

CLINICAL COMPARISON OF DIPIVALYL EPINEPHRINE AND EPINEPHRINE IN THE TREATMENT OF GLAUCOMA

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A prodrug is an agent that undergoes biotransformation to a pharmacologically active form in the body. Dipivalyl epinephrine is a prodrug of epinephrine, formed by the addition of two pivalyl side-chains to the parent molecule (Fig. 1). Dipivalyl epinephrine is 100 to 600 times as lipophilic as epinephrine,¹⁻³ leading to a significant increase in penetration. It penetrates the cornea approximately 17 times more easily than epinephrine.² Perhaps only one-tenth the dosage of dipivalyl epinephrine is required to cause a decrease in intraocular pressure comparable to that produced by epinephrine.^{1,3} Furthermore, use of lower concentrations of drug should reduce the incidence of external side effects and drug intolerance.⁴ We compared dipivalyl epinephrine, 0.1%, with epinephrine hydrochloride, 2%, in a double-masked study, with respect to decrease in intraocular pressure, increase of pupil size, and incidence of side effects.

SUBJECTS AND METHODS

Patient population—Twenty-five patients were initially selected on the basis of having symmetric (to within 5 mm Hg)

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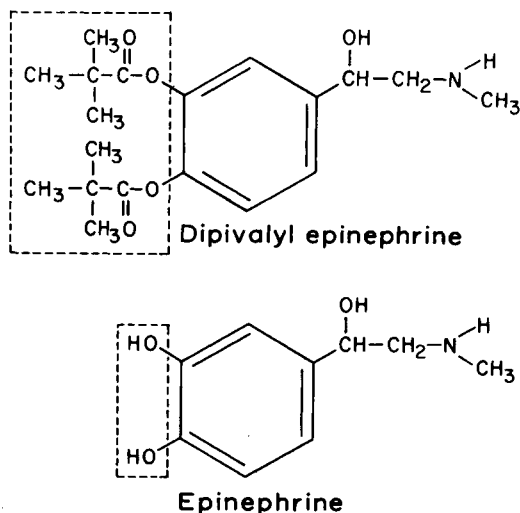


Fig. 1 (Kohn and associates). Molecular structure of dipivalyl epinephrine and epinephrine.

intraocular pressure ≥ 22 mm Hg in each eye. Seventeen patients completed the entire six-month study and formed the statistical base for the analysis of the drugs' effectiveness. Of the eight patients who did not complete the study, three had ocular complications and five had insufficient follow-up. Seven of the 17 patients who completed the study had primary open-angle glaucoma, six had increased intraocular pressures without field loss, three had chronic angle-closure glaucoma previously treated with bilateral iridectomies, and one had open-angle glaucoma and was monocularly aphakic. There were nine women and eight men in the group. Their ages ranged from 59 to 77 years among the women and 55 to 82 years among the men, except for one 26-year-old. Three of the patients were concurrently treated with miotics or acetazolamide (Diamox), or both, during the

entire study. Twelve of the patients had brown irides and five had either blue, green, or hazel irides.

Medications—The study was a double-masked crossover clinical trial comparing dipivalyl epinephrine, 0.1%, and epinephrine hydrochloride, 2%, over a six-month treatment period (Table 1). No epinephrine compounds were used during the initial and crossover two-week baseline periods. In the treatment periods, patients were randomly assigned one medication in a coded pink bottle for the right eye and the other medication in a coded white bottle for the left eye. Medications were taken every 12 hours and patients were examined at approximately the same time of day at least two hours after taking their drops. After the second washout period, new bottles were issued so that the eye that had received dipivalyl epinephrine now received epinephrine hydrochloride and vice versa.

RESULTS

Intraocular pressure—Seventeen patients completed the entire study, missing no more than one visit. For those patients,

we found a sustained decrease in intraocular pressure with the use of dipivalyl epinephrine, 0.1%. The decrease with dipivalyl epinephrine appeared consistently less than that for epinephrine hydrochloride, 2%, but the difference between the two drugs was statistically significant ($P<.05$) only after crossover (Fig. 2, Table 2). During the first half (three months) of the study, the average intraocular pressure decreased from a baseline of 27.5 ± 0.9 mm Hg (S.E.M.) to 20.5 ± 0.8 mm Hg after three months with dipivalyl epinephrine, and from a mean baseline of 28.1 ± 0.8 mm Hg to 19.1 ± 1.2 mm Hg with epinephrine. After the crossover period, the mean intraocular pressure over the second three-month treatment period decreased from 25.9 ± 0.9 to 18.2 ± 2.1 mm Hg with dipivalyl epinephrine and from 27.2 ± 0.8 to 17.0 ± 1.9 mm Hg with epinephrine. All decreases were statistically significant ($P<.05$).

There was no statistically significant difference ($P>.05$) in response between right and left eyes treated with the same drug, nor between brown and non-brown eyes for either drug.

