1.1. Clindamycin and dysgeusia

Introduction

Clindamycin is an antimicrobial agent of the class of lincomycins. It is widely used against susceptible aerobic and anaerobic Gram-positive bacteria in acne vulgaris, toxoplasmosis and bacterial vaginosis. Clindamycin has been on the market since 1968 [1]. Clindamycin can be administered orally through capsules or a suspension, via intravenous injection, via vaginal creams or topical via a lotion or gel. Case reports of taste disorders in association with clindamycin, especially a bitter taste, have been published, although only on topical formulation, when it is licked off or carried to the mouth while sweating [2]. Lareb received reports of taste disorders on oral or intravenous (i.v.) application.

The Summary of Product Characteristics (SmPC) of Dalacin® (oral, i.v. or topical administration) [1] and all other SmPC’s of generic clindamycin products do not mention taste disorders as a possible adverse drug reaction (ADR) except for the SmPC of clindamycin i.v. from manufacturer Hameln® [3] and clindamycin i.v. from Fresenius Kabi® [4], who mention altered smell and taste.

Reports

Until February 10, 2010 the Netherlands Pharmacovigilance Centre Lareb received twelve reports of taste disorders while using clindamycin. Complaints were reported on intravenous in one patient and on oral administration in ten patients. One patient (A) used both an oral and i.v. formulation. One patient (A) perceived a bitter taste that started ten minutes after and lasted for about one hour after every i.v. injection. When this patient switched to oral formulation, she perceived this bitter taste continuously.

Next to clindamycin, six patients used concomitant medication. Omeprazole, used by patient C, has been rarely associated with taste changes [5], but the latency time with the use of clindamycin is suggestive of a causal relation with the latter product. Inhaled steroid and bronchodilator aerosols used by patient A and D have also been associated with dysgeusia and loss of taste and smell [6].

Table 1. Reports of clindamycin and taste disorders

<table>
<thead>
<tr>
<th>Patient, Number, Sex, Age</th>
<th>Drug Indication for use</th>
<th>Concomitant medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, Action with drug outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 31729 F, 51 – 60 years</td>
<td>clindamycin i.v. 150mg/ml osteomyelitis, clindamycin capsule 300mg, osteomyolysis</td>
<td>salbutamol</td>
<td>taste bitter, loss of taste</td>
<td>10 minutes after every i.v. injection, discontinued, recovered</td>
</tr>
<tr>
<td>B 33010 F, 31 – 40 years</td>
<td>clindamycin capsule 300mg clarithromycin tablet 500mg erysipelas</td>
<td>tetanus toxicoid, tetanus immunoglobulin</td>
<td>tongue thick, taste bitter</td>
<td>6 days discontinued recovered</td>
</tr>
<tr>
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<td>---------------------------</td>
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</tr>
<tr>
<td>C 30637 M, 41 – 50 years</td>
<td>clindamycin capsule 300mg, neurosurgical complication</td>
<td>cephalaxin, fusidic acid, povidode-jodide, paracetamol, hydroquinine, tramadol, gabapentin, magnesium hydroxide, omeprazole, psyllium, verapamil, acetylcysteine</td>
<td>taste bitter, mouth dry</td>
<td>&lt; 1 day no change unknown</td>
</tr>
<tr>
<td>D 34953 F, 41 – 50 years</td>
<td>clindamycin capsule 300mg, surgical wound complication</td>
<td>beclomethasone, salbutamol, diazepam, fluoxetine</td>
<td>taste alteration</td>
<td>hours, not recovered while clindamycin was continued</td>
</tr>
<tr>
<td>E 39880 F, 41 – 50 years</td>
<td>clindamycin i.v. 150mg/ml, pulmonary infection</td>
<td></td>
<td>taste alteration</td>
<td>not reported unknown unknown</td>
</tr>
<tr>
<td>F 41612 F, 41 – 50 years</td>
<td>clindamycin capsule 300mg, gynaecological infection</td>
<td></td>
<td>therapeutic response unexpected with drug substitution, mouth irritation, stomach upset, taste bitter</td>
<td>hours unknown unknown</td>
</tr>
<tr>
<td>G 45242 F, 61 – 70 years</td>
<td>clindamycin capsule 300mg, bacterial infection on hand</td>
<td>nebivolol, nifedipine, losartan/hydrochlorothiazide</td>
<td>taste bitter</td>
<td>hour no change unknown</td>
</tr>
<tr>
<td>H 75802 F, 41 – 50 years</td>
<td>clindamycin capsule 300mg</td>
<td></td>
<td>taste metallic</td>
<td>1 day no change unknown</td>
</tr>
<tr>
<td>I 82066 M, 41 – 50 years</td>
<td>clindamycin capsule 300mg, postoperative wound infection</td>
<td>pantoprazole, fluvoxamine, prednisolone, verapamil, potassium chloride, phenprocoumon</td>
<td>dysgeusia</td>
<td>3 hours no change not yet recovered</td>
</tr>
<tr>
<td>J 83878 F, 41 – 50 years</td>
<td>clindamycin capsule 300mg</td>
<td></td>
<td>taste disturbance</td>
<td>3 hours no change unknown</td>
</tr>
<tr>
<td>K 90490 M, 51 – 60 years</td>
<td>clindamycin capsule 300mg</td>
<td>loss of smell, dysgeusia</td>
<td>6 weeks discontinued not recovered</td>
<td></td>
</tr>
<tr>
<td>L 90997 F, 70 years and older</td>
<td>clindamycin capsule 300mg</td>
<td>taste bitter</td>
<td>15 minutes no change recovered</td>
<td></td>
</tr>
</tbody>
</table>

