Graefes Arch Clin Exp Ophthalmol (2011) 249:145–146
DOI 10.1007/s00417-010-1361-6

LETTER TO THE EDITOR

Seizures following subconjunctival 5-FU therapy

René Hoehn · Julia Lamparter · Norbert Pfeiffer · Urs Vossmerbaeumer

Received: 26 December 2009 / Revised: 2 March 2010 / Accepted: 5 March 2010 / Published online: 30 March 2010

Dear Editor,

Antiproliferative treatment following glaucoma surgery includes subconjunctival 5-fluorouracil (5-FU) injections as a routine procedure. Cumulative dosage during the postoperative period is adjusted to individual needs ranging from 5 to 75 mg.

We report the case of a 68-year-old male Caucasian patient who underwent uneventful trabeculectomy for advanced primary open-angle glaucoma with intraoperative application of Mitomycin C. Under topical anesthesia with tetracaine eye drops, a subconjunctival injection of 5 mg 5-FU was administered on postoperative day 4. A few minutes later, a generalized tonic and clonic seizure occurred lasting for 3 min that ended spontaneously. A second episode of seizures happened 3 h later. The patient did not retain any memory of the episode and amnesia was observed for the immediate postictal period. However, epilepsy was hitherto unknown in this patient nor did his medical history give any hints as to such a condition. Known systemic conditions included arterial hypertension, coronary heart disease, congenital aortic coarctation, hyperlipidemia, and prostate hyperplasia. Neurologic examination including electroencephalography and cranial imaging revealed spike wave complexes, but no specific focus. Thirteen days later, two more subconjunctival injections of 5 mg 5-FU were applied without complications under anticonvulsive therapy with Valproic acid 300 mg twice a day. No more seizures occurred in the domestic environment.

When trabeculectomy was performed on the fellow eye 4 months later, 5 mg 5-FU was again applied to prevent bleb scarring without obvious complications. Upon a 5-h interval after the second injection, two more grand-mal convulsions occurred despite permanent therapy with gabapentin 300 mg three times a day and acute therapy with lorazepam 1 mg after the first seizure. Afterwards, the therapy was modified to Valproic acid 600 mg twice a day.

5-fluorouracil is a pyrimidine antimetabolite that prevents DNA synthesis and inhibits RNA processing and function. It quickly penetrates the blood–brain barrier and achieves significant concentrations within the cerebrospinal fluid.

Observed neurotoxicity of 5-FU as a commonly used, systemic chemotherapy agent is estimated <1% [1–3], but also up to 5.7% [4, 5] in high-dose chemotherapy. Acute neurotoxicity is dose-related and generally reversible [6]. It typically manifests as encephalopathy with somnolence and confusion or cerebellar syndrome. However, seizures are described in a few cases [3, 6], and in only one case as isolated generalized tonic-clonic seizures [7].

The exact pathways of neurotoxicity are not completely understood. The most plausible pathogenetic mechanism for developing seizures or paresis-like symptoms may be the Krebs cycle blockade by fluoroacetate and fluorocitrate, which results in a reduction of high-energy adenosine triphosphate [2, 8, 9]. Other proposed mechanisms are thiamine deficiency and inherited deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD), which metabo-

Presentation at a conference Parts of this case report were presented at the 107th Congress of the Deutschen Ophthalmologischen Gesellschaft (DOG), Leipzig

Financial disclosure There was no sponsoring organization involved and no financial relationship exists in this study.

R. Hoehn · J. Lamparter · N. Pfeiffer · U. Vossmerbaeumer
Department of Ophthalmology, Mainz University Medical Center,
Langenbeckstr. 1,
55131 Mainz, Germany

R. Hoehn (✉)
Augenklinik der Universitätsmedizin Mainz,
Langenbeckstraße 1,
55131 Mainz, Germany
e-mail: hoehn@augen.klinik.uni-mainz.de

lizes about 80% of fluorouracil [2, 7]. An animal model demonstrated that systemic 5-FU causes acute damage by induction of apoptosis to neuronal cells and delayed damage to myelinated tracts [10].

A supposed pathomechanism might be a rise in concentration in brain and cerebrospinal fluid (CSF) due to the close and direct communication between the subconjunctival/sub-Tenon space and the optic nerve sheath as part of the CSF system [11]. Through avoiding a significant systemic distribution of 5-FU, the DPD activity is thought to be of secondary importance, and a test for DPD activity was not performed in our patient.

The subconjunctival injection itself may also be a conceivable trigger for seizures. This, however, would imply an immediate temporal correlation to the injection in all events and there still would not be an explanation for the delayed onset of the third episode. Nevertheless, such an association has not been described in the literature yet. To the best of our knowledge, this is the first report of epileptic seizures following subconjunctival 5-FU application.

References

1. Bygrave HA, Geh JI, Jani Y, Glynne-Jones R (1998) Neurological complications of 5-fluorouracil chemotherapy: case report and review of the literature. Clin Oncol (R Coll Radiol) 10:334–336
2. Sucker C, Lambers C, Stockschlader M, Dolken G (2002) Neurotoxicity of 5-fluorouracil. Dtsch Med Wochenschr 127:2011–2014. doi:10.1055/s-2002-34361
3. Cheung WY, Fralick RA, Cheng S (2008) The confused cancer patient: a case of 5-fluorouracil-induced encephalopathy. Curr Oncol 15:234–236
4. Kim YA, Chung HC, Choi HJ, Rha SY, Seong JS, Jeung HC (2006) Intermediate dose 5-fluorouracil-induced encephalopathy. Jpn J Clin Oncol 36:55–59. doi:hyi214 [pii] 10.1093/jjco/hyi214
5. Moore DH, Fowler WC Jr, Crumpler LS (1990) 5-Fluorouracil neurotoxicity. Gynecol Oncol 36:152–154
6. Pirzada NA, Ali II, Dafer RM (2000) Fluorouracil-induced neurotoxicity. Ann Pharmacother 34:35–38
7. Elkiran ET, Altundag K, Beyazit Y, Guler N, Kars A (2004) Fluorouracil-induced neurotoxicity presenting with generalized tonic-clonic seizure. Ann Pharmacother 38:2171. doi:aph.1E070 [pii] 10.1345/aph.1E070
8. Okeda R, Shibutani M, Matsuo T, Kuroiwa T, Shimokawa R, Tajima T (1990) Experimental neurotoxicity of 5-fluorouracil and its derivatives is due to poisoning by the monofluorinated organic metabolites, monofluoroacetic acid and alpha-fluoro-beta-alanine. Acta Neuropathol 81:66–73
9. Yamashita K, Yada H, Ariyoshi T (2004) Neurotoxic effects of alpha-fluoro-beta-alanine (FBAL) and fluoroacetic acid (FA) on dogs. J Toxicol Sci 29:155–166
10. Han R, Yang YM, Dietrich J, Luebke A, Mayer-Proschel M, Noble M (2008) Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. J Biol 7:12. doi:jbiol69 [pii] 10.1186/jbiol69
11. Koevary SB, Lam V, Patsiopoulos G, Lake S (2003) Accumulation of porcine insulin in the rat brain and cerebrospinal fluid following ocular application. J Ocul Pharmacol Ther 19:377–384