# *Once Daily Slow-Release Hydralazine in Hypertension*

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Hydralazine has been used for the treatment of hypertension since 1950 (Gross et al., 1950), but only since the introduction of beta-adrenoceptor blocking agents has its use again become popular (Koch-Weser, 1976). Originally, hydralazine was given in four divided doses, but it has been shown to be equally effective and without increased side-effects when given by twice daily dosage (O'Malley et al., 1975). In the present study, the antihypertensive effect of a slow-release formulation of hydralazine given once daily was compared with conventional hydralazine (Apresoline) given twice daily in hypertensive patients being treated with oxprenolol. Compliance with both regimens was also compared.

## Methods and Patients

Thirty patients with essential hypertension, as defined by normal renal function and normal electrolytes, whose diastolic blood pressure (DBP) was greater than 90 mmHg (phase IV) while on slow oxprenolol in doses ranging from 160 mg to 480 mg for at least four weeks, entered a double-blind cross-over study in which patients received hydralazine and *slow* hydralazine in random order. Initially, patients were given a daily dose of 50 mg of either formulation and the dose was doubled until blood pressure was controlled (DBP $\leqslant$ 90, phase IV) or until a maximum dose of 200 mg was reached. Each patient remained on the optimal dose for four weeks and then crossed over to the alternative preparation for a further four-week period. Blood pressure measurements at the end of each four-week period were compared. Student's t test for paired observations was used for statistical analysis. All blood pressure measurements were taken with a Hawksley random-zero sphygmomanometer by one observer 16 to 23 hours after taking the *slow* hydralazine. Compliance was assessed by tablet counting. Side-effects were documented by questionnaire.

Patients were subdivided into groups of fast or slow acetylators using sulphadimidine as a test drug. One week after the end of the study each patient received sulphadimidine 10 mg/Kg, as a single oral dose. Urine produced in the period five to six hours afterwards was collected and the relative amounts of acetylated and unchanged sulphadimidine were determined using the simplified colorimetric test of Schroeder (1972).

## Results (Table 1)

Twelve male and twelve female patients, aged 27-63 years, completed the study. Six patients were withdrawn—four due to poor compliance, one because of gastrointestinal symptoms, and one because of severe hypertension with papilloedema. There were 12 fast acetylators and 11 slow acetylators. One patient failed to attend for assessment of acetylation status.

The mean fall in supine SBP on *slow* hydralazine was 18.9 ± 5.2 mmHg compared with 27.7 ± 4.6 mmHg on hydralazine ($p > 0.05$). The mean fall in supine DBP on *slow* hydralazine was 13.7 ± 2.2 mmHg compared with 16.7 ± 2.3 mmHg on hydralazine ($p > 0.1$) (Table 1). There was no significant difference in standing blood pressures. There was no correlation between acetylator status and fall in SBP or DBP on 200 mgs of either compound. Headache was experienced by nine patients, nausea by four patients and palpitations by three patients during the titration phase but there was no significant difference between the treatments and in all cases the side-effects subsided within one week of achieving the optimal dose. Tablet counting revealed that over the period of the study 27 evening doses of medication were omitted without a stated reason by 11 patients compared with only nine morning doses omitted by five patients ($p < 0.01$, $X^2$ test).

## Discussion

Hydralazine is now usually prescribed on a twice-daily basis and in the present study we compared the effect of this standard regimen with a single daily dose of a slow-release formulation. *Slow* hydralazine given once

**Table 1**
Supine arterial blood pressure and heart rate in hypertensive patients receiving hydralazine and *slow* hydralazine in combination with slow oxprenolol

| SUPINE | Slow oxprenolol (baseline) | Slow oxprenolol + Hydralazine | Slow oxprenolol + Slow hydralazine | p |
|---|---|---|---|---|
| Systolic BP (mmHg) | 175.9 ± 4.5 | 148.2 ± 4.2 | 157.0 ± 4.8 | >0.05 |
| Mean BP (mmHg) | 131.0 ± 2.2 | 110.6 ± 2.5 | 115.5 ± 2.8 | >0.05 |
| Diastolic BP | 108.5 ± 1.8 | 91.8 ± 2.1 | 94.8 ± 2.1 | >0.1 |
| Heart Rate ($min^{-1}$) | 68.5 ± 1.6 | 68.9 ± 1.3 | 67.8 ± 1.4 | >0.1 |

Values are means ± SEM, n = 24.

daily was as effective as twice-daily conventional hydralazine in controlling blood pressure in patients receiving a beta-adrenoceptor blocking agent. Though the numbers studied were small, the magnitude of antihypertensive effect of both preparations was not related to acetylator phenotype, which genetically determines the rate of acetylation—clinically, the most important metabolic pathway of hydralazine. Side-effects were transient and were no greater with the new preparation. Patients were more likely to omit the evening dose on a twice-daily dosage regimen and this suggests that once-daily dosage may benefit compliance.

