Buprenorphine and inflammation resulting in skin depigmentation

Introduction

Buprenorphine is a mixed agonist-antagonist agent. It exerts analgesic effects by binding to CNS opiate receptors. It produces partial agonistic effects at the mu-opioid receptors and antagonistic effects at kappa-opioid receptors. Buprenorphine has a long duration of action and an analgesic potency 25 to 40 times that of morphine sulfate.
Buprenorphine transdermal is indicated *for the management of non-malignant, moderate chronic pain, for which an opioid is needed in order to reach sufficient reduction in pain.*

Buprenorphine is available as transdermal patches:
BuTrans® 5, 10 or 20 µg / hour, Transtec® 35, 52,5 or 70 µg / hour or generic Buprenorfine Ranbaxy 35, 52,5 or 70 µg / hour. The active ingredient is buprenorphine. The inactive excipients ingredients in Butrans® are: levulinic acid, oleyl oleate, povidone, and polyacrylate cross-linked with aluminum. Butrans® was granted marketing authorization for the Dutch market in 2008.

Transdermal buprenorphine should be applied to a hairless or nearly hairless non-irritated skin site on the upper outer arm, upper chest, upper back, or side of chest. If necessary, the area can be cleansed with water only; it is advised not to use soaps alcohol, oils, lotions, or abrasive devices on the application site. The skin at the application site should be allowed to dry completely.
The transdermal buprenorphine patch should be applied immediately after removal from the protective pouch. Each patch provides analgesia for 7 days. After removal of the patch, a new patch should be applied to a different skin site every week making sure that at least 3 weeks pass before the same skin site is used again. When only 2 weeks had passed between applications on the same site, a doubling of drug exposition was observed.

In skin depigmentation no pigment in the macules is present, whereas in skin hypopigmentation macules have retention of some pigment. Skin hypopigmentation can be caused by systemic conditions, such as cutaneous T cell lymphoma, leprosy, tinea versicolor, auto-immune related conditions as sarcoidosis and vitiligo or pityriasis alba, as a result of post-inflammatory reaction [4].

