

Colistimethate sodium / bacitracin / hydrocortisone ear drops and signs that may indicate ototoxicity

Introduction

Colistimethate sodium / bacitracin / hydrocortisone acetate (Bacicoline B®) ear drops are indicated for *treatment of inflammation and infection of the external auditory canal: otitis externa diffusa, secondarily infected eczema of the external auditory canal, such as seborrheic and constitutional eczema, caused by bacitracin and colistin sensitive bacteria.*

Colistin is an antibiotic with bactericidal activity against gram-negative bacteria, particularly against *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *E. coli* and *Moraxella lacunata*.

Bacitracin is an antibiotic which is primarily active against gram-positive bacteria: streptococci, pneumococci and enterococci.

Hydrocortisone is a weak corticosteroid, and reduces the inflammatory symptoms that usually accompany the infection.

Colistimethate sodium / bacitracin / hydrocortisone acetate was granted marketing authorization in the Netherlands in 1989 [1].

Otitis externa is an inflammation of the external auditory canal. Bacterial infection is the most common cause of external otitis. Diffuse acute otitis externa can have signs and symptoms of ear canal inflammation (tender tragus and/or pinna), or diffuse edema or erythema of the ear canal, with or without otorrhea, regional adenopathy, erythema of the tympanic membrane, or cellulitis of the pinna and adjacent skin [2].

In acute otitis media (AOM) there is middle ear fluid and inflammation of the mucosal lining of the middle ear space. Through a ruptured tympanic membrane purulent otorrhea may be present.

In otitis media with effusion (OME) there is middle ear fluid without inflammation, usually resulting from barotraumas, allergy [3], or upper respiratory tract infection [4]. OME is often characterized by hearing loss or aural fullness. At otoscopy fluid (often yellowish, but sometimes clear), can be seen behind a retracted tympanic membrane [3].

This observation describes the association between dizziness, impaired hearing and other signs that might indicate ototoxicity, and the use of colistimethate sodium / bacitracin / hydrocortisone acetate ear drops.

Remarkably, there is a discrepancy between the registered indication of the drug, and the use in daily practice as recommended in guidelines: In the section “Contraindications” the SmPC mentions damage or perforation of the tympanic membrane as a contraindications for use [1], where guidelines concerning children, recommend the use in otorrhoea in otitis media in the presence of perforation or tympanostomy tube [5].

Acute otitis media is considered rather rare in adults [6]. To our knowledge, there are no Dutch guidelines considering prescription and use in adults with otitis media.

On the other hand, the Dutch guideline for general practioners “Otitis externa” does *not* mention colistimethate sodium / bacitracin / hydrocortisone acetate as therapeutic option for otitis externa [7].

Colistimethate sodium / bacitracin / hydrocortisone acetate (Bacicoline B®) ear drops are not routinely available outside the Netherlands and France. These ear drops are the most widely used, commercially available eardrops for acute tympanostomy tube otorrhea in the Netherlands that do not contain aminoglycoside [8].

Reports

From 7 March 2002 until 19 April 2015 the Netherlands Pharmacovigilance Centre Lareb received 34 reports concerning dizziness, impaired hearing and other signs that might indicate ototoxicity associated with the use of colistimethate sodium / bacitracin / hydrocortisone acetate ear drops. All reports concerned adults of 25 years or older, except for one report of a child in the age group 2 – 4 years, with vertigo who recovered after withdrawal of the ear drops. The mean age was 58 years. The reported reactions were dizziness (18 reports), vertigo (5 reports), vestibular disorder (1 report), balance disorder (5 reports), feeling drunk (1 report), ototoxicity (2 reports), deafness (2 reports), perceptive deafness (1 report), hearing reduced (1 report), hearing decreased (1 report), ear buzzing (1 report) and tinnitus (3 reports). 8 reports contained more than one reaction. The latencies varied between 1 minute to 7 days, and there was one report with a latency of 22 days, where the reporter

mentioned that initially she had an ear plug, which later diminished. The median latency was 2 days. There were 3 reports where the latencies were unknown. In 29 patients the drug colistimethate sodium / bacitracin / hydrocortisone acetate was withdrawn, in 1 patient the dose was not changed, and in 4 patients the action taken was unknown. 22 patients were recovering or had recovered. 2 patients had recovered with sequel, 6 patients had not recovered. In 2 reports it was unknown whether the patients recovered. 2 patients recovered from one of the reactions, and not from the other. In 6 patients the reaction had been treated with betahistine or cinnarazine, or in 1 patient with ciprofloxacin and prednisolone.