TABLE 1
EVALUATIONS OF STUDY PROTOCOL: PERFORMED DURING EACH VISIT

	Washout Baseline (Days)		Treatment 1 (Days)				Washout Crossover Baseline (Days)		Treatment 2 (Days)			
	-7	0	7	28	60	90	-7	0	7	28	60	90
Visual acuity	X	X	X	X	X	X	X	X	X	X	X	X
Pupil size	X	X	X	X	X	X	X	X	X	X	X	X
Applanation tonometry	X	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp examination	X	X	X	X	X	X	X	X	X	X	X	X
Visual fields (Goldmann)		X				X		X				X
Tonography		X				X		X				X
Heart rate		X				X		X				X
Blood pressure		X				X		X				X
Side effects												
Ocular and systemic			X	X	X	X			X	X	X	X

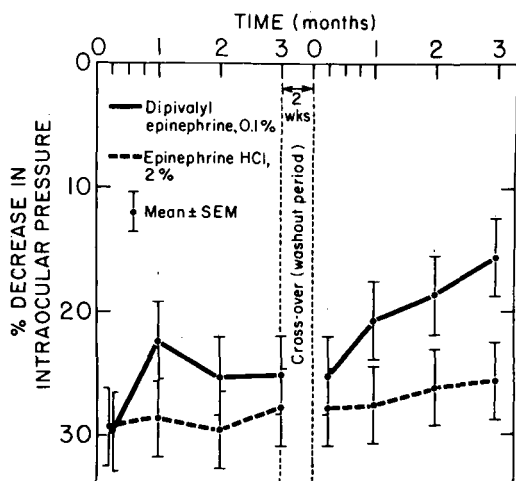


Fig. 2 (Kohn and associates). Percent decrease in intraocular pressure with dipivalyl epinephrine 0.1% vs epinephrine hydrochloride with 2% ($\pm$ S.E.M. averaged over entire study).

Pupil size—The mydriatic effect of dipivalyl epinephrine, 0.1% averaged $+0.65 \pm 0.13$ mm (S.E.M.) or $+25.1\%$, and of epinephrine hydrochloride, 2%, $+0.55 \pm 0.17$ mm or $+18.8\%$, including only those patients not receiving miotics. The increases were statistically significant ($P < .05$), but there was no significant difference ($P > .05$) between the two drugs.

Ocular side effects—Three patients were discontinued from the study, two for severe epinephrine side effects, including one for classical findings of epinephrine allergy consisting of conjunctival hyperemia and follicular reaction, eyelid edema, and itching. One patient was discontinued from the study because of inadequate pressure control and progressive field loss in both eyes. Five patients did not return for sufficient follow-up.

Of the 17 patients who completed the entire study, complaints of burning occurred for eight eyes (23.5%) receiving epinephrine, and for one eye (2.9%) receiving dipivalyl epinephrine. Two patients complained of mild hyperemia on

two occasions and one of blurry vision in the eye receiving dipivalyl epinephrine, but neither complaint could be confirmed on clinical examination.

Five eyes receiving dipivalyl epinephrine and four fellow eyes receiving epinephrine showed mild, inferior punctate corneal staining, each on only one occasion. One patient had bilateral involvement and four patients had involvement either only in the eye receiving dipivalyl epinephrine (one case) or at least somewhat more marked in the eye receiving dipivalyl epinephrine (three cases) than that receiving epinephrine.

Duration of effect—Residual drug effect was present between one and two weeks after cessation of both dipivalyl epinephrine and epinephrine during the crossover period. The mean increase in intraocular pressure two weeks after the final treatment day was $+6.40 \pm 3.9$ (S.D.) mm Hg for the eye treated with dipivalyl epinephrine and $+5.91 \pm 3.8$ mm Hg for the eye treated with epinephrine. Between the first and second week, the pressure increased $+3.1 \pm 4.4$ mm Hg for the eye that had been treated with dipivalyl epinephrine and $+2.9 \pm 3.8$ mm Hg for the eye that had received epinephrine. The increases over each week were statistically significant ($P < .01$), but the difference between dipivalyl epinephrine and epinephrine was insignificant (t -test).

Systemic side effects—A comparison of the average vital signs of patients during the treatment period with the vital signs in the second week of the two washout periods showed no significant effect on blood pressure or pulse rate. Mean blood pressure (mm Hg) when the patients were not receiving dipivalyl epinephrine or epinephrine was $140.4 \pm 2.8/85.4 \pm 1.5$ (S.E.M.), and during the two treatment periods the mean blood pressure was $139.4 \pm 2.9/85.0 \pm 1.6$. The mean pulse rate during the washout period was 73.1

TABLE 2
MEAN INTRAOCULAR PRESSURE (MM HG $\pm$ S.E.M.)

