

## USE OF METHOXAMINE HYDROCHLORIDE AS A PRESSOR AGENT DURING SPINAL ANALGESIA \*

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METHOXAMINE hydrochloride,‡ a synthetic pressor drug with prolonged action, was discovered during a systematic study of phenethylamine derivatives (1). It appeared to offer specific advantages over other sympathomimetic drugs in common use. Clinical trials (2, 3, 4, 5, 6) indicate that the drug is useful in the treatment of hypotension of various types, including that associated with spinal anesthesia. This is a report of its use for the maintenance of blood pressure during operations performed under spinal analgesia.

### PHARMACOLOGY

Methoxamine hydrochloride, beta-hydroxy-beta (2,5-dimethoxyphenyl) isopropylamine, has the characteristic feature of possessing methoxy groups on the ring structure. It is a white crystalline substance which is stable and may be sterilized by autoclaving. Solutions are nonirritating to the tissues.

One of the outstanding characteristics is its potent, prolonged pressor action following parenteral administration. In human subjects intravenous and intramuscular injections produced a powerful pressor response and the blood pressure curve was of the plateau type, with long duration of action. The average time of onset was two minutes after intravenous injection and seventeen minutes after intramuscular injection. The average duration was sixty minutes after intravenous injection and seventy minutes after intramuscular injection (6).

Fasset and Taube (6) concluded from their observations that: (1) cardiac output does not increase but probably decreases; (2) stroke volume does not usually show a marked change; (3) total peripheral resistance is greatly increased and (4) considerable rise occurs in the right auricular and ventricular pressure and also in peripheral venous mean pressure.

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King and Dripps (5) pointed out that the pressor effects appear to be due predominantly to actions on the peripheral vascular system either at the effector cells or through the vasomotor center or both. This apparent constrictor action appears to be exerted on both the arterial and venous systems. That the peripheral resistance is increased is indicated by blood pressure curves and by calculations from mean arterial blood pressure and cardiac output.

Severe headaches associated with marked sustained blood pressure elevations have been observed with larger doses and intravenous administration. King and Dripps have not observed a delayed pressor response.

Unlike most pressor amines, methoxamine hydrochloride slows the pulse rate. The bradycardia seems to be related to the extent of pressor response. Fasset and Taube concluded that this bradycardia is due to a carotid sinus reflex mediated over the vagus nerve. It is blocked by atropine. Electrocardiographic studies show only slight changes of short duration. An occasional premature contraction occurs at the height of the rise in pressure, especially after intravenous doses.

Methoxamine hydrochloride, with methoxy groups in the two and five positions, differs from most pressor amines in that it does not cause disturbances of rhythm in the heart which has been sensitized by cyclopropane (7). It appears to be a safe drug to use during cyclopropane anesthesia.

Another distinctive feature is the absence of central stimulation by the drug. This has been demonstrated by laboratory studies in intact animals and by electroencephalogram tracings of patients receiving the drug (6) as well as by clinical observation (5). Obviously, this is advantageous as the pressor drug does not counteract the effect of the preanesthetic medication or produce insomnia in the post-operative period.

Among the side effects observed in animals were marked and prolonged pilomotor response, profuse salivation and exophthalmos from large doses. Clinically, intense pilomotor effect over the body and extremities has been noted. Tingling (acanthesthesia) of the extremities and a feeling of coldness occur. The tendency toward excessive pilomotor activity is not considered deterrent to clinical use of the drug (3). There is some headache and a desire to void.

Drugs which have a methyl group on the second carbon atom of the side chain exhibit tachyphylaxis in succeeding doses. This property has been reported with methoxamine hydrochloride administered to animals. According to King and Dripps, true tachyphylaxis is not observed clinically. They are uncertain as to whether this response is ever of importance clinically unless relatively enormous doses are used and repeated within short periods of time.

The contraindications to the use of methoxamine hydrochloride are the same as for other sympathetic amines: cardiovascular disease, hypertension and hyperthyroidism.

#### INDICATION

In a series of 200 patients whose blood pressure was reduced by spinal anesthesia, Dripps and Deming (4) found that in approximately 80 per cent the fundamental circulatory abnormality responsible for the lowered blood pressure was reduction in the total peripheral resistance.

On the basis of pharmacologic activity, methoxamine hydrochloride should be useful to counteract the fall in blood pressure that commonly follows the administration of a spinal anesthetic. For this purpose, it is injected intramuscularly at approximately the same time as the spinal anesthetic is given. Caution should be exercised to avoid an overdose so that undesirable high blood pressure or excessive bradycardia will not occur. A prophylactic dose of 10 to 15 mg., given simultaneously with the administration of the spinal anesthetic, will usually serve to maintain the blood pressure at a satisfactory level for forty-five minutes. A second dose should not be given until the first one has had time to act (fifteen minutes after intramuscular injection). Intravenous injection is not recommended unless the systolic pressure falls to 60 mm. or less, and then a small dose (2 mg.) may be given.

