

1.1. Oxaliplatin and laryngospasm

Introduction

Oxaliplatin (Eloxatin®) is a platinum compound with antineoplastic properties and is registered in the Netherlands since 2005. Oxaliplatin is *used in combination with 5-fluorouracil and folinic acid in the treatment of metastatic colorectal cancer. It is also indicated as adjuvant therapy in the treatment of colon carcinoma (stage III) after a complete resection of the primary tumor* [1]. The platinum compound in oxaliplatin forms a complex with 1,2-diaminocyclohexane and an oxalate group [1] which interferes with DNA synthesis [2]. The complex is more hydrophobic than the complex formed by cisplatin and carboplatin, other platinum compounds and is therefore less nephro-toxic than cisplatin and less myelotoxic than carboplatin [3].

Laryngospasm is characterized as a brief episode of uncontrolled muscular contraction of the laryngeal cords [4,5]. This can lead to episodes of complete upper-airway occlusion [5]. Risk factors for laryngospasm are laryngopharyngeal reflux [6] (sleep-related [7]) and as post-surgery complication, especially in pediatrics [8].

Reports

On August 10, 2010 the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports concerning laryngospasm in association with the use of oxaliplatin. Of these four reports, report A is reported by a health professional and the other three are reported by the Marketing Authorization Holder (MAH).

Table 1. Reports of laryngospasm associated with the use of oxaliplatin.

Patient, Number, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, number of cycle, action with drug outcome
A 106930 F, 70 years and older	oxaliplatin 200 mg metastatic colon carcinoma	thiamazole, levothyroxin, sotalol, dorzolamide, candesartan, enalapril	laryngospasm	1 minute 45 days after first cycle drug withdrawn recovered
B 56403 F, 51 – 60 years	oxaliplatin 270 mg once per 3 weeks colorectal carcinoma cetuximab capecitabine bevacizumab	clemastine, diazepam, ondansetron, dexamethasone	laryngospasm muscle spasm	few hours after oxaliplatin infusion second cycle drug withdrawn outcome unknown
C 54749 = 54751 F, 41 – 50 years	oxaliplatin 178 mg once per 3 weeks unknown capecitabine irinotecan	estrogen with levonorgestrel, fentanyl	laryngospasm nausea vomiting	immediately after oxaliplatin infusion second cycle action and outcome unknown

Patient, Number, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, number of cycle, action with drug outcome
D 82048 F, 61 – 70 years	oxaliplatin unknown	diazepam, ondansetron, metformin, imipramine, paracetamol with codein, dexamethasone, bevacizumab, glimepiride.	laryngeal spasm, wheezing, pale, clammy	within 1 day third cycle administration time enlarged to 6 hours recovered

Case A was reported by a medical specialist. The laryngeal spasm occurred 45 days after the first infusion of the drug and 1 minute after the last infusion. The patient recovered after treatment with adrenaline, clemastine, ranitidine, hydrocortisone, *intubation* and admission to the intensive care.

Case B was reported by the Marketing Authorization Holder. The therapy date, route of administration and daily dose are unknown for the concomitant medication diazepam. There is no further information about the reported muscle spasms.

Latency time was in all cases within a day of the last oxaliplatin infusion. All patients experienced laryngospasm after administration of oxaliplatin.

Other sources of information

SmPC

The Dutch SmPC of oxaliplatin [1] does mention subjective feelings of dysphagia and dyspnoea and/ or feeling to choke, without *any* objective evidence with problems to breathe or laryngospasm or bronchospasm (no stridor or wheezing). Laryngospasm with objective evidence is not mentioned in the Dutch SmPC of oxaliplatin [1].

The US SmPC [9] mentions an acute syndrome of pharyngolaryngeal dysesthesia in 1-2% of patients. This syndrome is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Laryngospasm is mentioned as a clinical symptom when an overdosage of oxaliplatin is given [9].

Literature

Brandi et al [3] described hypersensitivity reactions related to oxaliplatin. Laryngospasm is mentioned as severe form of a hypersensitivity reaction. A total of 17 patients with hypersensitivity reactions were described, two of them experienced laryngospasm after their second and third infusion number. The infusion of oxaliplatin was stopped and replaced by a saline infusion. Antihistaminics and 100 -1000 mg hydrocortisone was administered. In this article, no difference was made between subjective or objective evidence for laryngospasm.