	Treatment 1					Treatment 2				
	Baseline	1 wk	4 wks	2 mos	3 mos	Crossover Baseline	1 wk	4 wks	2 mos	3 mos
Dipivalyl epinephrine, 0.1%	27.5 $\pm$ 0.9	19.5 $\pm$ 0.9	20.9 $\pm$ 0.6	20.4 $\pm$ 0.8	20.5 $\pm$ 0.8	25.9 $\pm$ 0.9	19.3 $\pm$ 0.8	20.4 $\pm$ 0.8	19.2 $\pm$ 1.3	18.2 $\pm$ 2.1
Epinephrine, 2%	28.1 $\pm$ 0.8	20.1 $\pm$ 1.0	19.6 $\pm$ 0.5	19.7 $\pm$ 0.7	19.1 $\pm$ 1.2	27.2 $\pm$ 0.8	19.5 $\pm$ 0.8	18.4 $\pm$ 1.2	17.2 $\pm$ 1.5	17.0 $\pm$ 1.9
No. of eyes	17	15	16	17	17	17	16	17	16	16

beats per minute ± 2.2 (S.E.M.), and during the treatment periods it was 73.6 beats per minute ± 1.8 . One patient was noted to have an irregular pulse on one treatment visit only.

DISCUSSION

Dipivalyl epinephrine, 0.1%, is effective in decreasing intraocular pressure,⁵⁻⁷ without causing the frequent side effects associated with epinephrine usage.⁵⁻⁸ The decrease in intraocular pressure is slightly less with dipivalyl epinephrine, 0.1%, than with epinephrine hydrochloride 2%. This may occur because the ocular penetration of dipivalyl epinephrine is 17 times that of epinephrine,² but the concentration of dipivalyl epinephrine used was only $1/20$ that of epinephrine. The apparent further decrease in effectiveness of dipivalyl epinephrine after the crossover period requires explanation. Dipivalyl epinephrine may lose some efficacy with prolonged use, although such an effect has not been previously reported. Indeed, McClure⁴ found no decrease in efficacy of dipivalyl epinephrine for periods as long as seven months. The decreased effectiveness of dipivalyl epinephrine in eyes treated with epinephrine before crossover may also result from decreased density of available β -adrenergic receptors caused by epinephrine pretreatment. Reduction of receptors has been demonstrated experimentally by Candia and Neufeld⁹ in rabbit corneas after long-term epinephrine therapy.

Bischoff⁵ found similar effectiveness of dipivalyl epinephrine, 0.1%, and epinephrine borate 1% in 33 patients over a three-month trial. Krieglstein and Leydhecker⁶ found no difference in the response of 16 patients to dipivalyl epinephrine 0.1% vs epinephrine hydrochloride 1%. They did find a significantly lower response with dipivalyl epinephrine 0.025%, and a greater response with

dipivalyl epinephrine 0.25%, as compared to epinephrine hydrochloride 1%. Dipivalyl epinephrine 0.1% is at least equal in ability to decrease intraocular pressure as epinephrine hydrochloride 1% or borate 1%, but is somewhat less effective than epinephrine hydrochloride 2%. Theoretically, dipivalyl epinephrine 0.1% should be as effective as an intermediate epinephrine concentration, such as 1.7%.

The mydriatic effect of dipivalyl epinephrine 0.1% appears to be comparable to that of epinephrine hydrochloride 2%. Kaback and associates⁷ have shown dipivalyl epinephrine 0.025% to cause no mydriasis, dipivalyl epinephrine 0.1% to cause an increase of from 0.7 to 1.6 mm over one to four hours, and dipivalyl epinephrine 0.5% to cause an increase of from 2.0 to 4.3 mm over one to four hours.

The incidence of side effects with dipivalyl epinephrine should be significantly less than with epinephrine, since the less active drug is available topically. Indeed, severe intolerance or allergy (two patients) and burning discomfort (24% of eyes) were almost uniquely associated with epinephrine usage in our study. Burning discomfort with dipivalyl epinephrine occurred in only 3% of eyes. Yablonski and associates⁸ studied 12 patients who had histories of epinephrine intolerance and found 83% of eyes developed allergic signs, blepharitis, or discomfort in the eye receiving epinephrine hydrochloride 2%, whereas only one eye (8%) developed allergic symptoms and signs with dipivalyl epinephrine 0.1% over an average 100-day follow-up. Kaback and associates⁷ also found no particular ocular or systemic side effects with dipivalyl epinephrine 0.1%. One-tenth to $1/20$ the amount of epinephrine on the eye should reduce not only ocular discomfort, but also other side effects, such as adrenochrome deposits and cardiovascular complications.

SUMMARY

Dipivalyl epinephrine, 0.1%, though slightly less effective in decreasing intraocular pressure, showed significantly fewer side effects than epinephrine hydrochloride, 2%. Seventeen patients with symmetrically increased intraocular pressures who completed a six-month double-masked crossover study showed a significant decrease in intraocular pressure averaging 23.7% for dipivalyl epinephrine over the entire study and 27.4% for epinephrine. In the first treatment period, dipivalyl epinephrine was slightly less effective than epinephrine. In the second treatment period, dipivalyl epinephrine was statistically less effective than epinephrine. Two of the original 25 patients were dropped from the study because of epinephrine allergy or intolerance, one had uncontrolled pressures with either drug, and five failed to maintain adequate follow-up. Complaints of side effects such as burning and irritation occurred much more frequently in eyes receiving epinephrine (24%) than dipivalyl epinephrine (3%). Mild mydriasis occurred with each drug, averaging +0.65 mm with dipivalyl epinephrine and +0.55 mm Hg with epinephrine. No effect on blood pressure or pulse rate was found for the two drugs.

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