Of the 34 reports, in 14 reports it was reported that the tympanic membrane was not intact, and in one (case F) this was very likely concerning the description in the report. These 15 reports are listed in Table 1.

Table 1. Reports of dizziness or other signs of ototoxicity associated with the use of bacitracine / colistine / hydrocortison eardrops where it was reported that the tympanic membrane was not intact.

Patient, number, sex, age group (years), source, reported defect in tympanic	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A, 34915, F, ≥ 71, pharmacist, tympanostomy tube	bacitracin/colistin/ hydrocortisone eardrops, 2 gtt, 3 times per day, otitis externa		dizziness	hour, withdrawn, not recovered
B, 41881, M, ?, pharmacist, tympanic membrane perforation	bacitracin/colistin/ hydrocortisone eardrops, 5 gtt, 3 times per day, infective otitis externa		tinnitus	5 days, withdrawn, not recovered
C, 63311, F, 41 - 50, pharmacist, artificial tympanic membrane with a small hole	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, otitis media	ibuprofen, amoxicilline, esomeprazol	dizziness	1 day, withdrawn, recovered
D, 88206, M, 61 - 70, consumer, ruptured tympanic membrane	bacitracin/colistin/ hydrocortisone eardrops, dose unknown, ear infection	metoprolol, bisoprolol / hydrochlorothiazide, atorvastatine	dizziness	2 days, withdrawn, unknown
E, 92757, F, 31 - 40, consumer, tympanic membrane perforation	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, ear infection	ethinylestradiol / levonorgestrel	vertigo, tinnitus	5 days, withdrawn, recovered with sequel (vertigo treated with betahistine)
F, 103327, F, ≥ 71, specialist doctor, very likely tympano-	bacitracin/colistin/ hydrocortisone eardrops dose unknown, indication unknown		deafness neurosensory	latency unknown, action and outcome unknown

stomy tube

G, 139089, M, 51 - 60 , specialist doctor, tympanic membrane perforation	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, otitis media		vertigo	5 days, withdrawn, recovering (treated with cinnarazine)
H, 143871, F 51 - 60, specialist doctor, tympanic membrane perforation by trauma	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, ear drum perforation		hypoacusis, dizziness	1 day, withdrawn, not recovered
I, 157789, M 51 - 60, consumer, hole in the tympanic membrane	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, tympanic membrane perforation	carbasalate calcium, simvastatin, ticagrelor	dizziness	7 days, action unknown, recovering
J, 157804, F 51 - 60, pharmacist, tympano- stomy tubes	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, indication unknown	ciclesonide	dizziness	latency unknown, dose not changed, recovering
K, 160955, M 61 - 70, pharmacist, absence or a perforated tympanic membrane	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, indication unknown		hyperhidrosis, dizziness, palpitations	latency unknown, withdrawn, recovered
L, 161596, F 21 - 30, consumer, tympano- stomy tubes	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, otitis		dizziness, nausea	1 day, withdrawn, recovering
M, 183564, F 51 - 60, specialist doctor, tympano- stomy tubes	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, infective otitis externa		dizziness	2 days, withdrawn, recovered
N, 194507, F, ≥ 71, pharmacist, hole in tympanic membrane right ear	bacitracin/colistin/ hydrocortisone eardrops, 3 gtt, 3 times per day, ear inflammation		dizziness, neck pain, movement disorder, disturbance in attention, nausea, headachte	1 day, withdrawn, not recovered
O, 196462, M, ≥ 71, consumer, tympano- stomy tubes	bacitracin/colistin/ hydrocortisone eardrops, dose unknown		vestibular disorder	1 week, withdrawn, recovered

Other sources of information

SmPC

The Dutch SmPC of colistimethate sodium / bacitracin / hydrocortisone acetate ear drops does not mention dizziness or decreased hearing or other signs that might indicate ototoxicity as an adverse drug reaction. The SmPC does mention as an adverse reaction that prolonged use of corticosteroids in the ear may lead to atrophy and perforation of the tympanic membrane. In the section "Contraindications" the SmPC mentions damage or perforation of the tympanic membrane as contraindications for use. In the section "Special warnings and precautions for use" the SmPC mentions that usage in a perforated tympanic membrane may result in damage of the inner ear [1].