Databases

On August 10, 2010 the Lareb database contained four reports on oxaliplatin and laryngospasm. In respect to the other reports in the database this association is disproportionally reported (ROR 56.2, 95% CI 18.4- 171).

Lareb also received reports of symptoms that can be part of laryngospams. Dyspnoea (10 reports), bronchospams (1 report) and the feeling to choke (1 report) was reported with the use of oxaliplatin. These events were also reported with the use of carboplatin or cisplatin, other

cytostatic drugs with a platinum compound. Laryngospasm is not reported before in associations with the use of carboplatin or cisplatin.

On August 10, 2010 the WHO Collaborating Centre had received 85 reports of oxaliplatin and laryngospasm which was disproportionally present in the database (ROR 13.6, 95% CI 10.5-16.2).

On August 3rd the Eudravigilance database contained 155 reports of laryngospasm associated with oxaliplatin use. All cases but four were rated serious. In three cases the reported reaction lead to the death of the patient involved. In 29 cases life-threatening aspects were indicated. Ages when specified ranged from 28 to 77 years. Fifty male patients were involved, 99 women. In the remaining six cases no sex was specified.

Prescription data

The prescription data for oxaliplatin are not available through the GIP database of the College for health insurances.

Mechanism

Laryngospasm can be part of a hypersensitivity reaction [3]. Because patients developed laryngospasm after multiple infusions of oxaliplatin, sensitization is likely [3]. The reactions occurred fast after the infusion. Therefore a type I hypersensitivity Ig-E mediated reaction is suggested [3].

There are also different hypothesis for hypersensitivity with the use of oxaliplatin suggesting the platinum salt can induce a cascade of reactions leading to cytokines of forming a major histocompatibility complex (MHC) [3].

Discussion

The four cases reported to the Netherlands Pharmacovigilance Centre Lareb suggest oxaliplatin can induce laryngospasm. This is also mentioned in the SmPC but without any objective evidence. In at least one report (patient A) objective evidence (intubation) was present. In addition three cases of laryngospasm were reported.

In reports B and C, there were also other suspected drugs. However, laryngospasm started within a few hours after oxaliplatin infusion so oxaliplatin is most likely for the events.

Although other factors for laryngospasm can not be excluded, risk factors like laryngopharyngeal reflux were not mentioned in the reports. The reported latency times also supports a causal relationship.

Conclusion

Lareb received four reports of laryngospasm associated with the use of oxaliplatin. Subjective feeling of laryngospasm is described in the SmPC. However, in at least one report there was also intubation and therefore objective evidence for laryngospasm. Therefore, laryngospasm should not only be mentioned as a subjective event in the SmPC of oxaliplatin.

- Laryngospasm should be mentioned as an objective event in the SmPC of oxaliplatin

References

1. Dutch SmPC Eloxatin®. (version date: 16-4-2010, access date: 9-8-2010) <http://db.cbg-meb.nl/IB-teksten/h32774.pdf>.
2. CVZ. Farmacotherapeutisch Kompas. (version date: 1-7-2009, access date: 14-9-2009) www.fk.cvz.nl.
3. Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, Di Marco MC, Biasco G. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer*. 2003;89(3):477-81.
4. Jochems AAF; Joosten FWMG. Coelho. *Zakwoordenboek der Geneeskunde*. 29 ed. 2009. 497p.
5. Gdynia HJ, Kassubek J, Sperfeld AD. Laryngospasm in neurological diseases. *Neurocrit.Care* 2006;4(2):163-7.
6. Obholzer RJ, Nouraei SA, Ahmed J, Kadhim MR, Sandhu GS. An approach to the management of paroxysmal laryngospasm. *J Laryngol.Otol*. 2008;122(1):57-60.
7. Roland MM, Baran AS, Richert AC. Sleep-related laryngospasm caused by gastroesophageal reflux. *Sleep Med* 2008;9(4):451-3.
8. Flick RP, Wilder RT, Pieper SF, van KK, Ellison KM, Marienau ME, Hanson AC, Schroeder DR, Sprung J. Risk factors for laryngospasm in children during general anesthesia. *Paediatr.Anaesth* 2008;18(4):289-96.
9. American SmPC Eloxatin®. (version date: 13-3-2009, access date: 10-8-2010) http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021492s011,021759s009lbl.pdf.

This signal has been raised on November 2010. 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).