**Summary**

Twenty-four patients with essential hypertension, uncontrolled on oxprenolol, completed a double-blind cross-over study in which they received slow-release hydralazine (once daily) and conventional hydralazine (twice daily) for 4-week periods. Blood pressure was compared at the end of each period and compliance was assessed by tablet counting. The mean fall in systolic blood pressure with slow hydralazine was 18.9 ± 5.2 mmHg compared with 27.7 ± 4.6 mmHg on hydralazine ($p > 0.05$). The corresponding mean falls in diastolic blood pressure were 13.7 ± 2.2 and 16.7 ± 2.3 mmHg ($p > 0.1$). Twenty-seven evening doses were omitted as against nine morning doses ($p < 0.01$). We conclude that slow hydralazine given once daily is as effective as conventional hydralazine in controlling blood pressure and may improve compliance.

**References**

Gross F., Drouey J. and Meier R. (1950). *Experienta*, 6: 19.

Koch-Weser J. (1976). *N. Engl. J. Med.*, 295: 320.

O'Malley K., Segal J.L., Israeli A.M., Boles M., McNay J.L. and Dayton P.G. (1975). *Clin. Pharmacol. Ther.*, 18: 581.

Schroeder M. (1972). *Brit. med. J.*, 3: 506.

# Book Reviews

**PROBLEMS IN BREAST PATHOLOGY. Vol. II in the series Major Problems in Pathology; J. G. Azzopardi, B.Sc., M.D., M.R.C.Path.; W. B. Saunders Co., 1979; £25 sterling.**

This is a book for the practising surgical pathologist to have and to keep within easy reach of his or her microscope. He or she, however, is in danger of losing it to any surgeon interested in breast problems because this book has, if not the answers to all the questions, at least the most accurate information available in one volume.

The first chapter on frozen-section diagnosis is balanced and full of sound advice, e.g. "if in doubt await the paraffin section". This is followed by a useful chapter on the microanatomy of the breast. Terminology of benign diseases is dealt with sensibly but one cringes at the use of the term "infiltration epitheliosis", p. 37, 174 et seq. One wonders if a better term could not be found for this variant of sclerosing adenosis. Understandably, malignancy and the special problems related to it occupy a large part of the text. Its various aspects are covered in a logical sequential manner beginning with a detailed account of histogenesis and the relationship of cancer to epithelial proliferation disease of the breast. Other chapters deal with over-diagnosis and under-diagnosis in a highly relevant and practical way. Elastosis in malignancy is comprehensively dealt with and a whole chapter is devoted to a miscellany of rare lesions. For completeness, two chapters — the last two — are contributed by other specialists, namely Dr. Ali Ahmed on Ultrastructure and Dr. Rosemary R. Mills on Mammography.

Altogether, this book achieves an ideal in that it is both an excellent reference work and a highly practical bench-book detailed and explicit. At £25 sterling it is worth the money even allowing for the punt and V.A.T.

**Cuimin T. Doyle.**

**RECENT ADVANCES IN GASTROINTESTINAL PATHOLOGY. Clinics in Gastroenterology, Supplement 1; ed. by Ralph Wright, M.A., D.Phil., M.D., F.R.C.P.; W. B. Saunders Co. Ltd.; £20 sterling.**

This is a compilation of papers presented at a symposium on Gastrointestinal Pathology organised by the Royal College of Pathologists and held at the Royal College of Physicians, London in February 1980.

It is an advantage to have been present at the symposium when reviewing the published proceedings. One can put personalities on the papers and cast one's mind back to the presentations and compare them with the published papers.

In this volume twenty-two papers, set out as chapters, are divided into three sections covering Pathophysiology, Inflammatory Diseases, and Gastrointestinal Malignancy. Up-to-date knowledge of the major problems in gastrointestinal pathology is given mostly by acknowledged specialists in the particular field. A few chapters (papers) deal with the authors' personal research into rather esoteric areas and as such do not really merit inclusion in a volume entitled "Recent Advances". The editing is excellent; nevertheless, this remains a collection of individual papers and would more accurately be titled Proceedings of a Symposium on Gastrointestinal Pathology.

At first sight £20 sterling does not appear expensive but add the difference between the punt and sterling and V.A.T. and the price to the Irish purchaser is close to £30.

This is a book for the hospital or Medical School library. The larger departments of Pathology will also have a copy. It is hardly a book to purchase for one's personal library, that is if anyone can afford such a luxury anymore.

**Cuimin T. Doyle.**