Ind. J. Physiol. Pharmac., 1990 (1): 67-69

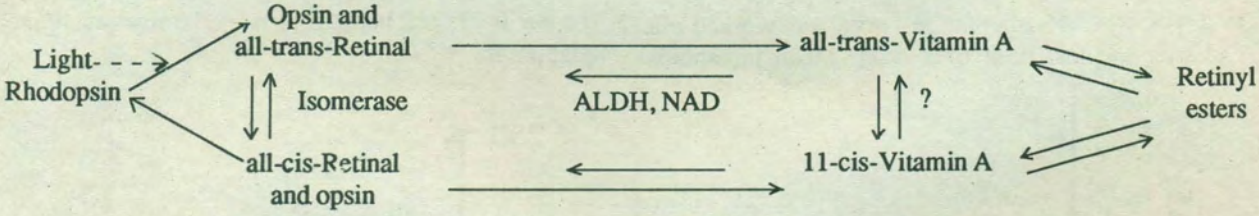
LETTER TO THE EDITOR

A STUDY OF THE EFFECT OF ISONIAZID AND CIMETIDINE ON DARK ADAPTATION OF HUMAN EYE

Sir,

(Received on November 2, 1989)

Isoniazid(1) and the H_2-receptor antagonists, cimetidine and ranitidine(2) inhibit the enzyme alcohol dehydrogenase (ALDH) in vitro. As a consequence isoniazid (1,3,4) retarded the elimination rate of ethanol in rats, rabbits and guinea pigs: Cimetidine had a similar effect in rabbits (4) and rats, if ethanol levels are high(2). It would be interesting to see if the two drugs affect ALDH in man. Besides its participation in degrading ethanol, ALDH is physiologically implicated in rhodopsin cycle in human retina (5) as shown below:



ADLH inhibitors may thus influence dark adaptation in one way or the other depending upon the direction of ALDH function. this possibility was earlier tested in volunteers given cimetidine (400 mg tds) or isoniazid (300 mg once) for one day (Bhavsar, Kelkar and Vachharajani: unpublished); visual threshold in dark was determined after bleaching retina with a flash gun, using Friedman Analyzer (MK 2; Clement Clarke). However no clear effect of the drugs could be demonstrated. We thought that the method needs to be made more specific to study rod function and drugs given longer before concluding absence of an effect on dark adpatation.

Periodic visual 'thresholds' are determined to study dark adaptation after a flash of light and the 'curves' attain maxima by 30 min. If the test stimulus is restricted in area only to focus on fovea (where the cones predominate), the curve is brief and monotonic. If the stimulus is wide enough to involve parafovea (wherein the rods predominate), the curve typically is 'kinked', the initial rapid cone recovery being followed by a slower, progressive phase due to recovery of rod function (see Fig. 1 for a typical Friedman curve. However, when initial bleaching is done with a weak light rather than by a flash, the cones already have maximal sensitivity and curves determined in dark are solely representative of rod function, there hardly being a kink. Naturally, if light adaptation is due to bleaching of rhodopsin, the dark adaptation could only involve its regeneration in rods.

In view of this, to get curves characteristic of rod function alone, we used a totally dark chamber (24" L X 14" H X l!" B) into which a subject looked with vision of one eye being shielded with a special hood. Interior of the chamber was duely ventilated with a blower. A deadwhite screen (reflectance, about 80%) was placed 18" away from the eye and uniformly illuminated with a milky 100 w bulb 15" away (brilliance was thus about 45 millilambert). The initial weak-light adaptation was continued for 2 min and then terminated. On the screen however, was projected a 4" × 4" square of red light (using a lens system for uniform illumination), intensity of which could be varied at will with a voltage regulator. The threshold of the red light perception was determined every 5 min for 30 min period. For this the voltage was varied up and down 4-5 times till the subject signalled the perception almost every time. The threshold was thus recorded as 'voltage', and the procedure occupied about 15-20 sec. Uninterrupted

projection of the red light was ensured by including a pilot lamp in circuit outside the box. The volunteers could identify the stimulus as having red hue in first 5-10 min only, but later, it was described as having only a white/very pale pink hue.

