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Case Report Open Access

Toxic Optic Neuritis due to Isotretinoin in a Child with Neuroblastoma: A Case Report

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Abstract

Retinoids, namely tretinoin and isotretinoin, are metabolically active derivates of vitamin A and used as therapeutic agents. Tretinoin is part of the standard therapy for patients with acute promyelocytic leukemia. Isotretinoin is applied to children with medium and high risk neuroblastoma. Further, both isomers are frequently administered to patients with acne and other skin or mucosal disorders.

Isotretinoin usage in dermatology has been associated with several ocular side effects. We report on the first pediatric patient with neuroblastoma who suffered from acute transient bilateral vision loss due to optic neuritis induced by systemical administration of isotretinoin. Therefore toxic optic neuritis needs to be considered as a potential adverse effect of isotretinoin therapy and weighed carefully against therapeutic benefits.

By quantum mechanical calculations it could be shown that 13-cis/trans-isomerism of tretinoin has only minor influence on the molecular shape and electrostatic potential suggesting that the biochemical interactions as well as adverse effects for tretinoin and isotretinoin might be similar.

Keywords: Retinoids; Adverse effect; Vision loss; Computational analysis

Context

Retinoids are chemical compounds deriving from vitamin A which play an important role in cell growth, cell differentiation and apoptosis and are therefore linked to tumorigenesis. Tretinoin [(all-trans-retinoic acid (ATRA)] is the all-trans isomer of isotretinoin (13-cis-retinoic acid, 13-cis-RA; Figure 1a); both represent metabolically active derivatives of vitamin A and are utilized in the fields of oncology and dermatology [1-7]. Tretinoin is systemically applied to patients with acute promyelocytic leukemia (APL) for induction of remission [8-15]. Isotretinoin is used in children with medium and high risk neuroblastoma; in vitro, therapy results in decreased cell proliferation and reduced expression of MYCN proto-oncogene protein [16-19]. High dose treatment was shown to be effective in the randomized CCG-3891 trial [10]. Therefore, isotretinoin is orally applied for 14 consecutive days followed by two weeks of rest in a course of six months. After a break of three months, therapy is continued for another three months. Overall, patients are scheduled to pass through nine cycles of isotretinoin.

Besides, tretinoin and isotretinoin are often applied locally or systemically to patients with acne and administered off-label in case of other skin or mucosal disorders [3]. For tretinoin, impaired vision and disorders of conjunctiva were described as side effects [20]. Isotretinoin may cause ocular adverse reactions in 3.4% of all patients treated for these indications [15] Predominantly, mild ocular manifestations not affecting the course of treatment have been reported so far; the most frequent seem to be blurred vision and keratitis [4]. However, the very serious adverse effect of optic neuritis, an inflammation of the optic nerve leading to complete or partial vision loss, has been associated with isotretinoin therapy in dermatologic patients [4,5,8]. Fraunfelder and colleagues identified 33 patients with optic neuritis possibly related to isotretinoin according to the World Health Organization Causality Assessment Guide of Suspected Adverse Reactions [4]. A Spanish group reported on a 16-year-old girl who suffered from unilateral vision loss and blurred vision three months after starting treatment with oral isotretinoin at a dose of ~0.5 mg/kg/d due to juvenile acne [13]. Pathophysiologically isotretinoin may cause conduction defects within the optic nerve [2].

Case Report

We report on a 5-year-old boy who was diagnosed with neuroblastoma stage IV originating from the left adrenal gland with massive bone marrow metastases. The patient was treated according to the study protocol NB2004-HR of the Society for Paediatric Oncology and Haematology (GPOH) with neoadjuvant chemotherapy (experimental arm with topotecan induction therapy), followed by tumor excision (R0 resection) and high-dose chemotherapy with autologous hematopoietic stem cell rescue.18 For consolidation treatment the child received isotretinoin at a dose of ~6 mg/kg/d. The first cycle was interrupted due to hypercalcemia and xerosis cutis. After normalization, the second cycle was started as scheduled.

16 weeks after beginning isotretinoin therapy (right at the beginning of the fifth cycle) the child presented with markedly impaired color vision and decreased visual acuity on both sides. Clinical neurological exploration did not show any other pathologic findings. The patient initially suffered from a mild headache but did not report painful eye movements. The ophthalmic examination showed bilateral choked disks but no evidence for an inflammatory genesis. Anterior eye segments were without pathological findings. The visual acuity was bilaterally decreased to 1/50. By use of the Ishihara test the child was not able to recognize any colors. The intraocular pressure was normal in both eyes. The visual evoked potential (VEP) responses were markedly delayed (P100 of right eye at 147 ms, amplitude 5.3 µV; left eye 135 ms; 4.9 µV) and hereby confirmed the presence of bilateral optic neuropathy.

Initial blood analysis showed fairly normal results for full blood count, clotting tests including D-dimers, C-reactive protein, creatinine and aspartate transaminase; serologically an acute infection was ruled out (negative tests for Borrelia, enterovirus, FSME, HSV-, HSV-, measles virus, mumps virus, mycoplasma, parvovirus B19, VZV).

Lumbar puncture was performed twice and displayed a regular cerebrospinal fluid (CSF) opening pressure in each case; CSF analyses were normal, there was particularly no evidence for either bacterial or viral CNS infection (Borrelia, enterovirus, HSV-, HSV-, mycoplasma, VZV) or an inflammatory affection of the CNS. Extensive neuronal autoantibody diagnostics from blood and spinal fluid revealed normal results.

