Triamcinolone acetonide injection and postmenopausal haemorrhage

Introduction

Triamcinolone acetonide (Kenacort-A®) is a synthetic glucocorticosteroid with marked anti-inflammatory action. It has been approved for the Dutch market since September 1966. The intra-articular injection is indicated for the treatment of *acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis, or osteoarthritis* [1].
Postmenopausal bleeding is uterine bleeding more than a year after the last menstruation. The incidence of postmenopausal bleeding for women aged 45 to 64 years and women older than 65 years is 4.5 and 3.3 per 1000 women per year respectively [2]. Endometrial atrophy and endometrial polyps are the most common causes of postmenopausal bleeding. Endometrial carcinoma is the cause in about 10 percent of patients. Hormone replacement therapy may also cause cyclical bleeding [3].

The current observation describes the association between triamcinolone acetonide injection and postmenopausal haemorrhage.

Reports

On July 16th 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained nine reports of postmenopausal haemorrhage associated with the use of triamcinolone acetonide injection. The reports are listed in Table 1.

Table 1. Reports of postmenopausal haemorrhage associated with the use of triamcinolone acetonide injection.

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 9768 F, 61-70 years pharmacist	triamcinolone acetonide injection 40mg		vaginal haemorrhage	2 weeks discontinued not reported
B 40278 F, 51-60 years general practitioner	triamcinolone acetonide injection 40mg pain left shoulder	lidocaine	vaginal haemorrhage, flushing	2 weeks discontinued not reported
C 131537 F, 61-70 years specialist doctor	triamcinolone acetonide injection 40mg polyarthritis	meloxicam	cramps in legs, vaginal bleeding	days discontinued recovered
D 132726 F, 51-60 years specialist doctor	triamcinolone acetonide injection 40mg arthritis	pantoprazole, topiramate, temazepam, eletriptan, amitriptyline	vaginal bleeding	days discontinued recovered

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 133846 F, 41-50 years specialist doctor	triamcinolone acetonide injection 40mg rheumatoid arthritis	celecoxib, omeprazole, salbutamol, salmeterol/fluticasone, tramadol, desloratadine, prednisolone	vaginal bleeding	days discontinued recovered
F 18975 F, 51-60 years general practitioner	triamcinolone acetonide injection 40mg bursitis	estriol, tolbutamide	postmenopausal bleeding	9 days discontinued not reported
G 43306 F, 61-70 years pharmacist	triamcinolone acetonide injection 10mg		postmenopausal bleeding	2 weeks not reported recovered
H 135761 F, 71 years and older pharmacist	triamcinolone acetonide injection 10mg knee pain, prednisolone tablet 30mg respiratory tract infection	vitamin c, amitriptyline, oxycodone, ibuprofen, omeprazole, ferrous fumarate, calcium/vitamin D, mirtazapine, quetiapine	vaginal haemorrhage	2 days discontinued recovered
I 136606 F, 61-70 years general practitioner	triamcinolone acetonide injection 40mg bursitis	artificial tears, amlodipine, metoprolol	postmenopausal bleeding	10 days discontinued recovering

Some of the characteristics of the reports are described below:

Patient B did not have vaginal blood loss for nine years prior to the corticosteroid injection.

Patient C did not have vaginal blood loss for ten years prior to the corticosteroid injection. She received three injections (one every four weeks) and after each injection she experienced vaginal bleeding.

Patient D did not have vaginal blood loss for two years prior to the corticosteroid injection.

Patient E had irregular menstruation and climacteric complaints since several years. Concomitant medication was prednisolone, known to cause menstrual irregularities.

Patient F also uses estriol tablets (start- and stopdate unknown). This is known to cause vaginal bleeding, however vaginal bleeding was reported after the triamcinolone acetonide injection and estriol was not reported as co-suspected.

Other sources of information

SmPC

The SmPC of triamcinolone acetonide injection only mentions menstrual irregularities, postmenopausal haemorrhage is not mentioned [1].

Literature

Postmenopausal haemorrhage after corticosteroid injections is not widely described in the literature. Kerner describes nine cases of postmenopausal bleeding associated with corticosteroid administration. The usual dose of corticosteroid was 40 mg of triamcinolone injection intramuscularly or, more commonly, into a joint. None of these patients had vaginal blood loss for many years. The time interval between the administration of corticosteroid and the occurrence of bleeding ranged from nine to 19 days. In all patients, pathologic examination revealed a nonsecretory endometrium; in no instance was carcinoma or atypical hyperplasia found [4].
In a randomised trial to compare the effectiveness of corticosteroid injections with physiotherapy for the treatment of painful stiff shoulder 53 patients received treatment with corticosteroid injections (maximum of three 40 mg triamcinolone acetonide injections during six weeks). Six of these patients reported irregular menstrual bleeding, two of whom were postmenopausal [5]. A case report describes a postmenopausal woman who was treated with 40 mg of triamcinolone acetonide epidurally twice with a two week interval. This was followed by a large amount of uterine bleeding [6].

