Systemic effects of epinephrine applied topically to the eye

Norman Ballin, Bernard Becker, and Melvin L. Goldman

The topical ocular use of epinephrine has been shown to be correlated with an increased frequency of cardiac extrasystoles. While generally considered benign, such extrasystoles provide evidence for the systemic absorption of topically applied epinephrine and a direct effect on the heart. In order to avoid the more serious cardiotoxic effects known to occur following systemic administration of epinephrine in comparable dosages, it is suggested that epinephrine be used cautiously in patients with known heart disease, hyperthyroidism, or abnormal sensitivity to the systemic effects of epinephrine.

The employment of potent pharmacologic agents in the treatment of disease is often accompanied by the corollary of side reactions to these agents. Recent medical literature reflects an increasing awareness of important side reactions to various medications. These may occur as a result of either topical or systemic administration.

With the development in recent years of relatively stable epinephrine preparations, the employment of epinephrine in the treatment of glaucoma has been revived. These drugs not only decrease aqueous secretion but also improve the outflow impairment of primary open-angle glaucoma. They avoid the side effect of miosis which may be disabling in young individuals and in those glaucoma patients with cataracts. In addition, epinephrine may result in a better status of glaucoma control when used in conjunction with miotic therapy and/or Diamox, and is often useful in the treatment of secondary glaucoma caused by iritis.

Local side effects from topically administered epinephrine are well known. These include burning, reactive hyperemia, headache, allergy, and the deposition of black oxidation products in the conjunctiva or cornea. In eyes with anatomically narrow angles, attacks of angle closure may be induced. In contrast to the well-known local side effects, however, systemic side effects of epinephrine applied topically have been recognized or documented only occasionally.

It has been our impression in reading numerous tonograms that cardiac arrhythmias as reflected in the tonographic tracings occurred more frequently in patients receiving topical epinephrine. The present study attempts to correlate the use of this medication with the frequency of these cardiac irregularities.

Methods

Simultaneous electrocardiography and tonography. Forty patients scheduled for tonography had simultaneous electrocardiographic tracings...
Fig. 1. Simultaneous recording of tonogram and electrocardiogram. Note difference of time scales. Tonographic deflections correspond in time to extrasystoles seen in electrocardiogram.

(Lead II) performed during their tonographic examinations. In order to rule out changes in the EKG caused by the lowering of the tonometer on the eye, the electrocardiographic tracings were begun approximately two minutes before tonography, and then continued throughout the eight minutes of tonography. Some of these patients were selected on the basis of having had cardiac arrhythmias noted on previous tonographic tracings. Others were selected at random.

Analysis of tonograms. The files of 535 consecutive patients over the age of 30 years referred to tonography from one office were reviewed. Tonograms were done with a Crescent tonometer and Houston recorder. The latest bilateral tonogram in each patient's file was reviewed as to the presence or absence and number of cardiac irregularities without knowledge of the patient's topical medication. The medications were then recorded for each patient. Those patients receiving epinephrine drops either alone or in conjunction with other medications are included in the epinephrine-treated group. Patients receiving other medications or no medication are included in the control group.*

Background and Methods

Simultaneous electrocardiography and tonography. The appearance of the tonographic tracing in patients with cardiac arrhythmias is generally rather typical. This appearance consists of one or more instances of sudden downward deflections of the tracing with a return to the predeflection level occurring during several heartbeats. Simultaneous electrocardiography and tonography revealed these deflections to be invariably the result of extrasystoles. Fig. 1 represents such a simultaneous recording, and, while the time scales of these tracings were quite different, it was evident in making the recordings that each extrasystole seen in the electrocardiogram was immediately followed by the typical change in the tonogram described above. The electrocardiographic tracings appeared similar both before and during tonography.

Results

Simultaneous electrocardiography and tonography. The appearance of the tonographic tracing in patients with cardiac arrhythmias is generally rather typical. This

*Epinephrine was supplied for some of our patients by Madland Laboratories, Inc., Milwaukee, Wis. (Glaucon) and Alcon Laboratories, Inc., Fort Worth, Texas (Lyoc- trin).
Table I. Frequency of extrasystoles in epinephrine-treated patients and controls

<table>
<thead>
<tr>
<th>No. of extrasystoles (per 8 min. of tonography)</th>
<th>Epinephrine (223 patients)</th>
<th>Control (no epinephrine) (312 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or more</td>
<td>41 (18%)</td>
<td>31 (10%)</td>
</tr>
<tr>
<td>2 or more</td>
<td>30 (13%)</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>3 or more</td>
<td>24 (11%)</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>4 or more</td>
<td>25 (10%)</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>5 or more</td>
<td>18 (8%)</td>
<td>13 (4%)</td>
</tr>
</tbody>
</table>

Table II. Age distribution of patients

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Epinephrine (223 patients)</th>
<th>Control (no epinephrine) (312 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-40</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>41-50</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>51-60</td>
<td>59</td>
<td>86</td>
</tr>
<tr>
<td>61-70</td>
<td>71</td>
<td>90</td>
</tr>
<tr>
<td>71+</td>
<td>43</td>
<td>46</td>
</tr>
</tbody>
</table>

Table III. Frequency of extrasystoles in epinephrine-treated patients and controls over age 40

