INTRODUCTION

Generally the world over, glaucoma has remained an increasingly disturbing cause of blindness especially when undetected earlier. Originally, glaucoma was thought to result solely from an increase in ocular tension which is clinically significant when the pressure rises above 21 mmHg. However, it is a well-established fact that glaucoma could develop or persist despite normal or low ocular tensions, conditions which have been clinically described as normal tension or low tension glaucoma respectively. The pathogenesis of both the normal tension and low tension glaucoma is gradual decrease in vascular perfusion to the optic nerve head that results in glaucomatous atrophy despite a normal intraocular pressure.

Isosorbide dinitrate (ISDN), being an organic nitrate and a vasodilator, affects both arteries and veins with a preponderant effect on the veins. This white crystalline odorless compound with a chemical nomenclature of 1, 4:3, 6-dianhydroisorbitol 2,5-dinitrate is an important cardiotherapeutic agent used in the management and treatment of congestive cardiac condition including angina pectoris. Its effects are mediated by its active moiety isosorbid-5-mononitrate. The principal pharmacological effect of isosorbide-5-mononitrate is relaxation of vascular smooth muscles and the consequent dilation of peripheral arteries and veins especially the latter. In humans, isosorbide-5-mononitrate is not subject to significant first pass metabolic changes in the liver. The absolute bioavailability of isosorbide-5-mononitrate from tablets is nearly 100%. The absorption is rapid, and maximum. Serum concentrations are achieved 30-60 minutes after dosing. The overall elimination half-life is about 5 hours and the rate of clearance is the same in healthy young adults, and in the elderly. ISDN may also serve to increase vascular perfusion to the optic nerve head.

ISDN is member of the nitric oxide (NO) group of drugs, which mediate their pharmacotherapeutic nitrates NO has also been established to be a mediator of physiologic and pathologic processes in the eye, for example regulation of aqueous humor dynamics, vascular tone, retinal neurotransmission, retinal ganglion cell death by apoptosis, phototransduction and ocular immunological responses. Hence, both an overproduction and underproduction of NO may contribute to pathological processes in degenerative diseases (uveitis, retinitis) in the eye and may have effects on the development and progression of glaucoma. NO also has a

ABSTRACT

The effect of isosorbide dinitrate (ISORDIL) on intraocular pressure (IOP) was studied using rabbits as experimental animals. There was a net decrease in IOP following administration of the drug. The study rabbits were divided into 2 groups (the 10mg per day group and the 20mg per day group) of 4 rabbits each. The initial IOP was taken before administration of the drug. The first group was given 1ml of 10mg/ml solution of the drug orally, once daily for five days and the second group received same regimen orally, but was given 2ml of the 10mg/ml solution. The IOP was monitored for seven days using Schiotz indentation tonometer. Statistical analysis using ANOVA showed significant difference (P>0.05) between the means of various days in the second group. There was no significant difference (P<0.05) between the means of various days in the first group. It can be inferred from the study that ISORDIL has no threatening effect on the ocular integrity if taken at normal does but one should guide against overdose as it might significantly raise the IOP.

KEYWORDS: Isosorbide dinitrate, Intraocular pressure, Congestive cardiac condition, Angina pectoris, Nitric oxide.
vasodilatory function for blood flow in the optic nerve head, causing researchers to propose nitrovasodilators as possible ocular hypertensive agents.

NO seem to be implicated in the regulation of intraocular pressure (IOP). In the anterior segment of the eye, NO donors or nitrovasodilators may regulate IOP at the level of ciliary’s muscle, trabecular meshwork and endothelial and vascular smooth muscle cells in the aqueous drainage system. Again, nitrergic nerves might dilate episcleral vessels, thereby lowering episcleral venous pressure and further the resistance to aqueous humour outflows, leading to decreased IOP. In addition, it has been hypothesized that NO or nitric oxide-derived radicals might result in neurotoxic glaucomatous effects at the optic nerve head and retina, leading to optic nerve head degeneration and visual field loss.

Although ISDN is very effective in cardiovascular therapy, suspicions are held concerning its effect on the ocular system. Because the drug is non-selective in its action and since the ocular integrity is to a large extent dependent on the quality and quantity of blood flow to the eye as is related to systemic changes, this research work thus emphasizes on the nitric oxide-donor action of ISDN, to investigate the effect it may have on IOP vis-à-vis its hemodynamic properties, using rabbit subjects.

