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Articles

The Immediate Effect of Phenylephrine on Aqueous Flow in Man

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Aqueous flow in normal human eyes was assessed at 1 hr intervals via fluorophotometric measurements, starting 4 hr after fluorescein instillation. The average coefficients of variation of the individual flow values were 5.3% and 8.4% for 1 hr and 1 week intervals, respectively. Aqueous flow was measured in 11 healthy volunteers after the instillation of phenylephrine. In the first hour the aqueous flow showed a significant increase: 131% ± 72% ($P < 0.001$) and in the second hour: 121% ± 92% ($P < 0.002$). Between 2 and 5 hr the average flow did not differ significantly from the flow in the untreated fellow eye. There was no marked effect of pupil dilation on aqueous flow. Invest Ophthalmol Vis Sci 29:1469–1473, 1988

Reliable flow values can be obtained using different fluorophotometric techniques, provided that fluorescein is instilled several hours before starting the measurements.[1]

We have adapted a method of flow calculation in order to determine the aqueous flow at 1 hr intervals. This makes it possible to detect flow changes which occur shortly after the instillation of drugs.

The purpose of this study was to investigate the reliability of flow determinations performed at short time intervals and to calculate the aqueous flow shortly after the instillation of phenylephrine. Conflicting results concerning the effect of phenylephrine have been reported previously.

Materials and Methods

Materials

Twelve volunteers aged 22–51 years were studied to determine aqueous flow at 1 hr intervals, and 11 volunteers aged 16–51 years underwent measurements after receiving phenylephrine. No volunteer was on medical drug therapy or had a history of ophthalmic or systemic disease; the phenylephrine volunteers had less than a 3 mm Hg intraocular pressure difference between their eyes.

Informed consent was obtained after the nature of the procedure had been fully explained.

Methods

Aqueous flow at 1 hr intervals: Four drops of a 10% fluorescein solution were instilled into the conjunctival sac of both eyes at a rate of one drop every 2 min. Ten minutes after the instillation of the last drop the eyes were flushed with saline. Cornea and anterior chamber fluorescein concentrations were measured every half hour from 4 to 7 hr after instillation. In six subjects measurements were also taken during the first 4 hr.

Fluorophotometric measurements were performed using the Fluorotron Master (Coherent Radiation Inc., Palo Alto, CA) equipped with an anterior segment adaptor. The commercial software was modified to omit scanning the lens, which reduced the scanning time to 8 seconds.

Aqueous flow after phenylephrine: At 8:00 AM six drops of a 10% fluorescein solution were instilled into both eyes at 5 min intervals. At 12:00 noon, 5% phenylephrine HCL solution was instilled into one eye, one drop every 2 min, to a total of four drops. Measurements were taken every 15 min from 12:00 noon through 2:00 PM and every half hour from 2:00 PM through 5:00 PM. The untreated eye served as a control, since in six subjects the flow in the untreated eye did not differ significantly from the flow determined in a previous experiment without phenylephrine in

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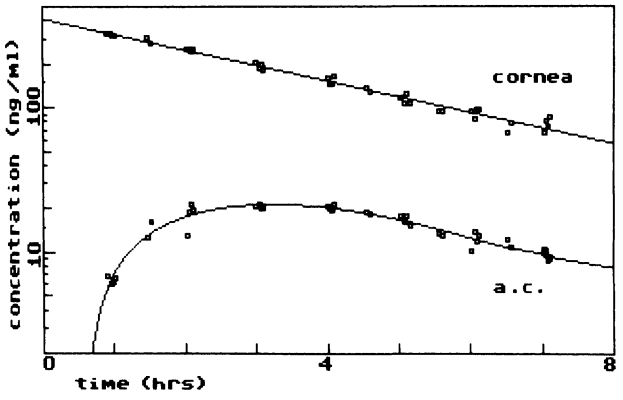

Fig. 1. Fluorescein concentration in the cornea and anterior chamber as a function of time after fluorescein instillation (subject 2).

either eye. One week later Goldmann applanation tonometry was performed on eight of the 11 volunteers, 1 hr and 4 hr after the instillation of the same dose of phenylephrine as used previously.

