DOI:10.1111/j.1365-2125.2007.02908.x

Clindamycin and taste disorders

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What is already known about this subject.
- The antibiotic clindamycin has a bitter taste when it is used orally.

What this study adds
- A case series on oral as well as i.v. use of clindamycin associated with taste disorders is presented.
- After corrections in a case-by-case analysis for several possible confounders such as indication, clindamycin is disproportionally associated with taste disorders.
- Serum and hence saliva and sputum clindamycin levels seem to be responsible for this reversible adverse drug reaction.

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Keywords
adverse drug reaction, clindamycin, dysgeusia, pharmacovigilance, taste disorder

Received
27 February 2006
Accepted
15 January 2007
Published *OnlineEarly*
17 July 2007

Aims
Topical use of clindamycin has been associated with taste disorders in the literature, but little is known about the nature of this adverse drug reaction. The aim of this article was to describe reports of clindamycin-induced taste disorders and to analyse the factors involved.

Methods
The adverse drug reaction database of the Netherlands Pharmacovigilance Centre was searched for reports concerning taste disorders with antibiotics. Clinical review of the cases and statistical analysis with logistic regression were performed. Characteristics of patients who reported taste disorders were compared for age, gender and formulation in clindamycin *vs*. other antibiotic users.

Results
Taste disorders were reported in seven (18%) of the clindamycin cases. In five reports an oral formulation was involved, in one report intravenous (i.v.) administration and in one report both formulations were used. Latency was <1 day after start and in one case taste disorders were present repeatedly at 10 min after every i.v. application. The adjusted reporting odds ratio was 7.0 (95% confidence interval 2.8, 17.3) and supports a possible causal relationship.

Conclusions
The association of clindamycin and taste disorders is supported by disproportionality analysis and seems to be independent of possible confounders such as age, gender and infections. The case reports suggest a role for clindamycin concentrations excreted in body fluids like saliva.

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. Between 1 January 1988 and January 2006 the Netherlands Pharmacovigilance Centre Lareb received seven reports of taste disorders while using clindamycin. Clindamycin has been on the market since 1968. The Summary of Product Characteristics does not mention

taste disorders as a possible adverse drug reaction (ADR). Case reports of taste disorders, especially a bitter taste, have been published, although only on topical formulation, when it is licked off or carried to the mouth while sweating [1]. As far as we know, taste disorders on oral or intravenous (i.v.) application have not previously been published in the literature. Although clindamycin itself has a bitter taste, our reports concern both oral and i.v. formulations, suggesting that dysgeusia is an effect related to systemic levels of clindamycin or its metabolites. Reports received by the Netherlands Pharmacovigilance Centre Lareb will be analysed in comparison with other reports on antibiotics and with regard to formulation, age and gender.

Methods

Lareb maintains the spontaneous reporting system for ADRs in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Reports from health professionals and patients are coded by qualified assessors, who also provide custom-made feedback before the reports are filed in the database.

Reports received between 1 November 1987 and 1 September 2005 for which gender and age of the patient are known were included in the analysis. The ADR database was searched for taste disorders which were defined as the Medical Dictionary for Regulatory Activities preferred terms *ageusia* and *dysgeusia*, including the lower level terms taste absent, taste loss, taste bitter, taste garlic, taste alteration, parageusia, taste metallic, taste peculiar and taste perversion.

A case–noncase design was applied on a subset of the database containing reports with an antibiotic as suspect or interacting medication [2, 3]. Cases were defined as reports mentioning one of the above-mentioned taste disorders; all other reports were considered as noncases. The index group consisted of reports where clindamycin had been mentioned as the suspected or interacting medication.

Comparisons of number of taste disorders between clindamycin and other antibiotics and oral *vs.* non-oral formulations were made to distinguish between the possibility of bad taste of the substance upon administration and systemic effects. Data were corrected for gender, age and formulation (either oral or non-oral administration) by means of logistic regression analysis. The strength of the association was expressed as point estimate with the corresponding 95% confidence interval. All statistics were performed using the SPSS software package, version 12 (SPSS Inc., Chicago, IL, USA).

Results

Reports

The Netherlands Pharmacovigilance Centre Lareb received 38 cases of patients using clindamycin. Taste disorders were reported in seven cases (Table 1). Complaints were reported on intravenous in one patient and on oral applications in five patients. One patient (A) used both an oral and i.v. formulation. The mean (± SD) age was 50.3 years (± 11.4) and six of the seven patients were female (Table 2).

One patient (A) perceived a bitter taste that started 10 min after and lasted for about 1 h after every i.v. injection. When this patient switched to oral formulation, she perceived this bitter taste continuously.

Next to clindamycin, four patients used concomitant medication. Omeprazol, used by patient C, has been rarely associated with taste changes [4], but the latency time with the use of clindamycin is suggestive of a causal relation with the latter product.

Strength of the association

As of 1 September 2005, the Lareb database contained a subset of 5051 reports with an antibiotic as suspected or interacting medication. A case–noncase 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.

