Possible drug-induced, vision-threatening maculopathy secondary to chronic pentosan polysulfate sodium (Elmiron®) exposure

R. Christopher Doiron, MD1; Mark Bona, MD2; J. Curtis Nickel, MD1
1Department of Urology, Queen’s University, Kingston, ON, Canada; 2Department of Ophthalmology, Queen’s University, Kingston, ON, Canada

Cite as: Can Urol Assoc J 2020 January 7; Epub ahead of print.
http://dx.doi.org/10.5489/cuaj.6401

Published online January 7, 2020

***

Interstitial cystitis/bladder pain syndrome (IC/BPS) remains a clinically challenging chronic urological pain syndrome that is difficult to treat with a limited number of therapies. In fact, the only FDA-approved oral medication for treatment of IC/BPS is pentosan polysulfate sodium (PPS).1 PPS — marketed as Elmiron®— is a synthetic polysaccharide that binds to the urothelium, providing a protective layer that may help prevent painful irritation from components of the urine. The FDA- and Health Canada-approved dosage regimen is 100 mg three times daily, although the most recent randomized, placebo-controlled study failed to confirm efficacy.2

In 2018, Pearce et al3 first described a unique pigmentary maculopathy affecting six patients who, after clinical ophthalmic evaluation and retinal imaging with fundus photography, spectral-domain optical coherence tomography, and wide-field fundus autofluorescence imaging, were found to have abnormalities of the retinal pigment epithelium (RPE). The patients’ clinical presentation was difficulty with reading and prolonged adjustment to darkness. All patients were female with a known diagnosis of IC/BPS treated with oral PPS; median exposure time was 186 months (144–240), with a median cumulative exposure at presentation of 2263 g (1314–2774 g).

Subsequent to this initial report, a multi-institutional case series4 described a further 35 cases retrospectively identified from a cohort of 404 patients with PPS exposure as having characteristic findings (as described in their initial case series3) consistent with this unique maculopathy. Extensive ophthalmic examination and imaging described the maculopathy as characterized by alterations in the RPE and photoreceptor-RPE interface, again, manifesting most commonly as blurred vision and prolonged dark adaptation. Patients in this case series had a median duration of IC/BPS diagnosis of 19 years (6–44), with a median exposure time to PPS of 15 years (3–22).

More recently, a large, administrative, U.S. database was used to examine the association of PPS use and a diagnosis of a macular disorder.5 Their exposure cohort (PPS users) was matched 1:5 with an unexposed cohort of patients (not necessarily IC/BPS patients). The primary
outcome was any new diagnosis of a hereditary or secondary pigmentary retinopathy or any new
diagnosis of dry age-related macular degeneration (AMD) or drusen in addition to the previously
described retinopathy. At five years of followup, there was not a statistically significant
difference between the exposed and unexposed groups in terms of the primary outcome, but at
seven years, there was a statistically significant increase in the exposed group in multivariate
analysis (odds ratio [OR] 1.41; 95% confidence interval [CI] 1.09–1.83; p=0.009]. Limitations of
the study included inability to confirm length or quantity of PPS exposure, and the imperfect
definitions of outcomes using administrative codes for retinopathies in the setting of studying a
rare and unique maculopathy — both of which would bias towards a null result.

At a recent meeting of the American Academy of Ophthalmologists in San Francisco,
Vora et al\textsuperscript{6} presented their findings using data from Kaiser Permanente and identified 140
patients (from the database of 4.3 million) who had taken an average of 5000 pills over a 15-year
period. Of the 140 exposed patients, 91 agreed to an examination and of those, 22 patients
showed clear evidence of this specific maculopathy, which authors believe was associated with
PPS exposure. Their data is currently unpublished, but reports suggest there did appear to be a
dose-response relationship with the toxicity.

These are alarming findings. However, several questions remain unanswered. For
example, in their response to a letter to the editor penned by Pearce et al, Nickel and Moldwin\textsuperscript{7}
pointed out the fact that an unexposed IC/BPS cohort has yet to be included in any of the
observational data reported to date. Are we truly observing a drug-associated toxicity or is the
described maculopathy another manifestation of IC/BPS itself? Though a randomized,
prospective study to answer this question would be lengthy, expensive, and unlikely, Nickel and
Moldwin suggested addressing this concern using a multicenter screening study of patients with
IC/BPS, including a chronically exposed cohort, as well as a control cohort of those unexposed
to the drug.

Although causation has yet to be established, some mechanisms of toxicity have been
posited. It is possible that the drug or one of its metabolites is directly toxic to the RPE or that it
may interfere with the interphotoreceptor matrix, which consists primarily of
glycosaminoglycans.\textsuperscript{4} Questions regarding length and quantity of exposure and their relationship
to degree of toxicity are still unclear.

It behooves us as scientists, urologists, and possible prescribers of this medication to fully
understand the relationship thus far reported in this population. Until that time comes, we
recommend disclosing the emergence of this potential toxicity to exposed patients. We further
suggest ophthalmic screening in any PPS-exposed patient with any vision complaints for
evidence of this maculopathy.
References