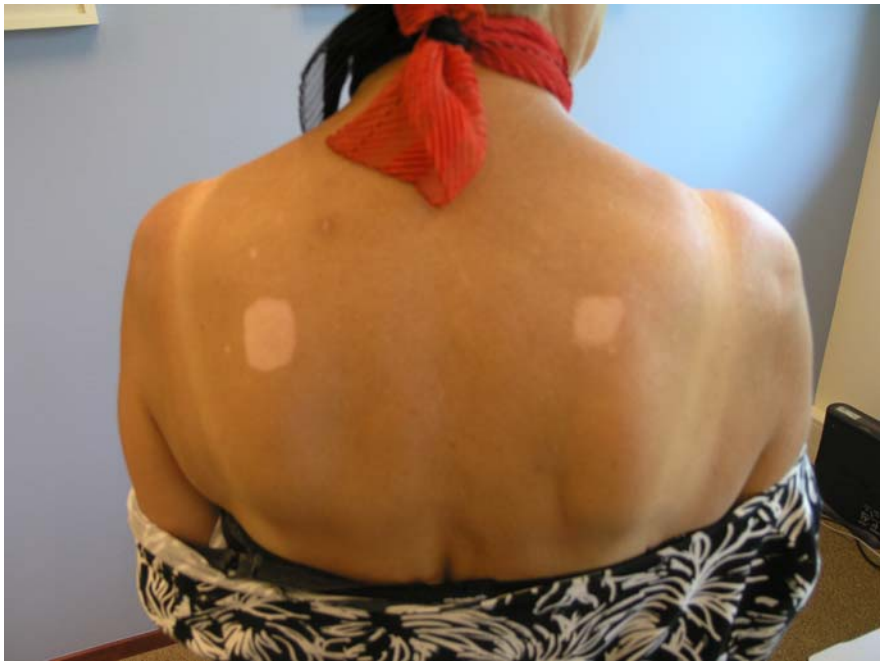
Reports

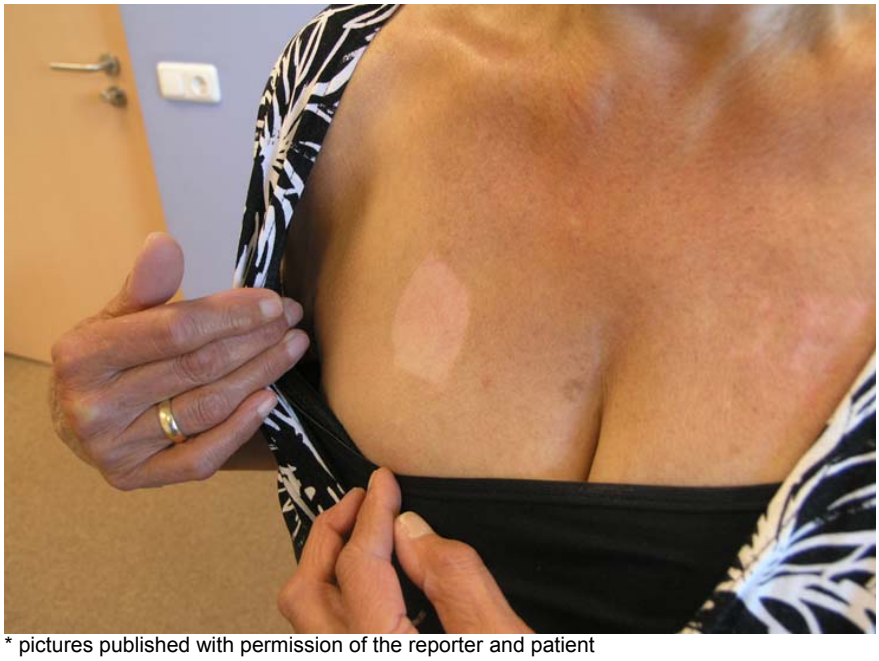
Until 17 October 15 2013, the Netherlands Pharmacovigilance Centre Lareb received 2 reports of skin depigmentation in association with buprenorphine dermal patches (Butrans®).

Case A (116659)
A specialist doctor (neurologist) reported skin depigmentation is a female aged 61-70 years, who used buprenorphine Butrans® 5 µg / hour for pain. She had used buprenorphine for 5 months (6 patches) when an inflammatory skin reaction with pus developed followed by skin depigmentation at the site of the patch. Buprenorphine was discontinued. The patient had not recovered at the time of reporting, almost four months later. Follow up information was requested but not

retrieved. Concomitant medication was carbasalate calcium, losartan, pantoprazole and prednisone.

Case B (153414)
A general practitioner reported skin erythema and irritation a female aged 61-70 years, who used buprenorphine Butrans® 5 µg / hour for chronic pain for a couple of days. After a couple of weeks skin discolouration and vitiligo developed in the shape of the transdermal patch. Concomitant medication was acetylsalicylic acid, perindopril, atorvastatin, hydrochlorothiazide, omeprazole and latanoprost eye drops. Buprenorphine was discontinued. Follow up information was requested. The patient had not yet recovered six months after discontinuation. Enclosed pictures show several square-shaped 3x3 cm depigmented areas on upper chest and back. As also some small depigmented spots are observed, it cannot not be ruled out that patient is susceptible to vitiligo.





* pictures published with permission of the reporter and patient

Other sources of information

SmPC

The most common adverse skin reactions described in the SmPC are pruritus and erythema (> 10 %), exanthema (1-10%), dry skin and urticaria (0,1 -1 %), and vesicles and pustules (< 0,01 %). Furthermore an inflammatory reaction is described at the site of application (0,01-0,1 %). In some cases a delayed allergic reaction is observed with evident inflammatory aspects. In such cases the treatment with buprenorphine Butrans® should be discontinued. Skin depigmentation is not mentioned in the SmPC's of buprenorphine patches [1-3].

Literature

No reports of skin depigmentation or skin hypopigmentation in association with buprenorphine could be found.
The US SmPC describes dose- related application site erythema, irritation, rash and pruritus. Beside this, marked inflammation (with burning, and vesicles), have been rarely reported within days to months of initiating buprenorphine transdermal system [5].
Several topical drug have been related to cause hypopigmentation, including tretinoine and corticosteroids. Depigmentation is associated primarily with the application of monobenzyl ether of hydroquinone or exposure to catechols, phenols or quinones [6]. Use of transdermal patches have been implicated in skin depigmentation: twice this was observed after transdermal clonidine [7,8] and chemical leukoderma resulted after the application of a transdermal methylphenidate patch [9].