Calculations: The fluorophotometric measurements in the cornea and anterior chamber were corrected for autofluorescence and spatial resolution of the fluorophotometer.[2]

The aqueous flow was calculated according to a method described previously[3-5] which is based on the assumptions that[6]: (1) all the fluorescein in the cornea leaves by diffusion into the anterior chamber; (2) all the fluorescein in the anterior chamber leaves by aqueous flow; and (3) there is a homogeneous distribution of fluorescein in the aqueous. The method was adapted for one hour intervals; the average flow f between t_1 and t_2 is given by:

$$f = \{[C_c(t_1) - C_c(t_2)] \times V_c + [C_a(t_1) - C_a(t_2)] \times V_a\} \Big/ \left\{\int_{t_1}^{t_2} C_a(t)dt\right\} \quad (1)$$

C_c, V_c, C_a and V_a are the fluorescein concentrations and volumes of the cornea and anterior chamber, respectively. V_c was assumed to be 70 μl[7,8] and V_a was determined via fluorophotometry.[9] The integral was calculated by means of a polynomial fit to the data points.

It should be noted that a steady state between the fluorescein in the aqueous and the cornea is not required for the calculations because the average flow in a given time interval depends only on the average fluorescein concentration in the anterior chamber and on the difference in total fluorescein mass between the start and the end of the interval.[4,5]

The average flow values between 4 and 5, 5 and 6, 6 and 7 and 4 and 7 hr after fluorescein instillation were calculated.

Results

Aqueous Flow at One Hour Intervals

An example of the fluorophotometric measurements as a function of time after fluorescein instillation is presented in Figure 1. The flow values of 12 volunteers at three consecutive 1 hr intervals, starting 4 hr after fluorescein instillation, are presented in Table 1. The mean flow in all subjects between 4 and 7 hr was 2.43 μl/min ± 0.48 SD. The mean and maximum coefficients of variation in the individual flow values were 5.3% and 12%, respectively. The average OD/OS ratio was 1.02 ± 0.15 SD.

Flow values were also determined in three individuals at 1 week intervals for 3 weeks which yielded mean and maximal coefficients of variation of 8.4% and 9.7%, respectively (Table 2).

Flow values measured between 1 and 4 hr were not used because of their large variability (mean and maximum coefficients of variation in hourly values: 24% and 50%, respectively, n = 6).

Aqueous Flow After Phenylephrine

An example of fluorophotometric measurements as a function of time before and after phenylephrine instillation is shown in Figure 2. The fluorescein concentration in the anterior chamber fell sharply within 1 hr after phenylephrine instillation and rose again after 2 to 3 hr, indicating a flow increase followed by a decrease. The flow values of 11 subjects at 1 hr intervals are presented in Table 3. The relative flow increase expressed as a percentage of the flow value in the control eye is shown in Figure 3. The mean relative flow increased significantly between 0 and 1 hr (131% ± 72% SD; $P < 0.001$), remained above normal between 1 and 2 hr (121% ± 92% SD; $P = 0.002$) and subsequently decreased to normal values (mean difference < 6%; $P > 0.1$).

In five subjects the flow first decreased to less than 75% of the control value before returning to normal.

One hour after phenylephrine instillation the IOP in the treated eye did not differ significantly from that in the control eye (12.4 ± 2.1 SD mm Hg and 14.5 ± 2.5 SD mm Hg, respectively, n = 8; paired student t-test: $P > 0.05$, two sample student t-test: $P = 0.1$).

Four hours after instillation the IOP in the treated eye was significantly lower than that in the control eye (13.0 ± 1.1 SD mm Hg and 15.6 ± 1.1 SD mm Hg respectively, n = 8; paired student t-test: $P < 0.01$, two sample student t-test: $P < 0.001$).