Databases

On July 16th 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained nine reports of postmenopausal haemorrhage/vaginal haemorrhage associated with the use of triamcinolone acetonide injection which was reported disproportionally. The Reporting Odds Ratio (ROR) is 40.3 (95% CI 20.2-80.3).
The WHO database of the Uppsala Monitoring Centre contained 18 reports of postmenopausal haemorrhage associated with the use of triamcinolone (14 reports concerned the triamcinolone acetonide injection and 4 reports did not specify the administration route) with a ROR of 21.6 (95% CI 13.5-34.4) which was also disproportional. Of these 18 reports 3 were from the Netherlands (3 cases in the Lareb database are coded as postmenopausal haemorrhage and 6 cases are coded as vaginal haemorrhage/bleeding). Furthermore, the WHO database contained 12 reports of vaginal haemorrhage in women ≥ 45 - >75 years. Of these 12 reports 9 concerned the triamcinolone acetonide injection, 3 reports did not specify the administration route and 1 report concerned the epidural route. It is not known how many of these women were postmenopausal. But this was also reported disproportionally with a ROR of 4.0 (95% CI 2.3-7.1).

On August 8 2012, the Eudravigilance database contained nine reports of postmenopausal haemorrhage/vaginal haemorrhage (5 from NL, 3 from DEU, 1 from USA) in association with triamcinolone, which was reported disproportionally (ROR = 2.7, 95% CI: 1.4 – 5.2). The median age was 60 years (range 45 – 77 years). In one case, the age was not reported. Three cases were classified as serious, the criterium being “other”.

Prescription data

The number of patients using triamcinolone acetonide injection in the Netherlands is shown in Table 2.

Table 2. Number of patients using triamcinolone acetonide injection in the Netherlands between 2007 and 2011 [7].

Drug	2007	2008	2009	2010	2011
Triamcinolone	167,120	171,330	170,910	173,930	180,070

Drug	2007	2008	2009	2010	2011
acetonide injection					

Table 3. Number of patients using systemic glucocorticoids in the Netherlands between 2007 and 2011 [7].

Drug	2007	2008	2009	2010	2011
Betamethason	30,350	31,004	31,541	34,069	18,248
Cortison	2,523	2,395	2,269	2,181	1,800
Dexamethason	32,442	32,484	34,918	35,015	46,536
Hydrocortison	5,756	6,085	6,502	7,235	8,037
Methylprednisolon	13,031	12,671	11,615	11,831	11,996
Prednisolon	368,460	390,550	412,080	427,550	454,850
Prednison	49,526	44,588	39,707	34,979	33,256

Mechanism

The mechanism by which triamcinolone acetonide injection causes postmenopausal haemorrhage is not completely elucidated. A proposed mode of action of triamcinolone acetonide could be a direct effect on the endometrium. A proliferation of the endometrium could be induced or sustained as long as the blood level is high, and vaginal bleeding follows at the moment the blood level decreases [8].

Class effect

The Netherlands Pharmacovigilance Centre Lareb has not received reports of postmenopausal haemorrhage when using other corticosteroid injections. Furthermore, it is not possible to select on route of administration in the WHO database. Therefore it is not possible to determine if this is a class effect of corticosteroid injections.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 9 reports of postmenopausal haemorrhage associated with the use of triamcinolone acetonide injection. Latency ranged from two days to two weeks. This is consistent with latency reported in the literature [4]. Malignancies can also cause postmenopausal haemorrhage. In these case reports that seems unlikely since six of the nine patients recovered after withdrawal of triamcinolone acetonide injection. In the remaining three the outcome was not reported. One patient reported estriol, known to cause vaginal haemorrhage [2], as concomitant medication. However, the startdate and duration of use of estriol was not reported.
Postmenopausal haemorrhage is a systemic effect of the triamcinolone acetonide injection. Therefore, it would be expected to occur with other administration forms also. However, Lareb only received reports concerning triamcinolone acetonide injections. This might be explained by the fact that triamconolone acetonide is more widely used than the other glucocorticosteroids for systemic use, except prednisolone. Triamcinolone and prednisolone have a comparable potency and prednisolone is more widely used therefore it would be expected that there would also be reports of prednisolone. However, Lareb did not receive any reports of prednisolone and postmenopausal haemorrhage.

The exact mechanism through which triamcinolone acetonide injections would cause postmenopausal haemorrhage remains unknown. A possible mechanism proposed in the literature concerns a direct effect on the endometrium [8].
The association of triamcinolone acetonide injection with postmenopausal haemorrhage is supported by a statistically significant disproportionality in the databases of the Netherlands Pharmacovigilance Centre Lareb, the database of the WHO and the Eudravigilance database.
It should be considered to mention postmenopausal haemorrhage in the Dutch SmPC of triamcinolone acetonide injection.

- Postmenopausal haemorrhage should be mentioned in the SmPC of triamcinolone acetonide injection

References

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This signal has been raised on November 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).