AMERICAN ACADEMY OF OPHTHALMOLOGY®

Reports

Prevalence of Maculopathy Associated with Long-Term Pentosan Polysulfate Therapy

Pentosan polysulfate sodium (PPS) (Elmiron; Janssen Pharmaceuticals, Titusville, NJ) is the only Food and Drug Administration–approved oral medicine for the treatment of interstitial cystitis (IC).[1] A recent original report studying 6 patients from a single academic practice linked chronic exposure to PPS with the development of a unique pigmentary maculopathy.[2] Further phenotypic details were defined in a larger follow-up retrospective multicenter study involving 35 patients.[3] Since those reports, presumed PPS-related maculopathy has been noted to progress despite drug cessation[4] and is associated with the development of choroidal neovascularization.[5] Retrospective studies that have looked at the relationship between PPS intake and maculopathy by reviewing claims databases have provided equivocal results.[6,7]

Because there are few alternative therapies available to manage IC, it is important that additional evidence be available to help counsel patients taking PPS. We evaluated the prevalence and risk factors for maculopathy in patients with long-term exposure to PPS at Kaiser Permanente Northern California (KPNC). Kaiser Permanente Northern California is a comprehensive medical care and coverage entity that cares for a diverse racial and socioeconomic population of approximately 4.3 million patients. The KPNC electronic medical record includes demographic and pharmacy data for all patients in the health plan, and an ophthalmic picture archive and retrieval system enables remote viewing of imaging studies from any facility. The pharmacy database can provide the exact number of pills dispensed to any member.

At KPNC, there are 1120 patients who have IC on their active problem list (0.03%). Of those, 475 (42%) are currently taking PPS (.01%). Pentosan polysulfate sodium is on the drug formulary within KPNC, with members only paying their copay or deductible for the prescription. After the initial publication by Pearce et al,[2] we undertook a quality operation to perform outreach on 138 patients who had been dispensed at least 500 g (5000 100-mg capsules) of PPS during the prior 20-year period and who still had an active prescription for the medication within KPNC in 2018. Within 1 year, 117 of 138 patients (85%) had been successfully screened with OCT and fundus photography. Fundus autofluorescence was performed where available. We determined sex, age at last eye examination, race, body mass index, height, weight, and smoking history from the electronic medical record. Two retina specialists (R.A.V., A.P.P.), who were aware of medication exposure but masked to total medication use, independently reviewed all available retinal imaging studies and scored each patient as having definite or no definite signs of PPS maculopathy. Charts were only scored as definite maculopathy if they met published clinical criteria and if both retina specialists scores were concordant.[2,3] The study was approved by the Kaiser Permanente Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. This is a retrospective study using deidentified subject details. Informed consent was not obtained. Statistical analysis was performed using Stata 15.1 (StataCorp LP, College Station, TX).

Of 117 patients screened, 27 (23.1%) had definite signs of maculopathy and 90 (76.9%) did not. The 21 patients (15%) who did not receive screening were slightly younger (mean age, 56.5 vs. 63.6 years; t test $P = 0.03$) and had a lower cumulative exposure (876 vs. 1110 g, t test $P = 0.04$) compared with those who were screened, but otherwise the 2 groups were similar. Visual acuity was generally preserved even in patients with signs of toxicity, with only 3 patients having reduced central vision to a level below 20/150 due to geographic atrophy involving the fovea. Univariate analysis of potential risk factors is shown in Table 1. Patients with maculopathy had been dispensed a mean of 1350 g (13 510 capsules) of PPS compared with 1040 g (10 387 capsules) in those without signs of toxicity (t test, $P < 0.01$). The likelihood of toxicity significantly increased with increasing dose from 12.7% of patients who had consumed 500 to 999 g to 41.7% in patients who were exposed to >1500 g (chi-square, $P = 0.01$). The odds ratio of developing toxicity relative to the 500 to 999 g group was 2.95 (95% confidence interval, 1.01–8.65, $P = 0.05$) in the 1000 to 1500 g group and 4.91 (95% confidence interval, 1.64–14.7, $P = 0.01$) in the >1500 g group. Multivariable regression analysis of patients with definite toxicity compared with those without suggested that the cumulative amount of PPS dispensed was the only significant factor linked to the development of maculopathy (Table S2, available at www.aaojournal.org). Two representative longitudinal examples of PPS maculopathy are shown in Figure S1 (available at www.aaojournal.org).