Table 1. Measurements in healthy subjects

Subj.	Age	Eye	AC volume (μl)	Flow (μl/min) between 4–5 hr	5–6 hr	6–7 hr	4–7 hr (mean flow)	Coeff. of variation (%)
1	22	OD	198	2.63	2.75	2.35	2.60	8.1
		OS	230	2.78	2.52	2.24	2.55	10.7
2	24	OD	216	1.63	1.83	2.03	1.81	10.9
		OS	195	1.48	1.66	1.78	1.64	9.1
3	25	OD	154	2.65	2.67	2.65	2.65	0.3
		OS	169	1.97	2.08	2.25	2.08	6.7
4	25	OD	196	2.09	2.08	2.03	2.07	1.4
		OS	205	1.88	1.97	2.16	1.98	7.0
5	26	OD	172	1.96	1.97	2.03	1.99	2.0
		OS	191	2.27	2.21	2.20	2.23	1.8
6	26	OD	134	1.88	2.02	2.16	1.99	6.9
		OS	126	1.55	1.59	1.57	1.57	1.3
7	26	OD	162	3.16	3.09	3.15	3.13	1.3
		OS	176	3.47	3.33	3.33	3.38	2.4
8	26	OD	209	2.75	2.63	2.17	2.55	12.3
		OS	224	2.52	2.55	2.47	2.52	1.6
9	26	OD	149	2.95	2.96	2.81	2.92	2.7
		OS	141	2.66	2.68	2.69	2.68	0.7
10	27	OD	181	2.67	2.55	2.48	2.5	3.9
		OS	190	2.99	2.69	2.81	2.83	5.3
11	30	OD	212	2.75	3.03	3.05	2.92	5.8
		OS	204	3.10	2.92	2.98	3.00	3.0
12	51	OD	132	2.32	1.96	1.80	2.05	13.3
		OS	121	2.42	2.57	2.84	2.56	8.0
Mean	27.8		179	2.44	2.43	2.37	2.43	5.3
SD	7.5		32	0.54	0.48	0.47	0.48	

Effect of Pupil Dilation

The effect of pupil dilation on the aqueous fluorescein concentration was assessed in three volunteers by means of a second phenylephrine instillation 3–4 hr after the first; at that time the pupil was still dilated but the flow value had returned to normal. A second decrease in the aqueous fluorescein concentration was observed in the volunteers in the first hour. The calculated flow increase was then about equal to that after the first (volunteer #1: 190% and 151%; volunteer #2: 100% and 85%; volunteer #3: less than 20% after each instillation).

The effect of pupil dilation was also assessed in two volunteers by comparing the flow values in both eyes after four drops of Tropicamide 0.5% had been instilled into one eye 4 hr after the fluorescein. The differences between the flow values in the mydriatic and control eye were +30% and −14% for volunteers #1 and #2, respectively.

Table 2. Aqueous flow measured at 1 week intervals

Subject	Flow (μl/min) measured in week: 1	2	3	Mean flow (μl/min)	Coeff. of variation (%)
1	1.65	1.64	1.90	1.73	8.7
2	2.65	3.17	3.13	2.85	6.7
3	2.64	3.01	2.90	2.98	9.7

Discussion

Aqueous Flow at One Hour Intervals

The aqueous flow measurements determined at 1 hr intervals were found to be reliable provided that the measurements were started at least 4 hr after fluorescein instillation. Diffusional fluorescein losses were not taken into account (these losses would not affect the results by more than 10%[10]).

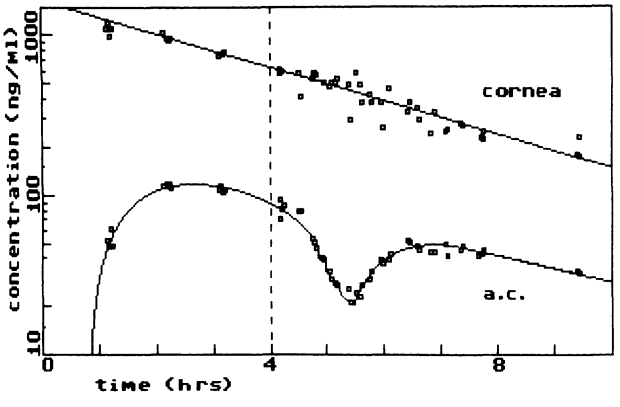

Fig. 2. As in Figure 1 (subject 3). Broken line: phenylephrine instillation.