Since patients with oral or salivary infections are more prone to perceive taste disorders, special attention was paid to the indication for use of clindamycin. Only one of the patients mentioned in
Table 1 received clindamycin for an indication that could cause or facilitate taste disorders (patient L). The close and repeated temporal relationship in which the effect follows administration at a predictable time in these cases is evidence of a causal relationship.

Other sources of information

**Literature**

Lareb previously described the reports of clindamycin-induced taste disorders received up to January 2006 (patient A to G) in the British Journal of Clinical Pharmacology [7]. At the time of this study, the Lareb database contained a subset of 5051 reports with an antibiotic as suspected or interacting medication. A case–non case design applied on this subset showed that reports of clindamycin and taste disorders are disproportionally present in the reports on antibiotics as expressed by the unadjusted reporting odds ratio (ROR), which is 7.89 [95% confidence interval (CI) 3.41, 18.3]. Males and females were equally reported to have taste disorders (ROR 1.23; 95% CI 0.88, 1.73) with clindamycin and other antibiotics. After adjustment of the reporting rate for age, gender and administration route, clindamycin and taste disorders were still disproportionally reported (ROR 7.02; 95% CI 2.84, 17.33), suggesting a possible causal relationship [7].

The case reports suggested a role for clindamycin concentrations excreted in body fluids like saliva [7]. Taste perversion has been described in the literature for patients treated with ophthalmic clindamycin [8] and topical clindamycin [2].

**Databases**

On February 10, 2010, the association of taste disorders with the use of clindamycin was disproportionally present in the Lareb database with a ROR of 15.1 (95% CI = 8.2 -27.8). The ROR was calculated on the whole database and not by using a subset of the database like de Groot and van Puijenbroek [6] did previously.

The database of the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, contained 92 cases of taste perversion in association with clindamycin. Taste perversion is disproportionally reported to the WHO (ROR 2.2, 95% CI 1.8 -2.7).

On February 4th, 2010, the Eudravigilance database contained 24 reports concerning clindamycin associated dysgeusia. In three cases the nature of the reaction was reported as disabling, in four cases dysgeusia was part of an event leading to hospital admission. In eighteen cases seriousness was due to other, non-specified causes. Ages of patient concerned ranged from one to 76 years, eleven male patients and thirteen female patients were involved.

**Prescription data**

The number of patients using clindamycin in the Netherlands is shown in Table 2.

Table 2. Number of clindamycin users in the Netherlands between 2004 and 2008 [8]

<table>
<thead>
<tr>
<th>Drug</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>clindamycin</td>
<td>24,764</td>
<td>27,434</td>
<td>32,860</td>
<td>37,370</td>
<td>44,764</td>
</tr>
</tbody>
</table>

**Mechanism**

Slazinski et al. attributed the bad taste of topical clindamycin to oral ingestion by licking off or sweating the bad tasting substance [2]. No mechanism has been found in literature. Clindamycin
has an unpleasant taste. Moreover, high proportions of serum concentrations are met in body tissues such as sputum [1]. Like its parent compound, lincomycin, it has an extremely bitter taste per se, which has resulted in attempts to synthesize better tasting formulations in the past [10]. The observation of taste disorders after i.v. administration of clindamycin in two cases supports the role of clindamycin concentrations in serum and body fluids. Taste disorders associated with use of antibiotics can be a primary effect of the chemical compound or a secondary effect due to disturbances in oropharyngeal microbial flora resulting from its pharmacological action. With regard to the first possibility, the antibiotic itself may have a certain taste, but it may also inhibit or induce distortion of tastant/odourant receptor function [6]. In addition, several (oropharyngeal) infections can influence the ability to smell and taste. Given the indication for use of clindamycin and the absence of reporting of stomatitis in the patients, involvement of a disturbance of the microbial flora is less likely.

Discussion and conclusion
The Netherlands Pharmacovigilance Centre Lareb has received twelve reports of taste disorders in patients using i.v. or oral clindamycin. Taste perversion is disproportionately reported in both the Lareb and WHO database. In the disproportionality analysis by de Groot and van Puijenbroek [7] this was also the case after adjustment for gender, age and route of administration. The unfavourable taste of clindamycin and its distribution into body fluids after absorption constitute a plausible mechanism of action. Based upon this information there seems to be a causal association between dysgeusia and clindamycin.

- Dysgeusia should be mentioned in the SmPC’s of all oral and i.v. clindamycin products.

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