Topical Timolol and the Nursing Mother

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A 34-year-old nursing woman with elevated intraocular pressure voluntarily and without our knowledge applied 0.5% timolol maleate twice daily to her right eye. A milk sample 1.5 hours after administration of drug showed a much higher level of timolol (5.6 ng/mL) than a plasma sample drawn at the same time (0.93 ng/mL). Three control milk specimens showed no measurable levels of timolol.

The patient's milk sample 12 hours after her last timolol dose contained 0.5 ng/mL of timolol. On the basis of our calculations, timolol should be used with caution by nursing mothers.

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The current general medical literature abounds with data on the teratogenic and postpuerperal effects on the breast-feeding child of various drugs taken by the mother. Therefore, when we were faced with a nursing mother with glaucoma, we were surprised to find that there is no information in the literature on the secretion of topical ophthalmic drugs in breast milk and little information in the files of the various ophthalmic pharmaceutical companies. A recently developed radioassay allowed us to measure both serum and breast milk levels of timolol in a nursing mother.

REPORT OF A CASE

A 34-year-old woman had been first seen approximately two years previously with a history of elevated intraocular pressure since the age of 25 that was believed to be related to pigmentary dispersion. She was resistant to not being treated. Initially, she had been treated with 2% pilocarpine with some success; over time her condition became refractory to this regimen, and she was treated with a pilocarpine derivative (P-40 Ocuserts), a combination of 1% epinephrine bitartrate and 2% pilocarpine hydrochloride, and 0.5% timolol maleate drops.

On initial examination, her corrected visual acuity was 20/20 OU, wearing +0.75 + 1.50 × 05 OD and −6.50 + 1.50 × 40 OS. Slit-lamp examination revealed Kruekenberg's spindles and iris transillumination in both eyes. Intraocular pressures were 25 mm Hg OD and 26 mm Hg OS. Visual fields were completely normal; gonioscopy demonstrated open angles (4+) and pigment (3+) in both eyes. Fundus examination revealed myopic discs, with approximately 0.8 cup-disc ratios and sloping temporal margins almost to the disc rims in each eye.

Treatment with 2% epinephrine hydrochloride and P-40 Ocuserts resulted in IOPs of about 20 mm Hg. Approximately one year later, she was three months pregnant. The epinephrine therapy was discontinued, and the Ocuserts therapy was retained. The IOPs remained in the low to middle 20s throughout her pregnancy.

Post partum, the patient decided that she could no longer tolerate the pilocarpine-induced miosis and independently carried out a therapeutic trial with timolol in the right eye while retaining the pilocarpine therapy in the left eye. When next seen, she was nine weeks post partum and nursing her daughter, and her IOPs were 21 mm Hg OD and 22 mm Hg OS. The discs and visual fields were unchanged; however, because of concern for the infant and recent case reports in the literature regarding side effects of timolol in children, including bradycardia, asthmatic attacks, dissociated behavior and light-headedness, and apnea,11 serum and breast milk samples were sent for determinations of timolol levels.

METHODS

A total of four lactating women were examined: three nonglaucomatous controls in addition to our patient. Each subject donated 5 mL of breast milk by manual expression just before beginning to nurse and another 5 mL 1.5 hours later, after the child had completed nursing. The patient, in addition, donated 5 mL of blood with the initial milk sample, drawing of which was timed to coincide with the next scheduled dosage of timolol. After obtaining the blood, 1 drop of 0.5% timolol maleate was given to one eye of the patient, and the child was nursed. One and a half hours later, milk and another 5 mL of blood were obtained. All samples, from both the patient and the controls, were frozen shortly after being drawn, and then were transported in dry ice for analysis by radioligand-receptor assay via the technique described by Barnett et al.

RESULTS

No appreciable level of timolol was found in any of the control samples. The predose samples of the patient registered 0.15 ng/mL in the plasma and 0.5 ng/mL in the milk. The patient's postdosage serum level was 0.93 ng/mL, and the breast milk level was 5.6 ng/mL. The oral dosage of timolol maleate for cardiac purposes is 10 to 40 mg/day, yielding serum levels of 40 to 60 ng/mL (J. Findlay Walker, MD, oral communication, December 1981). If one assumes that this level is based on the 70-kg man, the dosage for a 3-kg infant is 0.42 to 1.71 ng/day. If one assumes that an infant nurses every four hours and ingests 75 mL at each feeding, then a potential maximum amount of timolol received would be six feedings times 75 mL per feed times 5.6 ng/mL, or 2,520 ng/day, if one eye of the mother is treated. This figure is approximately 1/160 of the cardiac-effective dose or 1/80 if both eyes are treated. Gas-
trointestinal absorption and metabolic function in the newborn, however, are not known, and this dose may be adequate to overwhelm the clearance system of the nursing infant. In the absence of this information, we advised the patient to wean her daughter or to cease use of timolol; on the basis of these results, the manufacturer has revised their listing in the Physicians' Desk Reference to include an advisory to nursing mothers. Recent case reports in the literature have supported this action.

COMMENT

There are several obvious limitations to this report. One is that of sample number, since we have only one patient taking the timolol. However, our results in this one case are consistent with the limited data available in the literature, ie, not only is a β-adrenergic antagonist in the blood filtered through to breast milk, it is also actively secreted, with milk levels approximately six times that of serum levels for timolol in our study, 1.5 to 6.8 times that for atenolol (which is cleared by renal excretion), 2.6 times that for metoprolol (hepatic clearance), 5 and greater than 1.0 times that for propranolol (hepatic clearance). The proposed mechanism is that drugs that are weak bases may accumulate in breast milk because of pH differences between plasma and milk. Second, the control levels were close to 0 ng/mL as were both the plasma and milk levels (0.15 and 0.5 ng/mL, respectively) in our patient 12 hours after her last dose. Therefore, we must assume that the child will be receiving substantially less timolol than the maximum dose presumed in our calculations, even if both eyes are treated. However, it may still be clinically important.

A recent case 7 was reported of an 18-month-old child who had several spells of apnea associated with topical use of 0.25% timolol maleate. On the basis of the findings in our case, assuming half the absorption from the use of 0.25% vs 0.50% timolol maleate and using the smaller weight of the patient in the report, the 18-month-old's blood level should have been approximately 2.33 ng/mL (0.93/2 ng/mL X 55 kg/11 kg, where 0.93 is the blood level with one eye treated with 0.5% timolol maleate in our patient, 55 kg is our patient's weight, and 11 kg is the average weight for an 18-month-old). This value is 1/20 of the cardiac effective level, only four times higher than our patient's child's potential maximal dose. The 18-month-old represents the second reported case of apnea in children, a side effect not yet noted in adults, even with use for systemic effect. This finding suggests that timolol may have more immediate and possibly even lethal side effects in children.

Although the drug is concentrated in breast milk, the level obtained from a mother's milk (to a factor of 1/80 of the cardiac-effective dose) should probably not cause major concern, unless the infant's hepatic or renal function is impaired. It would have been interesting to measure the infant's plasma levels, but this procedure was not possible. We would therefore recommend not giving timolol to a nursing mother unless the treatment is absolutely necessary. If such therapy is warranted, the infant should be observed carefully for signs of β-blockade; however, an even better course would be to advise that the child be weaned.

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References