

Clindamycin and acute generalized exanthematous pustulosis (AGEP)

Introduction

Clindamycin (Dalacin C[®]) is a lincosamide antibiotic with a primarily bacteriostatic action against grampositive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains under anaerobic circumstances [1].

Clindamycin was first granted marketing authorization on 16 October 1969 and is currently available as capsule, oral suspension, and solution for infusion. Therapeutic indications for the capsule include *pneumonia, tonsillitis, chronic sinusitis caused by anaerobic bacteria, and several types of infection (skin, soft tissues, bone, joints, intra-abdominal, and female pelvis / genitals)* [1]. Although other lincosamide antibiotics exist, clindamycin is currently the only drug in this class which is registered in the Netherlands.

The SPC of clindamycin mentions several skin conditions including pruritus, morbilliform-like rash, and urticarial as uncommon (0.1 – 1%) drug reactions, whereas exfoliative and bullous dermatitis are considered rare (0.01 – 0.1%) [1]. The current observation describes the association between the use of clindamycin and the occurrence of acute generalized exanthematous pustulosis (AGEP).

AGEP is a rare pustular severe cutaneous adverse reaction, usually attributed to drugs, and has been associated with the use of several antibiotic therapies, including macrolides, sulphonamides and quinolones [2]. Next to medicines, it is also associated with viral and bacterial infections, exposure to mercury, dietary supplements, chemotherapy and radiation [3].

The condition is characterized by an acute oedematous erythema, with small non-follicular sterile pustules with a predilection of the big folds, or with widespread distribution. The clinical course typically shows the acute onset of the skin symptoms, which resolve spontaneously, and are typically followed by postpustular pinpoint desquamation. The time from onset of the symptoms until resolution generally takes up to fifteen days [2].

Since AGEP is difficult to diagnose, an algorithm for the validation of possible cases was proposed, taking into account the morphology of the lesions, the course of the disease, and laboratory/histopathological features [4].

Reports

On July 13th, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports concerning AGEP with the use of clindamycin.

Detailed information on the reported cases is described below:

Case number 53444

This well documented report from consumer (who is a health professional himself) concerns a male aged 51-60 years, with a history of mastocytosis, who

experienced AGEP following administration of clindamycin for a sinusitis with a latency period of 12 hours after start. The patient recovered after withdrawal of clindamycin and treatment with corticosteroids. The AGEP diagnosis was medically confirmed by a dermatologist. Concomitant medication was not reported. No association between mastocytosis and AGEP could be found in the literature

Case number 134094

This well documented report from a specialist doctor concerns a female aged 61-70 years, with a history of hypertension, polycythaemia vera, myelofibrosis, arteritis temporalis, an aneurysm of the abdominal aorta, and percutaneous transluminal coronary angioplasty (PTCA). She experienced AGEP, haemodynamic instability, fever, increased INR, and ventricular tachycardia following administration of clindamycin for a jaw abscess with a latency of 2 days after start. The patient was admitted to the hospital and recovered after withdrawal of clindamycin and treatment with clemastine, prednisolone, intravenous fluids, metronidazole/ciprofloxacin, topical corticosteroids, dalteparin, esomeprazole and paracetamol. Concomitant medications at the time of the event were furosemide, paracetamol, atorvastatin, tramadol, omeprazole, diltiazem, perindopril, prednisolone, loperamide, calcium carbonate, acenocoumarol, diclofenac.

Other sources of information

SmPC

The SmPC of clindamycin mentions several skin conditions including pruritus, morbilliform-like rash, and urticaria as uncommon (0.1 – 1%) drug reactions, whereas exfoliative and bullous dermatitis are considered rare (0.01 – 0.1%) [1,5]. Some SPCs mention that symptoms resembling Stevens-Johnson syndrome occur as an uncommon event [5].

Literature

Cases of AGEP in association with the use of clindamycin, have been described in the literature [6-9]. Three cases of interest are described below.

