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Toxic optic neuropathy due to voriconazole: possible potentiation by reduction of CYP2C19 activity

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Abstract. – OBJECTIVE: Voriconazole is an antifungal treatment with central neurotoxicity. Modifications of the electroretinogram can explain some of its visual complications: visual hallucination, blurred vision, altered visual perception or photophobia. However, reports from the literature or the French pharmacovigilance centers evoked toxic optic neuropathy due to voriconazole. The aim of this report is to analyze the role of voriconazole in the occurrence of toxic optic neuropathy or the role of the combination of voriconazole with other neurotoxic drugs.

PATIENTS AND METHODS: We report the case of a 15-year-old young boy treated with voriconazole and ethambutol for a severe lung infection due to aspergillosis and mycobacterium tuberculosis in the mucoviscidosis and pulmonary transplantation who developed a toxic optic neuropathy. A review of the literature on the role of ethambutol on the activity of CYP2C19 and its relationship with the serum concentration of voriconazole was conducted.

RESULTS: In our patients, visual acuity recovered after discontinuation of voriconazole. Other cases of toxic optic neuropathy due to voriconazole were reported in pharmaco-vigilance databases, often in association with ethambutol.

CONCLUSIONS: Ethambutol can reduce the activity of CYP2C19 leading to an increase of voriconazole concentration. Thus, it potentiates its risk of adverse event. Such mechanism leading to this neuro ophthalmological adverse effect would have an important clinical involvement. It would require a stricter monitoring and screening of patients treated by combination of neurotoxic molecules and VRZ to detect an adverse event.

Key Words:
MToxic optic neuropathy, Voriconazole, Ethambutol, CYP2C19.

Introduction

Voriconazole (VRZ) is an antifungal treatment that has central neurotoxicity[1-3]. Its visual complications included visual hallucination, blurred vision, altered visual perception or photophobia[4-7]. These symptoms can be explained by modifications of the electroretinogram (ERG). However, in a recent publication, Mounier et al[8] reported a case of ophthalmological complication that could be due to toxic optic neuropathy (TON). The French pharmacovigilance centers recorded six other unpublished cases of TON. Those cases of TON could be related to VRZ by themselves. They also can be due to the combination of VRZ with other neurotoxic drugs which potentiates the risk of adverse event. It was reported that some drugs can reduce the activity of CYP2C19 leading to an increase of serum concentration of VRZ[9,10].

Based on the case of a young boy and on a review of the literature, we would like to analyze the role of VRZ in the occurrence of TON and its possible potentiation by ethambutol. Such mechanism leading to this neuro ophthalmological adverse effect would have an important clinical involvement. It will require a stricter monitoring and screening of patients treated by combination of neurotoxic molecules and VRZ to detect an adverse event.

Case Description

A 15-year-old boy was referred in the ophthalmological department for a sensation of vision decrease in a context of severe pulmonary infection. His past medical history included a

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pulmonary transplantation 6 months before due to a mucoviscidosis. Antirejection therapy included Tacrolimus and cortisone. One month after his transplantation, he developed a severe lung infection and was admitted in reanimation. Two pathological agents: aspergillosis and mycobacterium tuberculosis were identified in bronchial secretions. A treatment with VRZ was initiated and Ethambutol (22.2 mg/kg/day) was introduced two months later.

One month after Ethambutol initiation, his visual acuity was 20/20 OU. Ophthalmological examination including optic discs was normal, as well as his visual field. Color vision testing revealed a mild dyschromatopsia compatible with the diagnosis of TNO. In this context, the ethambutol was suspected to be responsible for such adverse effect. This drug was then discontinued. However, the visual function continued to deteriorate. One month later, his visual acuity was reduced to 20/145 OR and 20/200 OS. Ophthalmological examination was still unremarkable. The coloration of the optic discs remained normal. A central scotoma appeared on visual field recording of each eye. The color testing displayed a red – green acquired dyschromatopsia. Although the diagnosis of TNO was evident, other diagnoses were ruled out, especially a meningitis in the context of induced immunosuppression. Due to the worsening of a TON despite discontinuation of Ethambutol and because of the occurrence of a deficit of a peripheral nerve in the leg, a pharmacovigilance advice was required. Among his different drugs, only Voriconazole had a specific neurotoxicity that could explain both visual function worsening and peripheral neuropathy. In addition, the fungal infection was no more active. It was decided to completely stop the administration of VRZ.

