Anginal Syndrome

Treatment with a Long-Acting Nitrate (Itramin Tosylate)

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The purpose of this report is to present our experiences with a new organic nitrate which appears to be safe and effective for the treatment of the anginal syndrome. Although the pharmacological properties of 2-aminoethyl-nitrate were reported as early as 1947, it was not until 1961 that studies by Ejrup and Kumlin and Ruskin indicated the clinical value of this preparation. The p-toluene-sulphonate salt of this nitrate is not only less toxic than other organic nitrates, but the availability of a chewing tablet which is well tolerated facilitates the rapidity of effect—as well as the ease of administration.

This study followed the concepts applied in the appraisal of other drugs used for the treatment of the anginal syndrome. The subjectivity of the painful anginal syndrome also required that the method of evaluation follow the principles that are applicable for the investigation of any analgesic medication.

Eighteen patients with angina pectoris were selected for the clinical trial with itramin tosylate. They had been under observation for several months or years before being chosen for this study. All patients had been thoroughly screened to exclude those with chest pain unrelated to coronary insufficiency. Previous experience with these patients, in numerous trials with other medications advocated for the anginal syndrome, ensured the cooperativeness and patient-physician rapport which is essential for accurate observation.

The patients were accustomed to routine questioning and to keeping individual records regarding the frequency and severity of their attacks. Therefore, their glyceryl trinitrate requirements and the status of their underlying heart disease were well known.

Two dosage strengths of itramin tosylate were studied. Eleven patients began therapy by chewing a tablet, containing 2 mg of the drug, every four hours for four daily doses. After a suitable period of observation ranging from two to five weeks, the dose was increased to the 4 mg tablet four times daily. Seven of the 18 patients took 4 mg tablets four times a day from the outset.

In each case the duration of therapy was dependent upon the effectiveness attained. A period of two to three weeks was considered sufficient time to note the effect upon the frequency and severity of the angina pectoris. When possible the effective dose (either 2 or 4 mg) was continued for approximately three months to note any evidence of the occurrence of tolerance and cumulative adverse effects.

Six patients, who had a favorable response, continued therapy with a substituted placebo chewing tablet identical in appearance to the tablet containing the medication. They were not told of the change to placebo.

Patients were required to keep a daily record of the occurrence of anginal attacks. In these records they noted the frequency and severity of attacks, as well as the use of glyceryl trinitrate. The records were reviewed at each clinic visit. At that time the patients were given a supply of tablets sufficient to last until the next clinic appointment. (The time interval between these visits ranged from one to three weeks.)

RESULTS

Although the 2 mg dosage level was satisfactory in controlling the frequency and severity of the anginal syndrome in five of the eleven patients treated, it was not considered to be optimum on the basis of achieving an adequate predictable response. The administration of the 4 mg dose in these same eleven patients resulted in a satisfactory or greater response in four patients and continuation of a
similar (and satisfactory) response in three patients. Four patients did not respond to either dose.

In 12 of the 18 cases in which trial with the 4 mg dose was carried out, control of anginal complaints was achieved. The response in these patients was greater than that previously observed with the use of pentaerythritol tetranitrate or various xanthine preparations.

Untoward reactions of a mild type (nausea and lightheadedness) were noted in only two patients receiving the 4 mg dose. The patient with nausea continued the medication for four weeks. For the one with the feeling of lightheadedness, the dose was reduced to 2 mg four times daily. This dosage was taken for 17 weeks with satisfactory relief. The patients who were treated with 4 mg four times a day for approximately three months continued to respond without development of tolerance or cumulative adverse effects to the medication.

Five of the six patients who were observed on placebo therapy, after an effective trial with 4 mg tablets had prompt recurrence of anginal pain as frequent and severe as before.

**DISCUSSION**

This preliminary evaluation of 2-aminoethyl-nitrate-p-toluene-sulphonate accords with the results of other investigators, relative to the effectiveness and safety of this drug for the treatment of the anginal syndrome. Until definitive therapy is available, the major therapeutic problem depends upon the use of a medication which will decrease the frequency and severity of the anginal attacks. The procedure that brings about therapeutic benefit may be one of several. The action for any particular medication might not be fully known and yet the drug be clinically useful because of its effectiveness and safety in the prevention of painful seizures.

This is the case with nitrate preparations. The exact mechanism of action is still unknown. This lack of knowledge does not, however, detract from their usefulness. The search for long-acting nitrates, with a minimal occurrence of tolerance and cumulative toxicity, has been in progress since the introduction of amyl nitrate and glyceryl trinitrate. Many products have been evaluated and discarded. The utilization of the toluene sulphonate salt of 2-aminoethylnitrate satisfies the prerequisites for a long-acting, effective, and well-tolerated organic nitrate for the usual patient with coronary insufficiency.

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**REFERENCES**