Databases

On October 17, 2013, the database of the Netherlands Pharmacovigilance Centre contained two reports of skin depigmentation in association with buprenorphine Butrans® 5 µg / hour. No reliable ROR could be calculated because of the low number of cases.

On October 17, 2013, the WHO database of the Uppsala Monitoring Centre contained 3 reports of skin depigmentation in association with buprenorphine with a ROR of 4.0 (1.3-12.3). Two of these originated from the Netherlands, one from Germany: this concerned a male aged 77 years.

On November 11, 2013, the Eudravigilance database of the EMA contained no reports of skin depigmentation in association with buprenorphine. It is not clear why there are no Dutch cases of this association present in Eudravigilance.

Prescription data
The number of patients using buprenorphine in the Netherlands is shown in table 1 [10].

Table 1. Number of patients using buprenorphine in the Netherlands between 2007 and 2011

Drug	2008	2009	2010	2011	2012
Buprenorphine (Butrans®)	7.822	8.603	25.186	36.095	41.179

Mechanism
Melanogenesis is a complex process which includes melanin synthesis, transport and release to keratinocytes. It is controlled by multiple mediators (growth factors, cytokines) acting on melanocytes, keratinocytes and fibroblasts.
The suggested aetiopathogenesis behind drug-induced vitiligo is:
(1) activation of cytotoxic T cells directed against melanocyte antigens,
(2) damage to sympathetic nerves that are connected by chemical synapses to melanocytes with a resultant functional disturbance, and
(3) a direct cytotoxic nature of the drug on melanocytes (apoptosis).
Most of the mechanisms suggested are hypothetical with no direct or scientific evidence to establish the exact role of the implicated drug [11].
In contact vitiligo following exposure to chemicals, it is suggested that the instigating factors result in susceptible fragile melanocytes to undergo apoptosis [12]. There is no indication that above mentioned mechanisms play a role in buprenorphine induced skin depigmentation.
Hypopigmentation is also observed after various inflammatory skin diseases, including atopic dermatitis, lichen striatus and pityriasis lichenoides chronica [13]. The variation in individual response to cutaneous inflammation is not well understood. Ruiz-Maldonado therefore proposed the term ‘individual chromatic tendency’. The tendency for post inflammatory hypopigmentation might be genetically determined and inherited in an autosomal dominant pattern. It is suggested that the hypopigmentation may result from inhibition of melanogenesis rather than destruction of melanocytes; however severe inflammation may lead to actual loss of melanocytes ore even melanocyte death and thus permanent pigmentary changes, resulting in hypopigmentation or depigmentation [14]. Depending on the severity of the hypopigmentation, re-pigmentation can likely take weeks to years.

Class effects
No cases of skin depigmentation in association with other opioid patches were reported to Lareb nor was any information found in a literature search.

Discussion

In both reactions reported to Lareb, at first the patients experienced a skin reaction at the application site of the transdermal patch. Over time, this resulted in long lasting skin depigmentation. This is in agreement with the mechanism as observed in post inflammatory hypopigmentation in inflammatory skin diseases. It is therefore suggested that the observed skin depigmentation in association with buprenorphine patches is a result of a post inflammatory process.
Skin reactions to transdermal patches, including depigmentation, can be induced by the active ingredient or other components of the patch. For transdermal clonidine, most studies have indicated that the skin reactions are related to the drug itself and not to other factors [8]. For buprenorphine, the severity of the initial reaction seems to be related to the dose of buprenorphine patches [5]. For this reason it is suggested that the reaction is caused by the active ingredient buprenorphine, and not by the adhesion matrix.

Conclusion

Lareb has received two reports of skin depigmentation in association with buprenorphine Butrans® 5 µg / hour. It is assumed that skin depigmentation occurred as a post inflammatory reaction after transdermal exposure of buprenorphine Butrans®. For this reason, it is suggested that buprenorphine Butrans® might have a causative role in the occurrence of skin depigmentation. Although only a small number of cases were reported, the specificity of the reaction warrants the elaboration of a signal.

- Skin depigmentation, as a result of inflammation, should be mentioned in the SmPC of buprenorphine Butrans® .

References

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This signal has been raised on February 2014. 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).