Table 3. Aqueous flow after instillation of phenylephrine

	Flow (μl/min)					
		Time after phenylephrine instillation (hr):				
Subject	*Normal*	*0–1*	*1–2*	*2–3*	*3–4*	*4–5*
1	1.65	3.19	2.09	1.81	1.39	1.83
2	1.70	4.11	2.08	1.05	1.34	1.97
3	2.78	6.03	3.46	1.57	2.44	2.03
4	3.51	7.25	9.08	3.59	3.33	3.73
5	3.19	7.82	5.60	4.74	4.53	4.41
6	3.65	5.17	6.98	4.83	3.83	3.30
7	2.10	3.51	4.78	3.38	2.32	2.03
8	2.43	6.12	7.98	0.99	1.05	1.14
9	2.19	8.23	7.23	2.31	1.63	1.91
10	2.59	4.29	4.37	1.89	2.56	2.21
11	2.12	7.18	8.09	3.46	2.81	2.69

The mean flow value found in this study (2.43 μl/min ± 0.48 SD, N = 24) agrees with results reported in other studies on human eyes which were based on measurements lasting 7 to 9 hr (1.9 μl/min to 2.9 μl/min).[11–14] The differences between the flow values at 4, 5 and 6 hr after fluorescein instillation may reflect actual flow changes in individuals.

Aqueous Flow After Phenylephrine

Aqueous flow after phenylephrine instillation increased to a value more than two times the control value, followed by a decrease to normal or below. A similar flow response after phenylephrine has been observed in rabbits using a preinvasive method.[15] The flow increase may be due to an increase in ciliary epithelial permeability as found in rabbits after α-stimulation.[16]

The rise in flow during the first hour after phenylephrine instillation did not cause the IOP to rise, which indicates a simultaneous increase in the outflow facility, as has been reported previously.[16–18]

The subsequent decrease in flow to less than 75% of the control value in five of the 11 subjects, possibly together with a persistent increase in outflow facility, can explain the slight pressure fall which has also been found by others.[18–20]

Pupil dilation per se did not prove to have any significant effect on aqueous flow because: (1) flow increased again after a second phenylephrine instillation performed in the period of decreasing flow when the pupil was still dilated; and (2) flow did not increase markedly after the instillation of an anticholinergic mydriatic.

Conflicting results have been reported on the effect of phenylephrine on aqueous flow, IOP and outflow facility. This can be explained by the differences in the species studied, the amount of phenylephrine instilled, the method of flow determination and the time between the instillation and the first measurement.[16–26]

The effect of phenylephrine on the aqueous flow in normal human eyes is considered to be negligible[25,26] as a result of either an insufficient concentration of phenylephrine in the ciliary body or the lack of influence of an α-receptor system on the aqueous flow[25]; we presume that a flow increase has been overlooked in these studies because measurements were not started shortly after the instillation of phenylephrine or were not repeated at about the time of maximal drug concentration in the anterior chamber (75 min[27]).

The finding by others[25] of a 30% lower fluorescein concentration in the anterior chamber after phenylephrine instillation followed by fluorescein ingestion, can also be explained by a flow increase which has been overlooked.

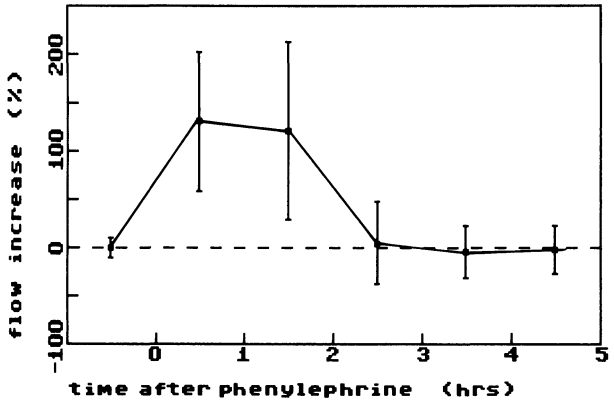

Fig. 3. Percentage increase of aqueous flow at 1 hr intervals after phenylephrine instillation. Bars correspond with one standard deviation.

Key words: fluorophotometry, aqueous flow, phenylephrine, intraocular pressure, fluorescein

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References

1. Topper JE, McLaren J, and Brubaker RF: Measurement of aqueous humor flow with scanning ocular fluorophotometers. Curr Eye Res 3:1391, 1984.
2. De Kruijff EJFM, Boot JP, Laterveer L, Van Best JA, Ramselaar JAM, and Oosterhuis JA: A simple method for determination of corneal epithelial permeability in humans. Curr Eye Res 6:1327, 1987.