<table>
<thead>
<tr>
<th>No. of extrasystoles (per 8 min. of tonography)</th>
<th>Epinephrine (216 patients)</th>
<th>Control (no epinephrine) (296 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or more</td>
<td>39 (18%)</td>
<td>28 (10%)</td>
</tr>
<tr>
<td>2 or more</td>
<td>29 (13%)</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>3 or more</td>
<td>24 (11%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>4 or more</td>
<td>23 (11%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>5 or more</td>
<td>7 (8%)</td>
<td>12 (4%)</td>
</tr>
</tbody>
</table>

Discussion

The occurrence of significant systemic absorption of epinephrine applied topically to the eye is suggested by several clinical phenomena. Occasional increases of blood pressure have been noted to occur after instillation of epinephrine drops. Some patients may complain of a sensation of palpitations after institution of epinephrine therapy. Several cases of faintness, pallor, and tachycardia have also been reported following topical epinephrine administration. It is important to realize that epinephrine preparations for topical ocular application contain what would be quite substantial doses of epinephrine if given systemically. The usual adult systemic dosage of epinephrine is 0.1 to 0.5 mg. given subcutaneously (0.1 to 0.5 c.c. of 1:1000). The intense local vasoconstriction produced by subcutaneous administration results in slow absorption of the drug such that a dosage of 0.5 mg. given subcutaneously is actually equivalent to a much smaller dosage (0.01 mg. or 0.01 c.c. of 1:1000 per minute) given intravenously. Because of this dosage, differential toxic effects have been noted to occur when a subcutaneous dosage has been inadvertently administered intravenously. The usual ophthalmic preparations of epinephrine are epinephrine salts in either 1 per cent or 2 per cent concentrations of the salt or epinephrine base. One drop of a 2 per cent preparation of epinephrine base if totally absorbed would provide approximately 1.0 mg. (1 c.c. of 1:1000) of epinephrine. Since the medication is usually instilled in both eyes, total absorption could provide twice this amount. The rapidity and nature of absorption from the eye are not known, but it is apparent that such a dosage, if absorbed in a manner analogous to either subcutaneous or intravenous administration, could provide epinephrine levels comparable to or significantly higher than those obtained in systemic therapy.

Cardiac irregularities from systemic epinephrine administration have been well documented both in experimental animals...
and in man. Changes in the T wave and ST interval, ventricular extrasystoles, and ventricular fibrillation occur in dogs after intravenous administration. In experimental animals and in man epinephrine combined with certain anesthetic agents can result in serious cardiac arrhythmias including ventricular fibrillation. Subcutaneous administration of 1 c.c. of 1:1000 in 18 patients with persistent extrasystoles resulted in a dramatic increase in the number of extrasystoles and the activation of additional centers of ectopic impulse. Injection of 0.3 mg. of epinephrine in normal subjects elicited extrasystoles in 9 per cent. Intravenous injections of even fractions of 1 mg. often cause extrasystoles. Dangerous extrasystolic arrhythmias and even auricular or ventricular fibrillation may be precipitated by 1 mg. intravenously. The symptomatology and electrocardiographic changes of coronary insufficiency may be produced by the systemic administration of epinephrine. Epinephrine may be dangerous in individuals who are abnormally sensitive to its action and in those with hyperthyroidism.

Extrasystoles are generally considered as a benign phenomenon, occurring in normal individuals, becoming more common with age, and capable of initiation by numerous factors including tobacco and coffee. They occur more frequently, however, with organic heart disease and may be premonitory of more serious arrhythmias.

In the present series, there is a striking statistical correlation between the use of topical epinephrine and the occurrence of extrasystoles. This is best explained by systemic absorption of epinephrine and a direct effect on the heart. We are not aware, however, of any instance in which the use of topical epinephrine was associated with any more serious cardiac abnormalities such as myocardial ischemia, auricular fibrillation, or paroxysmal tachycardia. While it is conceivable that such instances have occurred unrecognized, the present data do not confirm or deny such an association.

In view of the evidence presented for the systemic absorption of topically applied epinephrine, and the known cardiotoxic effects of the systemic administration of epinephrine in doses comparable to those used in the eye, it would seem prudent for ophthalmologists to be aware of the cardiac status of their patients and to use epinephrine with care in individuals with cardiac disease, hyperthyroidism, or abnormal sensitivity to the systemic effects of epinephrine.

We are indebted to Miss Dee Cooper and Mrs. Gay Ackerman for their help in reviewing the tonographic data.

REFERENCES
1. Shaffer, R. N.: Personal communication.
12. de Graff, A. C., and Weiss, S.: Observations on the extrinsic nervous control of the

Discussion

Dr. Waitzman. If observations concerning epinephrine therapy are to be compared, we must specify the salt used. The other thing to emphasize is the extreme lability of epinephrine.

Dr. Leopold. Dr. Vaughn, would you care to say anything about the salts of epinephrine? I know that you have done some work on this.

Dr. Vaughn. In the use of these drugs, the higher the pH, the more free base available, and therefore, the more active drug available. Also, the higher the pH, the less stinging. In the past four years we have been using one-half per cent Eppy borate, and have found it to be a very reliable pressure-lowering drug with fewer side effects.

Dr. Maurice Langham. Studies we have completed indicate that it is not the change in blood flow which is responsible for the decrease in formation of aqueous humor. It seems to be a direct effect upon secretion.

Dr. Sears (closing). With respect to the question of the effect of epinephrine on aqueous humor formation, the work of Berggren on excised rabbit ciliary processes suggests a direct effect. However, one must keep in mind possibilities of species differences.