The study was an open trial with two groups of 6 volunteers each. They were all male medical students/ staff members who had given a written consent. They were nonsmokers, 20 to 40 years in age, and with no systemic or ocular disease (though a few had minor refraction errors). No drug was used during 7 days before the tests. All tests were done between 10 A.M. to 1 P.M. after the volunteer passed half an hr in a room with usual mild illumination.

Control adaptation curve was worked out for each subject. One group was then given isoniazid (300 mg, po) every morning for 7 days; the other group was treated with cimetidine (400 mg tds, po for 7 days. On day-8, the dark adaptation curve was worked out 2 hr after the last dose of a drug. Mean thresholds (± SEM) at 5 min intervals in each group were compared with similar values obtained in control runs using unpaired t test.

The control curves we obtained had no kink as seen with those obtained using Friedman's apparatus (Fig. 1) Only in one volunteer in each drug-treated group the adpatation was somewhat delayed; however, the group data failed to reveal any major effect of the drugs on the adpatation process.

Use of a weakly illuminated, large area for initial light adaptation and a large stimulus area (4" X 4") for deciding the thresholds later would eminently favour the study of red function alone (6). This stimulus-area would subtend an angle of about 16° at the eye and is large enough to cover the parafoveal rod regions (if angle subtended is 2°, the vision involves foreal cones only). The rate of dark adaptation also depends on size of test-field(7), and even from this view point the test field used hopefully ensured a reasonably rapid adaptation.