After discontinuation of VRZ, visual function slowly improved as well as peripheral deficit. His visual acuity was 20/40 OU three months later and returned to 20/20 OU after one year. At that time, visual field and color vision testing were normalized, but a slight pallor of the optic discs persisted. There was no recurrence of this optic neuropathy.

Discussion

This case report highlights the role of VRZ in the occurrence of TON. It also highlights the possible potentiation of this neurotoxicity by ethambutol. The chronology of the evolution of visual function and the occurrence of peripheral nerve damage raises suspicion of the involvement of VRZ. If the role of ethambutol can be evoked, it seems to be to potentiate the neurotoxic action of VRZ by playing on the activity of the enzyme CYP2C19.

VRZ is an antifungal therapy with a central neurotoxicity, as well as direct toxicity for ocular tissues[1-3]. Patients treated by VRZ complained of visual disturbance including blurred vision, altered visual perception or color perception, photopsia and photophobia[1,6,7,11,12]. The pooled risk of an incidence of visual toxicity was between 15 and 33%[13]. Such complications seldom needed premature discontinuation of treatment[14]. Since they were not linked to keratitis, a retinal involvement could be suspected as well as a toxicity directed to the optic pathway. This direct toxicity on retina can explain the modification of the ERG that was previously reported. Zrenner et al[15] and Harisson et al[16] observed that intravitreal injection of antifungal drugs, including VRZ, induced a reduction of the amplitude of the b-wave of the ERG. In addition, among the antifungal drugs tested, VRZ induced a more severe reduction of this b-wave than micafungin and amphotericin B[16]. Recently, Mounier et al[8] reported a patient who complained of dyschromatopsia three days after the introduction of VRZ. The coherent optical tomography of the macula was normal. But multifocal ERG confirmed a global decrease in the foveal peak in both eyes, which is coherent with previous data. However, VRZ had no toxicity *in vitro* on optic nerve head astrocytes when administered in therapeutic concentrations[17.] On the other hand, the visual hallucinations, that are associated with other types of hallucinations, are rather a sign of neurotoxicity due to the VRZ[18].

Despite its neurotoxicity, TON is not a characteristic complication of the VRZ[19,20]. Its implication is suspected, but there are only few cases in PubMed[19,20]. A patient with bilateral blind spot enlargement and unilateral reduction of the VEP amplitude was recently reported in association with a bilateral electrophysiological macular involvement[8]. Six cases of TON in a context of treatment with VRZ were reported as unpublished post marketing data in VigiAcess or pharmaco-vigilance databases. In one case, the implication of VRZ is probably based on clinical history. The patient did not take any other drugs responsible for TON. There was no

recovery (Table I cases n° 1). In two of these cases, the implication of VRZ is only possible (Table I cases n° 2-3). The patients did not take any other neurotoxic drug. But, in case n° 2, the delay of occurrence of visual manifestations was not precisely established. In the other case, there is no indication of the evolution of the visual function according to the discontinuation of the different treatments. In three other cases, the role of the VRZ can be suspected due to the clinical history. But this treatment was prescribed in association with Ethambutol (Table I cases n° 4-6).

The usual guidelines were used to calculate the probability of the involvement of VRZ in occurrence of TON[21]. There are previous conclusive reports on this adverse event from pharmacovigilance data seen above (+1). Results of ophthalmological examination as well as ancillary testing (visual field recording and color vision test) confirmed the reality of this TNO (+1). According to the clinical history, TNO appeared after the administration of VRZ (+2). It improved and disappeared when the drug was discontinued (+1). VRZ was stopped as it was the only remaining drug that had a neurotoxicity. Thus, this drug was the only one prescribed to this patient that can be responsible for TNO. In addition, since aspergillosis was no more present in this patient, it was not necessary to reduce the dose of this antifungal therapy. For the same reason, reintroduction of VRZ was not required. At this time, the prescription of a placebo was not considered to verify the reality of this adverse event. Thus, the score is 0 for all these points. The preliminary score of ADR probability scale is +5.

