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Gastrointestinal Adverse Effects of Prostaglandin Analogues

Prostaglandin analogues are the first choice of treatment for glaucoma in part because of their limited systemic adverse effects. Only the Travan (Alcon Laboratories Inc, Fort Worth, Texas) (travoprost ophthalmic solution, 0.004%) label lists gastrointestinal adverse effects, noting dyspepsia and gastrointestinal disorders at a rate of 1% to 5%.1 Neither Xalatan (Pfizer Inc, New York, New York) (latanoprost ophthalmic solution, 0.005% [50 µg/mL]) nor Lumigan (Allergan Inc, Irvine, California) (bimatoprost ophthalmic solution, 0.03% [0.3 mg/mL]) lists any gastrointestinal adverse effects on their labels.

Prostaglandin analogues have a favorable systemic adverse effect profile, with rare reports of discontinuation of treatment secondary to adverse events.2 We describe 3 patients with transient gastrointestinal adverse effects after prostaglandin analogue use. The adverse effects in all 3 patients were confirmed by means of unmasked challenge-rechallenge tests, and all 3 patients were tested with at least 2 prostaglandin analogues. The adverse effects were different for each of the 3 patients, and severity differed depending on which medication was used.

Report of Cases. Case 1. A 59-year-old male university professor with ocular hypertension and a medical history of intermittent mild heartburn (now resolved) had acute gastrointestinal distress 30 minutes after taking latanoprost, despite proper punctal occlusion. He reported nausea, lightheadedness, and substernal fluttering lasting a few seconds, which occurred every 5 to 10 minutes for approximately an hour. He noted gastric reflux up to 12 hours after ingestion, constipation, bloating, and generalized malaise. The symptoms improved after discontinuation, and an unmasked rechallenge resulted in the same symptoms, which resolved on discontinuation of drug use.

Case 2. A 60-year-old sculptor with juvenile open-angle glaucoma was given latanoprost. He self-discontinued using the drug because of "aspirin-like side effects," despite punctal occlusion. He described the adverse effects as a severe gastric burning sensation, acid reflux, and an acidic aftertaste in his mouth, unrelieved by taking antacids. He also noted sinus congestion and neck muscle tension. The patient reported a history of minor heartburn readily relieved by taking antacids. The symptoms resolved within 2 days of discontinuation of the drug. Unmasked rechallenges with all 3 available prostaglandin analogues resulted in the same symptoms, which resolved on discontinuation of drug use.

Case 3. An 84-year-old woman with normal-tension glaucoma was given latanoprost, and she self-discontinued using it after developing dizziness, nausea, and vomiting. The symptoms improved after discontinuation, and an unmasked rechallenge resulted in the same complaints, with resolution on discontinuation of drug use. She was later challenged with travoprost and bimatoprost and experienced similar adverse effects with both; in both cases, the symptoms were relieved by drug discontinuation.

Comment. All 3 patients had severe gastrointestinal adverse effects after initiating treatment with prostaglandin analogues. The first patient developed esophageal spasm, regurgitation, constipation, and generalized malaise. The second patient noted a burning sensation in his stomach, heartburn, and an acidic aftertaste. The third patient developed nausea, vomiting, and dizziness. The adverse effects in all 3 patients were con-
firmed by means of unmasked challenge-rechallenge tests, and all the patients were given at least 1 additional prostaglandin analogue.

We could find only a single case describing rapid-onset gastrointestinal cramping after travoprost use; however, no causal relationship was suggested. The symptoms that the present patients experienced were directly related to the drugs. Although the mechanism of action for all these symptoms is unclear, we speculate that many effects are secondary to stimulation of the smooth muscle of the intestinal tract by the prostaglandins. Prostaglandin F$_2$ analogues have been shown to induce contraction of cat esophageal and lower esophageal sphincter circular smooth muscle. Stimulation of the esophageal muscle could explain the esophageal spasms, and an increase in lower esophageal sphincter tone preventing food passage to the stomach could account for the regurgitation of undigested food. The constipation, described as increased straining during defecation, could be accounted for by a similar effect on the internal anal sphincter.

The Naranjo adverse drug reaction probability scale categorizes the causality of each of these adverse reactions as probable, with scores of 6, 5, and 5 for the 3 patients, respectively. The Naranjo scale uses 10 questions on the temporal nature and quality of adverse effects, the presence of previous reports, and the effects of placebo or antagonists on adverse effects to provide a systematic method for assessing the probability of an adverse reaction in a clinical setting. Causality is categorized as definite (score, 9), probable (score, 5-8), possible (score, 1-4), or doubtful (score, 0).

Although apparently a rare effect, gastrointestinal distress secondary to prostaglandin analogue use should be a consideration for patients given these medications and returning with such complaints.

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Eye on the Web

Four-Eyed Fish

Although they are commonly called the 4-eyed fish, Anableps species actually have just 2 eyes each divided into 2 parts, one adapted for seeing above the water and the other for seeing below. These fishes swim at the surface so that the water level separates each eye horizontally (Figure 1). The 2 halves of the eye are divided by a band of pigment at the waterline. Like a pair of conjoined twins, each eye has 2 pupils that share a single lens, retina, and optic nerve (Figure 2). The top half of the lens is flattened as in a human eye, whereas the bottom half is rounded, which is typical for a fish eye. Also, the upper cornea is thicker, is flatter, and contains a much higher concentration of glycogen than the lower cornea. The resulting difference in refractive power provides an undistorted image of objects both above and below the water level. There is also an iris flap that shields the upper pupil from the glare of light reflected from the water surface. As wearing bifocals, these amazing fishes can see their prey under water and predators in the air at the same time.

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