurantoin for urinary tract infection. The drug was withdrawn immediately, the patient was hospitalized. The reaction worsened in the following week and spread to the legs, trunk and arms with haematomas and was diagnosed as vasculitis by the consulted dermatologist. No thrombopenia, no eosinophilia, ESR and CRP were normal. Recovery started after two weeks and the patient was dismissed from hospital. Treatment with prednisone was proposed but not given because the patient had given birth 10 weeks earlier and was still breastfeeding.

In case D (59737), the patient had disseminated miliair and lenticular purpura on both lower legs, extending to the inguinal region, with haematoma formation. The reaction started five days after start of nitrofurantoin 50 mg for cystitis (unknown number of dosages per day). There was also interaction with concomitant acenocoumarol, which elevated the INR. The patient recovered after withdrawal of nitrofurantoin, purpura dissolved in a few days, she had recovered completely after two weeks. The INR also normalized. The concomitant medication was continued. Medical history was renal impairment, cardiac failure, hypertension, coxarthrosis, gonarthrosis, M. Graves.

In case E (65329) the patient developed fever and vasculitis after using nitrofurantoin for two days, After five days the patient also developed a hepatic function disorder. She was hospitalized and nitrofurantoin was withdrawn and the patient recovered.

In case F (125066) the patient developed a leukocytoclastic vasculitis following administration of nitrofurantoine for cystitis with a latency of 14 days after start. The medical history indicates that the patient had a hysterectomy, hypertension Raynaud's disease, a thyroid disorder that was treated with a strumectomy and a bladder disorder.

In case G (128557) the patient developed vasculitis and dyspnoea following administration of nitrofurantoin for an urinary tract infection (latency 3 days), dipyridamole for a cerebrovascular accident (latency 6 months), simvastatinefor cerebrovascular accident (latency 6 months), calcium with cholecalciferol for osteoporosis (latency 5 months). According to the reporter, nitrofurantoin is seen as the drug which is most suspect for causing the reaction. The patient is treated with prednisone and is recovering. Lung test revealed no abnormalities. Concomitant medications were acetylsalicylic acid, salmeterol with fluticasone and tiotropium. The patient has also chronic obstructive pulmonary disease, but this is stable. It cannot be excluded that the vasculitis is a pulmonary vasculitis in this case.

Other sources of information

SmPC

In the Dutch SmPC of nitrofurantoin (Furadantine®) vasculitis is not mentioned as an adverse drug reaction [2]. This is also the case for the US SmPC of nitrofurantoin [6].

Literature

Lareb recently published about the first five cases of cutaneous vasculitis that were received [7].
Similar to the search performed for the previous quarterly report about this subject, a Medline search for cutaneous vasculitis and nitrofurantoin revealed no relevant results (("Vasculitis"[MeSH] OR "Vasculitis, Hypersensitivity"[MeSH] OR "Vasculitis, Allergic Cutaneous"[MeSH]) AND "Nitrofurantoin"[MeSH]]). Most articles refer to pulmonary hypersensitivity reactions, which are a well-known adverse drug reactions for nitrofurantoin.

Databases

On February 14th, 2012 the Lareb database contained seven reports on (leukocytoclastic) vasculitis associated with the use of nitrofurantoin. The reporting odds ratio for the association was 4.3 (95%CI 2.0-9.0), making this association disproportionally present in the database.
The database of the Uppsala Monitoring Centre of the WHO contained 49 reports of nitrofurantoin with (leukocytoclastic) vasculitis (ROR 2.4; 95%CI 1.8-3.1).

Table 2. Reports of vasculitis in the Lareb and WHO database

Database	Preferred Term	Number of reports	ROR (95% CI)
Lareb	Vasculitis	6	5.5 (2.4-12.5)
	Leukocytoclastic vasculitis	1	-
	Total	7	4.3 (2.0-9.0)
WHO	Vasculitis	38	2.3 (1.6-3.1)
	Leukocytoclastic vasculitis	11	2.8 (1.8-3.1)
	Total	49	2.4 (1.8-3.1)

On 30 January 2012, the Eudravigilance database contained eight reports of vasculitis associated with the use of nitrofurantoin, of which six were classified as ‘serious’. The criterion for seriousness was “Hospitalization” in five cases and “Other” in two cases. The reports concern six females and two males with a median age of 74 years (range 33 – 86 years). Vasculitis was reported disproportionally (ROR = 1.92 , 95% CI: 0.96 – 3.85).

Prescription data

The number of patients using nitrofurantoin in the Netherlands is shown in table 3.

Table 3. Total number of users of nitrofurantoin per year since 2006 [8]

	2006	2007	2008	2009	2010
Nitrofurantoine (Furabid ®)	479,820	513,130	554,300	587,050	612,240

Mechanism

The aetiology of vasculitis is broad and unknown in 45-55% of cases. Bacterial and viral infections are a known cause as well as an immunological response; in diseases like SLE vasculitis can occur due to the formation of immuncomplexes and autoantibodies. In approximately 10-15% of cases, drugs are the cause of vasculitis [5]. Vasculitis is caused most frequently by ACE inhibitors, hydantoin derivatives, minocyclin, NSAID's, sulphonamides, (propyl)thiouracyl, hydralazin, colony-stimulating factors, allopurinol, cefaclor, D-penicillamin, phenytoin, isotretinoin, methotrexate [9]. In addition it can be caused by all types of antibiotics, but as bacterial and viral antigens can cause vasculitis reactions, a causal relationship is hard to prove [9].
There is no clear mechanism that explains the development of vasculitis associated with drugs. It is thought to be a hypersensitivity reaction in which drugs or drug metabolites (or any other trigger like bacterial or viral pathogens or immune complexes) can illicit an inflammatory reaction [5,7]. There are no significant differences in clinical presentation, serologic abnormalities and pathologic findings compared to idiopathic vasculitis, but tissue eosinophilia is a histological clue to drug aetiology. Latency can vary from hours to years. Due to the immunological basis of the reaction, positive rechallenge is to be expected. The very rapid and extensive reaction to only one tablet of nitrofurantoin in patient C could have been a rechallenge reaction after previous sensitization.

Class effects

Since nitrofurantoin is the only nitrofuran on the Dutch market, there is no relevant information on a class effect.

Discussion and conclusion

This signal is an update of the previous Quartly Report 2007-2 on cutaneous vasculitis associated with nitrofurantoin use. In the Lareb database the association between nitrofurantoin and cutaneous vasculitis is now reported seven times. These reports were generally well documented and the association is disproportionally present in the databases of Lareb, Eudravigilance and the WHO.
Although no literature reports could be found on cutaneous vasculitis, the proposed hypersensitivity mechanism of drug-induced vasculitis and the well-known pulmonary hypersensitivity reactions to nitrofurantoin strongly suggest an association.
As mentioned before in Quarterly Report 2007-2, in the reports to Lareb the cutaneous vasculitis could have been attributed to confounding factors like an underlying bacterial infection. Positive and prompt recovery after withdrawal of nitrofurantoin, while other factors persisted, supports the association in these cases.
In the Quarterly Report 2007-2 Lareb suggested that cutaneous vasculitis should be added to the SmPC. In 2012 we recommend the MEB to mention cutaneous vasculitis in the SmPC of nitrofurantoin.

- Consider to mention cutaneous vasculitis in the SmPc of nitrofurantoin

References

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This signal has been raised on April 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).