The role of Ethambutol must be discussed too[22-24]. Three most used anti-tuberculosis drugs are responsible for toxic optic neuropathy: Isoniazid, linezolid and ethambutol. Prescription of the latter is associated to a frequent and often severe complication leading to poor vision: the Ethambutol Optic Neuropathy. More than a hundred publications and cases were published. The chronology of visual impairment is interesting to consider. Visual prognosis seems quite favourable in young patients. However, improvement is not always observed, and some patients remain severely disabled with a dramatic visual loss. In addition, visual acuity can even worsen for one or two weeks after the discontinuation of ethambutol[22]. But, in our present case, visual acuity presented an extremely severe deterioration. It decreased from 20/20 to 20/145 in less affected eye. A large central scotoma appeared on both

Table I. Cases of TON in patients treated with VRZ in VigiAcess or pharmacovigilance databases.

	Age (Years)	Medical history	Treatment indication	Treatment	Delay of onset of optic neuropathy	Symptoms	Evolution
N° 1	35	Cystic fibrosis		Voriconazole	?	Visual decrease	No recovered
N° 2	57	Acute myeloid leukemia		Voriconazole Aracytine Cerubidine	13 days	Confusion Inferior limb weakness Visual decrease	Unknown
N° 3	21	Acute lymphoblastic leukemia		Voriconazole Vincristine Zelitrex Daunorubicine Methotrexate Endoxan	1 month	Tubular visual field	No recovered
N° 4	50	AIDS Lymphoma	Atypical mycobacterium	Voriconazole Ethambutol	3 months	Visual decrease	No recovered
N° 5	44	AIDS	1. Pulmonary tuberculosis 2. Cryptococcal meningitis	a. Voriconazole b. Ethambutol	a. 7 months b. 12 weeks	Visual decrease	Unknown
N° 6	61		1. Pulmonary tuberculosis 2. Aspergilosis	Voriconazole Ethambutol	9 days	Right eye: Abnormal visual field	Recovered

eyes, which did not exist at the time the ethambutol was stopped. Thus, the evolution of visual function cannot be related to a toxicity of the ethambutol for three reasons. Firstly, the visual degradation was too severe. It persisted for a too long time after ethambutol discontinuation. Thirdly, our patient complained of another symptom of neurotoxicity. He developed a peripheral neuropathy that was not related to ethambutol therapy. The pharmacovigilance department confirmed that our patient did not receive other neurotoxic drug except for VRZ after the discontinuation of the ethambutol. Thus, no other alternative causes could have caused on their own the TNO. This data adds +2 to the ADR probability score. The final score is then +7.

According to this probability score, VRZ seems to be responsible of the TON observed in our patient. The risk factors for such adverse event could be linked to the ability of CYP2C19 enzyme to ensure the metabolism of VRZ[25,26]. According to the alleles of the CYP2C19 gene, this enzyme is associated with reduced, absent, or increased drug metabolism[25]. Patients who are *CYP2C19 poor metabolizers* have an increased concentration of VRZ in serum theoretically. This higher concentration is associated with increased risk of neurotoxicity[27,28]. Lee et al[29] showed that ethambutol exhibited moderate inhibitory potential against CYP2C19. Ethambutol increases the serum concentration of VRZ and could potentiate the occurrence of TNO due to this drug. Thus, TNO observed in association with ethambutol and VRZ does not seem fortuitous. This could explain the three cases reported in pharmacovigilance data (Table I). Since the effect of ethambutol on CYP2C19 is mild, the risk of TNO exists only in poor metabolizer patients. This explained the low frequency of such complication since only 15% of patients are poor metabolizer[25,30]. The same mechanism was reported for the association with VRZ and cyclosporin or omeprazole. These two drugs can reduce the CYP2C19 activity although in those cases the toxicity of VRZ was mostly hepatic[9,10].

Prevention is the best way to avoid the adverse effect. Different authors consider that there is a beneficial effect of concentration drug monitoring and enzyme CYP2C19 genotyping in patients treated by VRZ in association with drugs known to decrease the activity of this enzyme[31-33]. If the genotyping of the gene CYP2C19 is not possible, the detection of TNO must be strengthened in such cases. This is important in association with VRZ with ethambutol. In our case, discontinuation of ethambutol did not allow to stop the TNO. It is not possible to know if it is mandatory to stop all treatments to improve visual function in such cases.

Conclusions

By its action on CYP1C19, ethambutol potentiates the neurotoxicity of VRZ, leading to the occurrence of classical TNO[5]. Such mechanism was not previously reported in this context. It has an important clinical consequence. The detection of such complication must be strengthened in those patients.

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Conflict of Interest
The Authors declare that they have no conflict of interests.

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