Concerning the use of the different compounds in other forms than eardrops, the Dutch SmPC of colistimethate sodium powder for nebuliser Colistin® does mention dizziness as an adverse drug reaction with an unknown frequency of occurrence. In the section "Effects on ability to drive and to operate machinery" this SmPC mentions that the drug can influence responsiveness to an extent that, for example due to dizziness, the patient should not drive or operate machinery. Decreased hearing or other signs of ototoxicity are not mentioned [9].

Bacitracine is only indicated for the use in eardrops [10].

The Dutch SmPC of hydrocortisone tablets does not mention dizziness, decreased hearing or other signs of ototoxicity as adverse drug reactions [11].

Literature

In a randomized controlled trial in 230 children Dutch children from 1-10 years old, 76 children received hydrocortisone-bacitracin-colistin ear drops for acute tympanostomy-tube otorrhea. As adverse drug reactions 21% had pain or discomfort during administration, and 4% had a rash [8].

The Dutch guideline for General Practitioners "Acute otitis media" advises for the use in children, to use colistimethate sodium / bacitracin / hydrocortisone acetate ear drops (off label) for otorrhea with a tympanostomy tube [6]. The guideline mentions that there are indications, particularly in animal studies that antibiotic-containing eardrops may damage the inner ear. Therefore, perforated eardrum is often referred to as a contraindication for the use of these ear drops. Ototoxicity has been demonstrated in local use of aminoglycosides (neomycin, framycetin, gentamicin), polymyxin B and to a lesser extent, polymyxin E (colistin) [12]. The guideline underlines though as consideration, based on the view of the Dutch Association of ear, nose and throat specialists, the risks of hearing damage from an (ongoing) infection of the middle ear, and it is suggested that in chronic secretory otitis media, the inner ear is protected by the swollen middle ear mucosa against ototoxic components of the ear drop. The guideline advises to stop administering the eardrops 24 hours after the ear is dry and clean in the morning upon waking, and advises to avoid prolonged or repeated use.

The Dutch guideline "Otitis Media bij kinderen in de tweede lijn" [Otitis media in children under medical specialist care] of the "Nederlandse Vereniging voor KNO" [the Dutch Association of ear, nose and throat specialists] mentions that an active chronic mucosal otitis media (ACMOM) is a chronic inflammation of the middle ear with a non-intact tympanic membrane, i.e., a perforation or tympanostomy tube, and otorrhea (ear discharge) for at least 2 weeks. The guideline mentions that when treating ACMOM in children ear drops with non-quinolone antibiotic combinations (chloramphenicol or neomycin or oxytetracycline with polymyxin B, clioquinol, framycetin / gramicidin, colistin / bacitracin), usually combined with corticosteroids, are preferred [13].

The guideline for medication in children "Kinderformularium" mentions as indication for colistimethate sodium / bacitracin / hydrocortisone acetate ear drops "Otorrhea in otitis media in the presence of perforation or tympanostomy tube". A warning is added, mentioning that the use of topical agents in an open middle ear brings a small potential risk of ototoxicity, allowing high frequency hearing loss, and vestibulotoxicity, causing balance problems, to occur. The guideline mentions that, in a clinical setting, ototoxicity is assessed as a rare event, estimated 0.01 to 0.03%, being significantly less frequent than sensorineural hearing loss due to a chronic secretory otitis media. Furthermore the guideline suggests, that a swollen middle ear mucosa as a result of chronic secretory otitis media, offers protection against the ototoxic components of the ear drop [5].

In an article from 1965 where intramuscular colistimethate sodium was used by 17 patients for urinary or respiratory tract infections, vertigo was reported as side effect in 7 patients [14].