3. Gaul GL and Brubaker RF: Measurement of aqueous flow in rabbits with corneal and vitreous depots of fluorescent dye. Invest Ophthalmol Vis Sci 27:1331, 1985.
4. Carlson KH, McLaren JW, Topper J, and Brubaker RF: Effect of body position on intraocular pressure and aqueous flow. Invest Ophthalmol Vis Sci 28:1346, 1987.
5. Brubaker RF: Clinical Evaluation of the circulation of aqueous humor. *In* Clinical Ophthalmology, Vol. 3, Duane TD and Jaeger EA, editors. Philadelphia, J. B. Lippincott Co., 1986, pp. 1–11.
6. Schenker HI, Yablonski ME, Podos SM, and Linder L: Fluorophotometric study of epinephrine and timolol in human subjects. Arch Ophthalmol 99:1212, 1981.
7. Olsen Th and Ehlers N: The thickness of the human cornea as determined by a specular method. Acta Ophthalmol 62:859, 1984.
8. Bennett AG and Francis IL: The eye as optical system. *In* The Eye, Vol. 4, Davson H, editor. New York, Academic Press, 1962, p. 101.
9. Van Best JA, Kappelhof JP, Laterveer L, and Oosterhuis JA: Blood aqueous barrier permeability versus age by fluorophotometry. Curr Eye Res 6:855, 1987.
10. Jones RF and Maurice DM: New methods of measuring the rate of aqueous flow in man with fluorescein. Exp Eye Res 5:208, 1966.
11. Nagataki S: Aqueous humor dynamics of human eyes as studied using fluorescein. Jpn J Ophthalmol 19:235, 1975.
12. Yablonski ME, Zimmerman TJ, Waltman SR, and Becker B: A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics. Exp Eye Res 27:135, 1978.
13. Coakes RL and Brubaker RF: Method of measuring aqueous humor flow and corneal epithelial permeability using a fluorophotometric nomogram. Invest Ophthalmol Vis Sci 18:288, 1979.
14. Brubaker RF, Nagataki S, Townsend D, Burns RR, Higgins RG, and Wentworth W: The effect of age on aqueous humor formation in man. Ophthalmology 88:283, 1981.
15. Araie M: Time change of rabbit aqueous flow under influence of adrenergic drugs. Exp Eye Res 41:391, 1985.
16. Green K and Griffin C: Adrenergic effects on the isolated ciliary rabbit epithelium. Exp Eye Res 27:143, 1978.
17. Schimek RA and Lieberman WJ: The influence of cyclogyl and neosynephrine on tonographic studies of miotic control in open-angle glaucoma. Am J Ophthalmol 51:781, 1961.
18. Green K and Padgett D: Effect of various drugs on pseudofacility and aqueous humor formation in the rabbit eye. Exp Eye Res 28:239, 1979.
19. Holland MG and Wei C: Chemical sympathectomy in glaucoma therapy: An investigation of alpha and beta adrenergic supersensitivity. Ann Ophthalmol 5:783, 1973.
20. Potter DE and Rowland JM: Adrenergic drugs and intraocular pressure: Effects of selective β-adrenergic agonists. Exp Eye Res 27:615, 1978.
21. Lee P: The influence of epinephrine and phenylephrine on intraocular pressure. Arch Ophthalmol 60:863, 1958.
22. Barbee RF and Smith WO: A comparative study of mydriatic and cycloplegic agents. Am J Ophthalmol. 44:617, 1957.
23. Becker B, Gage T, Kolker AE, and Gay AJ: The effect of phenylephrine hydrochloride on the miotic treated eye. Am J Ophthalmol 48:313, 1959.
24. Macri FJ and Cevario SJ: The inhibitory actions of dopamine, hydroxyamphetamine and phenylephrine on aqueous humor formation. Exp Eye Res 26:85, 1978.
25. Lee DA and Brubaker RF: Effect of phenylephrine on aqueous humor flow. Curr Eye Res 2:89, 1982.
26. Araie M: Acute effects of topical phenylephrine on aqueous humor dynamics and corneal endothelial permeability in man. Jpn J Ophthalmol 27:340, 1983.
27. Matsumoto M, Tsuru T, Araie M, and Komuro Y: Pharmacokinetics of topical phenylephrine hydrochloride in the normal human eye. Jpn J Ophthalmol 26:338, 1982.