

## Isotretinoin and anal fissure

### Introduction

Isotretinoin (Roaccutane<sup>®</sup>) is indicated for *severe forms of acne (such as nodular acne or acne conglobata or acne with a risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibiotics and topical therapy.*

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail. It has been established though, that the improvement of the clinical symptoms of severe acne is associated with suppression of sebum production and a histologically demonstrable reduction of sebaceous gland size. Furthermore, an anti-inflammatory effect in the dermis of isotretinoin has been noticed.

Isotretinoin was granted marketing authorization in the Netherlands in 1984 [1].

An anal fissure is a benign anorectal condition. An anal fissure is a tear in the anoderm distal to the dentate line [2]. The pathogenesis is due to multiple factors: mechanical trauma, sphincter spasm, and ischemia [3]. Dependant of the etiology, the fissure can be primary (e.g., local trauma, such as passage of hard stool or prolonged diarrhoea) or secondary (e.g., inflammatory bowel disease, malignancy). Anal fissures can be acute (healing within six weeks with conservative local management) or chronic (where a surgical approach may be required). An anal fissure is the result of stretching of the anal mucosa beyond its normal capacity [2].

Most often infants and middle-age individuals are affected by anal fissures. The true prevalence of anal fissures in adults is not known, because anorectal discomfort is often attributed to symptomatic haemorrhoids [2].

Anal fissures can be prevented by using proper anal hygiene, which includes keeping the anal area dry, and wiping with a soft cotton or moistened cloth. Other measures that may be helpful include preventing constipation, avoiding straining during defecation, avoiding trauma to the anus, and prompt treatment of diarrhoea [2].

This observation describes the association between anal fissure and the use of isotretinoin.

### Reports

From 28 March 2008 until 20 October 2014 The Netherlands Pharmacovigilance Centre Lareb received two reports concerning anal fissure associated with the use of isotretinoin.

#### Case A (report number 76188)

This non-serious spontaneous report from a consumer concerns a female aged 21-30 years years, with anal fissure, fatigue, eye irritation, headache, epistaxis, abdominal cramp and dry lips, following administration of isotretinoin for acne with a latency of 4 days after start for the fissures and an unknown latency for the other events. The dose has not been changed. About 4.5 months after start of the reaction, the patient is recovering from the fissures using isosorbidedinitrate vaseline cream, the outcome of the other events was not reported. The reporter mentioned that the isotretinoin makes the skin and mucous membranes vulnerable.

Concomitant medication was levothyroxine. The past drug therapy indicated isotretinoin use without a similar reaction, 6 years before the current reaction.

#### Case B (report number 161161)

This non-serious spontaneous report from a consumer concerns a female aged 11-20 years, with anal fissures following administration of isotretinoin for acne with a latency of 2 weeks after start. The dose for isotretinoin was reduced. The patient was treated with botox injections into the anal sphincter. About 8 months after start of the reaction, the patient is recovering. Concomitant medication was not reported.

The patient has no known medical history. The patient has no known past drug therapy.

## Other sources of information

### SmPC

The Dutch SmPC of isotretinoin does not mention anal fissure as an adverse drug reaction. The SmPC does mention dryness of the skin; and dry mucous membranes, e.g. the lips (cheilitis), dry nasal mucosa (epistaxis), dry eyes (conjunctivitis) [1]. In the section “Special warnings and precautions for use” the Dutch SmPC mentions, concerning the skin that the patient should be recommended to use moisturizing ointment or cream and a lip balm from the start of the treatment because isotretinoin probably causes dryness of the skin and lips. Concerning the eyes the SmPC mentions that dry eyes can be corrected by applying a soothing ointment or by using artificial tears [1].

Furthermore the SmPC of isotretinoin describes inflammatory bowel disease as an adverse reaction [1].

The US SmPC of the FDA of isotretinoin Claravis® does not mention anal fissures as an adverse reaction. The US SmPC does mention that many of the side effects and adverse reactions seen in patients receiving isotretinoin Claravis® are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, e.g., of the lips, nasal passage, and eyes) [4].

### Literature

In the literature four cases were described, in 3 articles.