The KNMP Kennisbank, an electronic information source for Dutch pharmacists, reports that in the use of intravenous infusion of colistine dizziness had been reported [15].

Databases

Table 1. Reports of reactions where a reliable ROR can be calculated (3 or more reports) associated with colistimethate sodium / bacitracin / hydrocortisone acetate ear drops, in the Lareb [16]. The WHO database [17] only contained the reports from The Netherlands of these reactions.

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Dizziness	20	11.0 (6.5-18.6)
	Vertigo	5	37.4 (14.9-93.6)
	Balance disorder	5	48.2 (19.2-120.8)
	Tinnitus (including the case with LLT ear buzzing)	4	11.2 (4.1-30.8)

Prescription data

Table 2. Number of patients using colistimethate sodium / bacitracin / hydrocortisone acetate ear drops in the Netherlands between 2009 and 2013 [18].

Drug	2009	2010	2011	2012	2013
Colistimethate sodium / bacitracin / hydrocortisone acetate eardrops	215,410	195,080	193,600	196,010	198,950

Mechanism

As mentioned in the text above the guideline for medication in children "Kinderformularium" describes the occurrence of ototoxicity in the use of topical agents in an open middle ear estimated 0.01 to 0.03%, and it suggests that a swollen middle ear mucosa as a result of chronic secretory otitis media, offers protection against the ototoxic components of the ear drops [5]. Although a precise mechanism is not described, this suggests that the authors assess that there might be a direct toxic effect. When colistine is administered by other routes than in eardrops (intravenously, intramuscular or per inhalation), dizziness is an adverse reaction that is described in several sources [9,14,15,19,20]. No data about mechanism of action are available though.

Concerning the eardrops it is unlikely that the temperature of the drops may play a role in the dizziness, because the drops are not stored in the refrigerator or freezer [1].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 34 reports concerning dizziness, impaired hearing and other signs that could indicate ototoxicity associated with the use of colistimethate sodium / bacitracin / hydrocortisone acetate ear drops. Of these 34 reports, in 14 reports it was reported that the tympanic membrane was not intact, in 1 report the tympanic membrane was likely not intact concerning the description in the report.

Concerning the dizziness, confounding by indication cannot be ruled out, also when the drug was used for the indication otitis externa. Otitis externa can be confused with chronic suppurative otitis media (CSOM), where vertigo can be one of the symptoms [21].

In the Lareb databases the association is disproportionally present.

The Dutch SmPC of colistimethate sodium / bacitracin / hydrocortisone acetate mentions damage or perforation of the tympanic membrane as contraindications for use, and it mentions in the section "Special warnings and precautions for use" that usage in a perforated tympanic membrane may result in damage of the inner ear [1]. In Dutch guidelines though colistimethate sodium / bacitracin / hydrocortisone acetate eardrops also has a place in the treatment of otitis media with a perforation or tympanostomy tube, where the change of ototoxicity caused by the drug is assessed less than sensorineural hearing loss due to a chronic secretory otitis media [5]. Because of this place in the guidelines, colistimethate sodium / bacitracin / hydrocortisone acetate ear drops is probably widely used off label with an open middle ear, because of the assessment that the benefits outweigh the risks. It must be remarked that these guidelines concern children, and all the received reports except for one, were adults. It is not likely though that this is a reaction that could only occur in children or adults.

- Lareb want to inform the Medicines Evaluation Board of the many cases with signs of possible ototoxicity received of the use in a not intact tympanic membrane, and the fact that this off-label use indication is a recommendation in several Dutch guidelines.