Sulewski et al. [8] described AGEP in a 82-year old female with a history of fibromyalgia, idiopathic peripheral polyneuropathy, osteoarthritis, osteoporosis, obesity, hypertension, peripheral vascular disease, bilateral lower extremity lymphedema, and several drug allergies (including Stevens-Johnson syndrome secondary to levofloxacin). She denied personal history of psoriasis. The patient experienced a severe generalized rash two days after administration of two doses of clindamycin prophylaxis for a dental procedure. On the third day erythematous papules and pustules were present on the right arm, which disseminated to the lower extremities and trunk over the next two days. Treatment with oral diphenhydramine and triamcinolone 0.1% cream was not successful. After one week the symptoms were accompanied by constitutional complaints including fevers, chills, malaise and arthralgia. On physical examination, a diffuse red papular eruption coalesced into plaques on her arms, legs, abdomen, and back studded with numerous, scattered, non-follicular pustules was seen. In addition she had a butterfly-shaped erythema on her face and desquamation on her back. Treatment with intravenous methylprednisolone, 1% hydrocortisone cream, hydroxyzine, doxepin, and acetaminophen was started in combination with whirlpool baths twice daily. After one day of treatment, the erythema and pustules stopped spreading and they resolved after five days, as did her other symptoms. At a follow-up visit after two weeks she was free of skin eruptions.

Valois et al. [9] described two cases of clindamycin associated AGEP. Case A was a 69-year-old male who presented with an oral abscess, two weeks after an oral biopsy. Treatment with clindamycin was initiated (300mg 4x daily), and after 3 days the patient developed a pruritic rash on his trunk. One day later his temperature rose to 39.4°C and his rash spread distally. Clindamycin was replaced with penicillin and metronidazole. The following day, the patient experienced fever and generalized exanthema, after which penicillin and metronidazole were withdrawn. A skin biopsy showed characteristics compatible with a pustular drug reaction. The patient recovered from the rash within two weeks. Patch testing several weeks later showed positive results for both ampicillin and clindamycin at day 2 and day 3. An oral challenge with penicillin V was negative, as were the intradermal test and oral challenge for metronidazole. Case B was a 76-year-old male with a history of a necrotic finger ulcer, unresponsive to oral cephalexin treatment. The patient was treated with intravenous prostaglandin E1 for three days in the hospital and was discharged on levofloxacin and clindamycin (300mg 4x daily). Less than 36 hours later he developed a mild pruritic generalized erythematous rash, after which he immediately discontinued both antibiotics. The rash resolved after approximately one week and subsequent patch testing revealed a pustular patch reaction for clindamycin at day 2 and day 4. Tests for other drugs were negative.

Databases

On July 13th, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports of AGEP associated with the use of clindamycin. Because of this low number, the Reporting Odds Ratio (ROR) could not be calculated.

On July 16th, 2012, the WHO database of the Uppsala Monitoring Centre contained 27 reports of AGEP associated with the use of clindamycin and this was reported disproportionately (ROR = 17.9, 95% CI 12.2 – 26.3).

On July 16th 2012, the Eudravigilance database contained 26 reports of AGEP in association with clindamycin, which was reported disproportionately (ROR = 11.6, 95% CI: 7.9 – 17.1). It concerned 18 females, 6 males and in two cases sex was not reported. The median age was 61 years (range 9 – 89 years). In two cases, the age was not reported. All reports were classified as serious, with “hospitalisation” and “other” being the most common criteria for seriousness.

Prescription data

The number of patients using clindamycin in the Netherlands is shown in table 1.

Table 1. Number of patients using clindamycin in the Netherlands between 2007 and 2011 [10].

Drug	2007	2008	2009	2010	2011
clindamycin	37,924	44,127	50,192	56,452	60,636

Mechanism

Although AGEP is generally considered a drug-induced condition, the pharmacological mechanism has not been fully elucidated yet. It has been hypothesized to be a subtype of delayed hypersensitivity type IV reaction [11], with a role for both CD4+ (helper) and CD8+ (cytotoxic) T cells [12]. No specific pharmacological mechanism for clindamycin could be found.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two well documented reports of AGEP with the use of clindamycin. Both were medically confirmed, one of them by a dermatologist. Latencies were 12 hours and 2 days after starting clindamycin which seems consistent with drug-induced AGEP. Both patients recovered after withdrawal of clindamycin and additional treatment. It should be noted that one of the patients concomitantly used diltiazem, which is strongly associated with AGEP [13].

The association between clindamycin and AGEP is statistically supported by the WHO database and Eudravigilance database. In addition, there are several cases of clindamycin-associated AGEP described in the literature, which supports a possible causal relationship for this association. Although AGEP is difficult to diagnose and several other risk factors exist, AGEP should be mentioned in the SmPC's of clindamycin.

- AGEP should be mentioned in the SmPC's of clindamycin

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).