MATERIALS AND METHODS

Eight health rabbits weighing between 2.80 and 3.30kg were used for the study were the Schiøtz instruments and materials used for the study were the Schiøtz indentation tonometer, 0.5% ophthalmic lignocaine drops (by Maxheal pharmaceutical, India), ISDN tablets (10mg oral preparation, by Wyeth, batch no. 03G0345, expiring date July, 2006), distilled water, methylated spirit (by Senco, Nigeria), timepiece, and 5ml hypodermic syringe.

Drug mixture was prepared by dissolving the tablets in clean distilled water. Each 10mg tablet was dissolved in lml of distilled water to obtain 10mg/ml of ISDN solution. Fresh preparation of ISDN solutions were made daily throughout the days of study in order to maintain its freshness, and to prevent chemical denaturing of the drug compound. Pupillary sensitivity to light and shadow tests were carried out using the pentorch to rule out pupillary and anterior chamber abnormalities, which could affect the IOP value.

The animals were divided into 2 (4 in each group) groups. Group1 (G1) received lml of 10mg/ml ISDN solution orally once a day and Group 2 (G2) received 2ml of 10mg/ml ISDN solution orally once a day. Schiøtz tonometer was used to determine the IOP of the rabbits before the administration of the ISDN solution. The treatment with ISDN solution lasted only 5 days (D1 to D5) in both groups. The IOP was taken at 15min interval, for one hour at about similar time for the seven days, although the drugs were not administered on the 6th and 7th day. The IOP was always measured 3 times at each instance and the average reading recorded. Data was analyzed using the two-way ANOVA with one variable per cell.

RESULTS

An initial increase in IOP was noted for the first quarter of the period the ISDN solution was administered in the two groups, which was accompanied by a sustained decline in the remaining intervals and on withdrawal of treatment, the pressure began an incline towards baseline.

For G1, the mean initial IOP, was 19.5mmHg, which increased to 19.8mmHg at the first interval, and later on, began reducing subsequently to 19.0, 18.8, and 18.2mmHg in the third, fourth, and fifth intervals respectively (fig. 1). A similar trend was observed for G2.

Statistical analysis showed that there was no significant (P<0.05) change in IOP for the number of days (D1 to D5) the measurement was taken, when given lml of 10mg/ml of the drug solution orally, F1,2 <F1,6,1.66. On the other hand, G2 experimental animals showed a statistically significant difference (P>0.05) for the days the drug was administered. This indicated a significant IOP-increasing effect of the drug on these animals.

The increase however, was not sustained as the IOP suddenly began declining between D4 and D5 with a peak decline on the 6th day (fig.2). Despite these undulations, it was observed that the variation remained within the physiologic range of IOP, which is between 10-21mmHg.

DISCUSSION

The net effect of the drug was a reduction in IOP. Despite the slight initial increases in IOP observed for both groups at about the first quarter following administration of drug, subsequent intervals demonstrated an IOP-lowering effect of the drug. However, it was also observed that the IOP increased significantly with a prolonged
administration of the drug (see Figs 1 and 2). This may perhaps be resulting from some kind of compensatory mechanisms or additive effects, since this increase was also within physiologic range. The lowering effect observed could possibly have resulted from the NO action of the drug, which is capable of inducing a relaxation of the ciliary muscles leading to decreased trabecular meshwork resistance and thus the alteration in the outflow facility of aqueous humour. There is evidence that the trabecular meshwork has intrinsic contractile elements, which can be relaxed by nitric oxide, leading to increased aqueous humour outflow.

Although glaucoma is usually the result of ocular hypertension, glaucoma that does not result from high IOP may equally benefit from vasodilatory effects of NO. Neufeld' posits that the increased presence of endothelial NO synthetase (eNOS) in the vascular endothelia could be neuroprotective in causing vasodilation and increased blood flow in the optic nerve head.

This study has demonstrated the safety of the use of ISDN in the management of congestive cardiac conditions vis-à-vis its ocular effect. It is however not clear by this work, the effect higher doses of this drug may have on the ocular system. Further studies are recommended on the possibilities of using NO donors as future ocular hypotensive agents.

**FIGURE 1:** VARIATION OF THE IOP READINGS WITH DAYS OF DRUG ADMINISTRATION FOR G1.

**FIGURE 2:** VARIATION OF THE IOP READINGS WITH DAYS OF DRUG ADMINISTRATION FOR G2.
REFERENCES