Magnetic resonance imaging (MRI) of the brain did not reveal an underlying reason for the patient's vision loss; there was no evidence for a compression of the optic nerve due to elevated intracranial pressure or an intracerebral mass. Spinal MRI and negative aquaporin-4 antibodies gave no hint at the manifestation of a neuromyelitis optica.

Therapy with isotretinoin was interrupted immediately. Based on the suspicion of optic neuritis treatment with methylprednisolone pulse therapy (~30 mg/kg/d) for five days and acetazolamide for three days because of elevated optic disks was initiated. Under therapy, daily performed ophthalmic follow-ups revealed a discrete but continuous improvement of both color vision and visual acuity; at the end of methylprednisolone pulse therapy the latter was determined with 1/15 (right eye) and 1/20 (left eye), respectively. At the time of discharge on day 10, right eye visual acuity even ameliorated to 3/10; bilaterally elevated disks were on the decrease. Six weeks later the ophthalmic reevaluation (including Meso and Hue discrimination test) showed normal results. Therapy with isotretinoin was not continued according to the recommendations of the neuroblastoma study group.

Computational analysis was performed to analyse the geometries of tretinoin and isotretinoin. The influence of molecular shape changes was studied applying quantum mechanics. Figure 1 illustrates both the molecular structures (b) and electrostatic potentials (c) calculated with density functional theory (DFT) in water. ESP plots provide information on the molecule's potential for coulombic (electrostatic) interactions with other (bio) molecules. These structures and electrostatic potential plots support the hypothesis of only minor structural differences between tretinoin and isotretinoin.

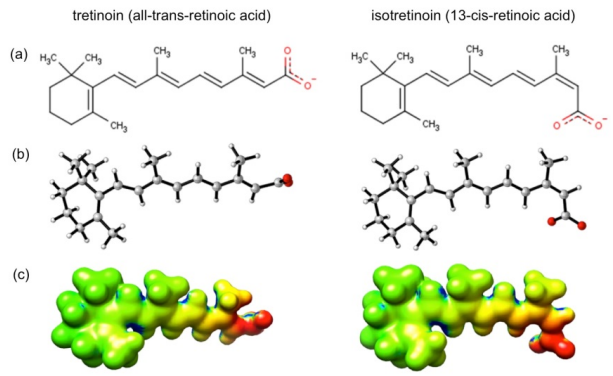

Figure 1: Illustrates both the molecular structures (b) and electrostatic potentials (c) calculated with density functional theory (DFT) in water.

In detail, molecular structures of tretinoin and isotretinoin (deprotonated at physiological pH) were built by ArgusLab (4.0.1) and preoptimized during 100 cycles of BFGS optimization by means of the universal force field (UFF). Final optimization was performed using ORCA (3.0.2), applying the BLYP density functional including Grimme's empirical dispersion correction (D3) and the def2-TZVPP basis set in water utilizing COSMO [7,11]. For the visualization of structures and electrostatic potential CYLview (v1.0.561 BETA) and UCSF Chimera (1.8) were used [9,14].

Discussion

In genereal, cis-/trans-isomerism can lead to significant changes in the three-dimensional structure of molecules which is of great importance for the interaction of a chemical compound or drug with biomolecules. Due to isomerism relevant differences in pharmacological properties do occur. However, the 13-cis/trans-isomerism observed in case of (iso-) tretinoin is expected to have only minor influence on the molecular shape and electrostatic potential due to the terminal location of the double bond involved in isomerism. This can be regarded as an argument for potential similar biochemical interactions as well as adverse effects for tretinoin and isotretinoin.

Regarding the different indications for retinoids in oncology and dermatology the dosage is strikingly different. For acne therapy isotretinoin usually starts at a dose of 0.5 mg/kg/d for four weeks, is then increased to 1 mg/kg/d and continued until a cumulative dose of 120 to 150 mg/kg was applied [6]. In patients with neuroblastoma 5 to 6 mg/kg/d isotretinoin are applied for nine cycles of 14 days duration each (cumulative dose ~700 mg/kg). Concerning pediatric and adult APL patients tretinoin is administered at a dose of ~1.5 mg/kg/d for a maximum of 90 days (maximal cumulative dose 135 mg/kg). Although the cumulative dose of isotretinoin is around five-fold higher in neuroblastoma patients compared to isotretinoin in dermatological patients optic neuritis has not been reported yet as an adverse effect in the patients first mentioned.

In respect of the patient described in this case report the improvement in symptoms after interruption of treatment and the absence of other convincing causes support our diagnosis of an isotretinoin adverse effect. Besides optic neuritis (sub) acute bilateral

vision loss may be caused by a transient ischemic attack (duration of symptoms <24 hours), idiopathic intracranial hypertension or neuromyelitis optica which were excluded in the patient described. In respect of timing, suspected ocular adverse effects were observed within days or up to years after initiating isotretinoin therapy in dermatologic patients [4].

Taken all together, toxic optic neuritis must be regarded as a severe potential adverse effect of isotretinoin therapy. Peinemann and colleagues recently reviewed 3891 patients with high-risk neuroblastoma comparing treatment with isotretinoin to no further consolidation therapy following high-dose chemotherapy and autologous hematopoietic stem cell rescue. Regarding overall and event-free survival there was no clear evidence in favor of either treatment group. Thus, the effects of isotretinoin therapy in patients with high-risk neuroblastoma seem to require further evaluation [12].

During therapy, patients should be monitored continuously concerning ophthalmologic alterations to allow an early detection of even subclinical changes and prevent long-term complications.

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