A 50 year old male patient developed anal fissure and proctitis a few days after start of isotretinoin (twice daily 20 mg). There was no improvement after routine treatment. After 15 days the isotretinoin was withdrawn and within 2 weeks the symptoms improved. A 27-year old male patient who was diagnosed with anal fissure and dry anal mucosal membrane, one week after start of isotretinoin (twice daily 20 mg). After withdrawal the problem subsided within 2 weeks [5].

A 17-year old male patient with anal fissure and rectal bleeding two months after start with isotretinoin (twice daily 30 mg). Two weeks after withdrawal the patient had recovered [6]. Furthermore a case of a 15-year old female patient was described [7] with rectal bleeding and pain, two months after start of isotretinoin (40 mg twice daily). Anal fissure was diagnosed. The patient was treated with stool softeners and conservative treatment. Despite this, the anal pain was not relieved after a month. The patient also experienced cheilitis, xerosis and epistaxis. The isotretinoin was withdrawn and over the next four weeks there was gradual improvement of the symptoms.

### Databases

Table 1. Reports of anal fissure associated with isotretinoin, in the Lareb [8], WHO [9] and Eudravigilance database [10].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Anal fissure	2	
WHO	Anal fissure	310	107.8 (94.1-123.4)
Eudravigilance	Anal fissure	369	147.3 (127.7-169.9)

### Prescription data

Table 2. Number of patients using isotretinoin in The Netherlands between 2009 and 2013 [11].

Drug	2009	2010	2011	2012	2013
Isotretinoïne	17,186	18,654	17,919	18,848	19,642

## Mechanism

Dry skin is a known adverse reaction of isotretinoin, described in the SmPC [1]. The SmPC describes as one of the possible mechanism of actions, that improvement of the clinical symptoms of severe acne is associated with suppression of sebum production and a histologically demonstrable reduction of sebaceous gland size [1]. This might also be applicable for the anoderm. Consequently, this dryness might make the anoderm more vulnerable to mechanic trauma e.g. hard stool, or possibly to mechanic stretching (although no literature is available on the latter).

Of inflammatory bowel disease while using isotretinoin, described proposed mechanisms include: inhibition of epithelial cell growth, resulting in ulceration and inflammation of the gut mucosa; inhibition of glycoprotein synthesis affecting the integrity of the mucosal wall; and stimulation of killer T cells, leading to epithelial cell injury and a resultant inflammatory response [12]. Of the cases received by Lareb there were no clues that the symptoms were part of inflammatory bowel disease.

The literature provides no indications of other possible mechanisms (e.g. change in muscle tonus or changes in vasculature) concerning isotretinoin and anal fissure.

## Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two reports concerning anal fissure associated with the use of isotretinoin. The latencies were 4 days and 2 weeks. Both patients in the reports received by Lareb were treated and were recovering. Of one of the patients the dose of isotretinoin was not changed, and of the other patient the dose was reduced. Other factors, e.g. hard stool, were not reported. Of the cases received by Lareb there were also no clues that the symptoms were part of inflammatory bowel disease. In the WHO database there are 310 cases present of anal fissure associated with isotretinoin. In the WHO- and Eudravigilance databases the association is disproportionally present, with a ROR in the WHO database of 107.8 (95% CI 94.1-123.4). The ROR in the Lareb database can't be reliably calculated because of the small number of reports. The Dutch SmPC mentions dryness of the skin and of the mucous membranes, but does not mention anal fissure as an adverse reaction. The SmPC also mentions in the section "Special warnings and precautions for use" concerning the skin that the patient should be recommended to use moisturizing ointment or cream and a lip balm from the start of the treatment because isotretinoin probably causes dryness of the skin and lips, and that dry eyes can be corrected by applying a soothing ointment or by using artificial tears [1], but it mentions no warnings or precautions concerning prevention of anal fissures.

Because of the two strong cases received by Lareb, the very high ROR in the WHO-database, and the in the Dutch SmPC described adverse reaction dryness of the skin and mucous membranes, it is suggested that isotretinoin might have a causative role in the occurrence of anal fissure. It could be considered to formulate evidence-based preventive measures, and describe these in the section "Special warnings and precautions for use".

- Anal fissure should be mentioned in the SmPC of isotretinoin

## References

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*This signal has been raised on March 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbq-meb.nl](http://www.cbq-meb.nl)*