References

1. Dutch SmPC Bacicoline-B® oordruppels, poeder en oplosmiddel voor suspensie, bevat na reconstitutie per ml: 250.000 E (ongeveer 20 mg) colistimethaatsnatrium, 500 E bacitracine (ongeveer 8 mg) en 10 mg hydrocortisonacetaat. (version date: 13-1-2012, access date: 5-3-2015) <http://db.cbg-meb.nl/IB-teksten/h01761.pdf>.
2. UpToDate. (version date: 19-9-2014, access date: 24-3-2015) http://www.uptodate.com/contents/external-otitis-pathogenesis-clinical-features-and-diagnosis?source=search_result&search=otitis+externa&selectedTitle=2~29.
3. UpToDate. (version date: 17-10-2014, access date: 24-3-2015) <http://www.uptodate.com/contents/acute-otitis-media-in-adults-suppurative-and-serous?source=machineLearning&search=otitis+media+with+effusion&selectedTitle=2~48§ionRank=1&anchor=H22#H22>.
4. Dutch guideline for General Practitioners "Otitis media met effusie bij kinderen" [Acute otitis media with effusion in children]. "NHG standaard". (version date: 2014, access date: 26-3-2015) <https://www.nhg.org/standaarden/volledig/nhg-standaard-otitis-media-met-effusie-bij-kinderen>.
5. Kinderformularium. (version date: 2015, access date: 26-3-2015) <http://www.kinderformularium.nl/search/stof.php?id=327>.
6. Dutch guideline for General Practitioners "Otitis media acuta" [Acute otitis media], "NHG standaard". (version date: 2014, access date: 29-4-2015) <https://www.nhg.org/standaarden/volledig/nhg-standaard-otitis-media-acuta>.
7. Dutch Guideline for General Practitioners "Otitis externa", "NHG standaard". (version date: 2014, access date: 26-3-2015) <https://www.nhg.org/standaarden/samenvatting/otitis-externa>.
8. Van Dongen TM, Van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N Engl J Med*. 2014;370(8):723--33
9. Dutch SmPC Colistin poeder voor verneveloplossing, met oplosmiddel, 1.000.000 IE. (version date: 24-6-2011, access date: 5-3-2015) <http://db.cbg-meb.nl/IB-teksten/h29664.pdf>.
10. KNMP Kennisbank. (version date: 2015, access date: 26-3-2015) https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum--S341.html.
11. Dutch SmPC Hydrocortison CF 20 mg, tabletten. (version date: 11-5-2011, access date: 5-3-2015) <http://db.cbg-meb.nl/IB-teksten/h50730.pdf>.
12. Mylanus EAM, Feenstra L, Van der Hulst RJAM. "Gebruik van oordruppels bij otitis media met trommelvliesperforatie en in operatieholtes". [The use of ear drops with otitis media with tympanic membrane perforation and surgical cavities]. *Ned Tijdschr KNO-Heelk* 2004;10:31--6
13. Dutch guideline "Otitis Media bij kinderen in de tweede lijn" [Otitis media in children under medical specialist care] of the "Nederlandse Vereniging voor KNO" [the Dutch Association of ear, nose and throat specialists]. (version date: 2012, access date: 26-3-2015) <http://www.nvk.nl/Portals/0/richtlijnen/Otitis%20Media/R!%20otitis%20media.pdf>.
14. Roodger KC, Nixon M, Tonning HO. Treatment of infections with colistimethate sodium (Coly-mycin). *Can Med Assoc J* 1965;93:143-6.
15. KNMP Kennisbank. (version date: 2015, access date: 26-3-2015) https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum--S1311.html.
16. Lareb database. (version date: 2014, access date: 21-11-2014) <http://www.lareb.nl/Bijwerkingen/Zoek-op-geneesmiddel>.
17. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2014, access date: 21-11-2014) <https://tools.who-umc.org/webroot/> (access restricted).
18. College for Health Insurances. GIP database. (version date: 7-3-2014, access date: 17-7-2014) <http://www.gipdatabank.nl/>.

19. Micromedex® Healthcare Series, (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Searched for Colistimethate sodium. (version date: 2015, access date: 26-3-2015) <http://www.micromedexsolutions.com/home/dispatch>.
20. KNMP Kennisbank. (version date: 2015, access date: 26-3-2015) https://kennisbank.knmp.nl/article/Informatarium_Medicamentorum_-_S1311.html.
21. UpToDate. (version date: 19-9-2014, access date: 26-3-2015) http://www.uptodate.com/contents/external-otitis-pathogenesis-clinical-features-and-diagnosis?source=search_result&search=otitis&selectedTitle=5~150.