Taste disorders with other antibiotics were reported in 149 cases on oral formulation and only twice on non-oral formulation. With clindamycin, five cases were on oral formulation, one on non-oral and one on both oral and non-oral formulation. This indicates that taste disorders may be caused by a 'systemic effect' and not by the taste of a tablet at the moment of ingestion.

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

Discussion

Taste perversion has been described in patients treated with ophthalmic clindamycin [5] and topical clindamycin [1]. To the best of our knowledge, this is the first report of taste perversion in association with i.v. or oral clindamycin use.

Table 1
Reports of taste disorders associated with the use of clindamycin

Patient, sex, age (years)	Indication for use, dose, administration route	Concomitant medication	Adverse drug reaction	Time to onset, outcome
A F, 57	Osteomyelitis, 4 × 300 mg i.v. injection +3 × 600 mg oral	Salbutamol	Taste bitter, loss of taste	10 min after every i.v. injection, recovered
B F, 32	Erysipelas, 3 × 600 mg oral	Tetanus toxoide, tetanus immunoglobulin	Taste bitter, hairy tongue	Unknown, recovered
C M, 47	Neurosurgical complication, 4 × 300 mg oral	Cephalexin, fusidic acid, povidone–jodine, paracetamol, hydroquinine, tramadol, gabapentin, magnesium hydroxide, omeprazole, psyllium, verapamil, acetylcysteine	Taste bitter, dry mouth	<1 day, unknown
D F, 47	Surgical wound complication, 2 × 300 mg oral	Beclometasone, salbutamol, diazepam, fluoxetine, tolbutamide, rabeprazole	Bad taste	<1 day, not recovered while clindamycin was continued
E F,	Pulmonary infection, Injection		Taste alteration	Unknown, Unknown
F F, 53	Gynaecological infection, 4 × 300 mg oral		Taste bitter, mouth irritation, stomach upset	<1 day, unknown
G F, 66	Infection on hand 3 × 600 mg oral		Taste bitter	<1 day, unknown

Table 2
Characteristics of dataset antibiotics users

	Clindamycin	Other antibiotics
Total	38	5013
Men	11 (29%)	1846 (37%)
Women	27 (71%)	3152 (63%)
Mean age (years)	52.7 ± 3.4	47.8 ± 0.3
Taste disorders	7 (18%)	144 (3%)
Oral application	33 (87%)	4857 (97%)

Age values are shown as mean ± SD.

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. None of the patients mentioned in Table 1 received clindamycin for an indication that could cause or facilitate taste disorders. 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.

The case–noncase design in this study shows that reports of clindamycin are strongly associated with taste disorders, even after correction for age, gender and administration route. Since reporting to a pharmacovigilance centre is influenced by various factors, the outcome of the case–noncase analysis is supportive only of a causal relationship. Additional studies under more controlled circumstances are needed to determine the actual incidence of this ADR. In the analysis, users of clindamycin were compared with users of other antibiotics. Since the antibiotics may have been prescribed for upper respiratory tract infections, confounding by indication may have occurred in the control group. Despite the fact that this may lead to a dilution of the effect, the association is highly significant for the use of clindamycin.

In the clindamycin reports concerning taste disorders, the ratio of non-oral to oral therapy was about 24 times higher than in reports of taste disorders on other antibiotics.

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. In users of other antibiotics there is no difference between non-oral and oral formulation.

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. For this reason, we decided to account for this possible confounding factor by analysing the occurrence of taste disorders with clindamycin in a subset of the Lareb database containing only reports having antibiotics as suspected or interacting medication.

The database of the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, which collects ADR reports from 78 countries, contains 67 cases of taste perversion in association with clindamycin, seven cases of taste loss and only six cases of parosmia. Taste perversion is also disproportionally reported to the WHO (uncorrected ROR 2.14, 95% CI 1.65, 2.77), which is quite similar to the findings in our database. As of 1 September 2005, six of the seven reports concerning clindamycin and taste disorders from the Netherlands had been filed in the WHO database.

Slazinski *et al.* attributed the bad taste to oral ingestion by licking off or sweating the bad tasting substance [1]. No mechanism has been found in literature. Clindamycin seems to have an unpleasant taste. Moreover, high proportions of serum concentrations are met in body tissues such as sputum [7]. 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 [8].

Cases of smell disorders were not reported to Lareb at all and the WHO received only six cases of smell disorders, compared with 74 cases of taste disorders. This supports the assumption that neither modification nor inhibition of the function of the odourant receptors is involved.

Conclusions

The Netherlands Pharmacovigilance Centre Lareb has received seven reports of taste disorders in patients using i.v. or oral clindamycin. Taste perversion is disproportionally reported in both the Lareb and WHO database, also 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. Therefore, health professionals should be aware that patients can perceive taste disorders with clindamycin not only on topical administration but also on oral and even i.v. application.

Conflict of interest: None declared.

The authors are indebted to the national pharmacovigilance centres who contributed data for this study. The opinions and conclusions, however, are not necessarily those of the various centres, nor of the WHO.

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