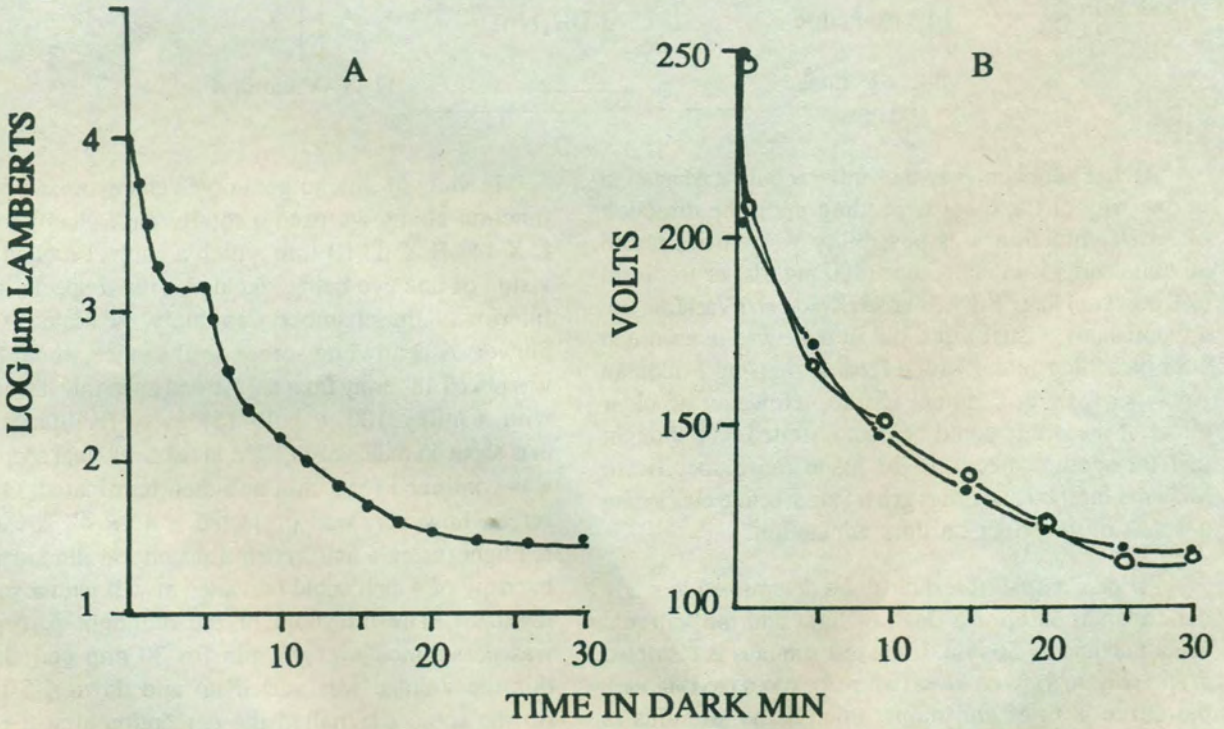


Fig. 1: Dark adaptation curves with centrally fixated field, subtending 16° angle at the eye. (A) A typically 'kinked' curve obtained after bleaching with a flash of light. (B) Curves obtained using present method have no 'kink'. The control curve (●) did not significantly differ from that (o) obtained after isoniazid treatment (300 mg OD po for 7 days). Points are mean thresholds from 6 volunteers. SEM (which was <5% of the value) is not shown. Similar results were obtained with cimetidine.

Though the product intensity X time of exposure of test-light is constant when the latter is less than 200 msec (Bunsen-Roscoe law), if exposure time is more than this 'critical time' (time for back reaction to get going), intensity alone decides the threshold. Exposure we used was much in excess (15-20 sec). Furthermore, the red light hardly affects the rods (5), hence bleaching is hardly possible during our process of deciding the thresholds. After first 5-10 min, the light was not perceived as red and on all these grounds most part of our adpatation curves was assumed to express recovery of rod function only.

Despite the use of better methodology of threshold determination and a longer drug treatment, the lack of any major effect of the two drugs on scotopic vision does not imply that the drugs have no effect on ALDH. The possibility still remains that the two drugs even when given for a week may not be well distributed to/concentrated enough in the retina. Alternatively, the kinetic characteristics of the retinal and the hepatic ALDH may not be the same as far as interaction with these two drugs is concerned.

ACKNOWLEDGEMENTS

The willing co-operation of our volunteers is gratefully acknowledged.

V. H. BHAVSAR*, S. D. MISTRY AND M. V. VACCHARAJANI**

Departments of Pharmacology and Ophthalmology, Government Medical College, Surat - 395 001

REFERENCES

1. Whitehouse LW, Paul CI, Thomas BH. Isoniazid induced tolerance to ethanol in rabbits, guinea pig and rat. *Bhiohem Drug Dispos* 1980; 1:235-45.
2. Seitz HK, Veith S, Czygan P et al. *In vivo* interactions between H2-receptor antagonists and ethanol metabolism in man and in rats. *Hepatology* 1984; 4: 1231-4.
3. Joshi NJ, Bhavsar VH, Kelkar VV. Effect of some drugs on ethanol sleeping time and ethanol levels in small animals. Read at XII Annual Conference, Indian Pharmacological Society, 1979.
4. Patel SR, Joshi NJ, Bhavsar VH, Kelkar VV. The Effect of Isoniazid and Cimetidine on Ethanol and Methanol Elimination in Rabbits. *Acta Pharmacol et Toxicol* 1986; 58: 1-3.
5. Davson H. Photochemical aspects of vision. In: Physiology of the eye. *London: Churchill Livingstone* 1980; 217.
6. Woodworth RS, Schlosberg H. Vision. In: Experimental Psychology. *London: Mathuen & Co. Ltd.* 1963; 362-402.
7. Arden GB, Weale RA. Nervous mechanisms and dark adaptation. *J Physiol* 1954; 125: 417-26.

*Corresponding Author
**Present address : Ophthalmic Institute, New Civil Hospital, Ahmedabad.