Our results confirm the recent reports of a correlation between chronic exposure to PPS and the development of a characteristic maculopathy.[2–5] Approximately one-quarter of patients with intake >500 g developed retinal changes consistent with the abnormalities described by Pearce et al[2] and Hanif et al.[3] A significant trend of increasing probability with higher exposure was noted, ranging from 12.7% in the group with the least exposure to 41.7% in the highest consumption group.

A weakness of the study was that neither genetic nor electrophysiologic testing was performed routinely. The absence of these data makes it impossible to rule out a primary or concurrent retinal dystrophy, or to detect whether some patients may be at higher genetic risk for PPS maculopathy. Also, despite our best outreach efforts, this study may nevertheless suffer from selection bias and a slight overestimate of prevalence. In contrast, the design of this study avoided referral bias because we performed outreach to all members, not just patients who had previously been seen in ophthalmology or retina clinics.

We believe that our findings add strong support to the growing body of evidence that links long-term PPS use to the potential development of a toxic maculopathy. We hope that further studies will refine the risk factors associated with this complication and lead to effective screening guidelines.

Table 1. Univariate Analysis

Variable	Maculopathy (n=27)	No Maculopathy (n=90)	P Value
Sex (female)	22 (81.5%)	77 (85.6%)	0.27*
Race (white)	24 (88.9%)	69 (76.7%)	0.17
Mean (SD)			
Age, yrs	65.8 (15.7)	63.0 (12.3)	0.33†
Weight (kg)	73.1 (17.6)	74.3 (16.3)	0.75
Body mass index	28.1 (5.0)	26.7 (5.5)	0.24
Duration of therapy (yrs)	14.4 (4.6)	13.1 (4.8)	0.22
Daily dose (mg)	268.5 (103.6)	234.5 (95.9)	0.12
Cumulative dose (g)	1351 (581)	1042 (449)	<0.01
Cumulative dose tertile			0.01‡
500–999 g	8 (12.7%)	55 (88.3%)	
1000–1500 g	9 (30.0%)	21 (70.0%)	
>1500 g	10 (41.7%)	14 (58.3%)	

SD = standard deviation.
*t test.
†Chi-square test.
‡Logistic regression.

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No animal subjects were used in this study.

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References

1. Hanno AM. Analysis of long-term Elmiron therapy for interstitial cystitis. *Urology*. 1997;49:93–99.
2. Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology*. 2018;125:1793–1802.
3. Hanif AM, Armenti ST, Taylor S, et al. Phenotypic spectrum of pentosan polysulfate sodium-associated maculopathy. *JAMA Ophthalmol*. 2019;137:1275–1282.
4. Huckfeldt RM, Vavvas D. Progressive maculopathy after discontinuation of pentosan polysulfate sodium. *Ophthalmic Surg Lasers Imaging Retina*. 2019;50:656–659.
5. Mishra, Patel TP, Singh MS. Choroidal neovascularization associated with pentosan polysulfate toxicity. *Ophthalmol Retina*. 2020;4:111–113.
6. Jain N, Li ALL, Yu Y, VanderBeek BL. Association of macular disease with long-term use of pentosan polysulfate sodium: findings from a US cohort. *Br J Ophthalmol*. 2019 Nov 6 [Epub ahead of print].
7. Ludwig CA, Vail D, Callaway NF, et al. Pentosan polysulfate sodium exposure and drug-induced maculopathy in commercially insured patients in the United States. *Ophthalmology*. 2020;127(4):535–543.

Evaluating Amblyopia Treatment Success Using the American Academy of Ophthalmology IRIS50 Measures

There are few consensus measures of treatment success for amblyopia. Most published studies measure relative improvement in visual acuity (VA) without establishing concrete success criteria. Furthermore, there is inconsistency in outcome measures and reporting timelines among investigators.[1] Definitive measures of success may better inform individual practitioners of their performance while allowing for assessment of new treatment strategies. The American Academy of Ophthalmology developed criteria for measuring amblyopia treatment success (known as IRIS7), recently modified in 2019 (IRIS50). In patients aged 3 to 7 years with starting interocular difference (IOD) >0.29 logarithm of the minimum angle of resolution (logMAR), success was defined as having final IOD <0.23 logMAR, final VA of 20/30 or better (≤0.18 logMAR), or VA improvement of 2 or more lines (≥0.18 logMAR) in the affected eye at 3 to 12 months follow-up (AAO 2019).[2] In this study, we report our amblyopia treatment outcomes based on the IRIS50 and IRIS7 measures and evaluate the predictive value of multiple baseline variables.