#### CLINICAL OBSERVATIONS

For approximately one year methoxamine hydrochloride has been used as a vasopressor agent to maintain blood pressure during spinal analgesia. This report deals with 200 cases. The patients were unselected, other than that spinal analgesia was the method of choice for operation in each case. Mainly, gynecologic and general surgical operations were involved. The vasopressor was administered in an intradermal wheal and in the subcutaneous tissues immediately before induction of the spinal analgesia. A solution of pontocaine and glucose was the anesthetic agent in most cases.

During a trial period, it was observed that the recommended dose tended to be too large. We found that for medium and high spinal anesthesia 10 mg. was adequate. For saddle block and some cases of low spinal anesthesia, 5 mg. was adequate.

The onset of the vasopressor effect varied; the usual time interval was about fifteen minutes. The effect lasted about forty-five minutes in the majority of cases. In some cases, the effect was prolonged sixty minutes or longer.

Methoxamine hydrochloride, given in single dose injections prophylactically, did not maintain the blood pressure at clinically acceptable levels in all cases. Nine per cent of the patients required addi-

tional vasopressor drugs because the original drug did not maintain the blood pressure. Ephedrine was given intravenously as the supplementary agent in 6 cases and methoxamine hydrochloride in 7 cases.

Bradycardia was common, a pulse rate from 50 to 60 being noted frequently. In one case, a pulse rate of 44 was recorded. The pilomotor response was often seen, and occasional complaints of coldness and of tingling (acanthesthesia) of the skin occurred. Symptoms of central stimulation did not appear.

#### COMPLICATIONS

Of a group of 4 patients, 3 had an alarming and sustained rise in blood pressure forty-five minutes or more after injection of the drug. Whether this was a cause-effect relationship was uncertain. In Case 4 marked elevation of the blood pressure occurred twenty minutes after the administration of methoxamine hydrochloride (table 1).

In Case 1, the blood pressure had been stabilized at 140/95 throughout an operation lasting two and one-half hours. The elevation in pressure to 240/140 occurred after the patient was returned to the

TABLE 1

| Case | Onset, minutes | Duration, minutes | Remarks  |
|------|----------------|-------------------|--|
| 1    | 180            | 180               | Secondary closure 12 hours after operation<br>Ephedrine given as vasopressor during a subsequent spinal anesthesia |
| 2    | 105            | 25                |  |
| 3    | 45             | 120               |  |
| 4    | 20             | 30                |  |

ward, approximately three hours after the administration of methoxamine hydrochloride. The blood pressure remained elevated, with fluctuations, for three hours. Bleeding from the abdominal wound was noted three hours after operation and continued until the wound was reopened and closed twelve hours after the original procedure.

In Case 2, the blood pressure was stable at 120/60 until one hundred and five minutes after the administration of methoxamine hydrochloride. At that time a sudden elevation to 200/140 with an auscultatory gap was noted in the systolic pressure; this elevation persisted for twenty-five minutes.

In Case 3, the blood pressure rose forty-five minutes after methoxamine hydrochloride had been given. Twenty-five minutes later it reached 200/120, then slowly began to fall. The blood pressure level returned to the preoperative reading after ninety-five minutes.

In Case 4, the blood pressure was 110/75. Twenty minutes after the injection of methoxamine hydrochloride, a sudden elevation occurred and within five minutes the blood pressure was 200/130. It remained

at this level for ten minutes, then fell gradually to 112/80 during the next twenty-five minutes.

No untoward effects were noted following the last three episodes of hypertension. Hypertensive cardiovascular disease was not present in any of these patients.

A delayed pressor response has not been reported. It may have been possible that the vasopressor effects of the drug were more prolonged than the circulatory depressant effects of the spinal analgesia. This phenomenon may have accounted for the late occurrence of elevation of the blood pressure. In 3 patients the onset of hypertension appeared when the anesthetic level was waning.

#### SUMMARY

The pharmacologic properties of methoxamine hydrochloride are reviewed, and the clinical use of this drug as a vasopressor in conjunction with spinal analgesia is reported. Our impressions are in accord with other published reports that this drug provides an effective prophylactic for hypotension associated with spinal anesthesia. Caution must be exercised to avoid an overdose. A slight excess of the drug causes marked rise in blood pressure, nausea and pilomotor response, particularly in young individuals. An alarming delayed hypertension was observed in three patients. In one of these postoperative hemorrhage occurred.

#### REFERENCES

1. Hjort, A. M.; Randall, L. O., and de Beer, E. J.: Pharmacology of Compounds Related to  $\beta$ -2,5-Dimethoxy Phenethyl Amine; Ethyl, Isopropyl and Propyl Derivatives, *J. Pharmacol. & Exper. Therap.* **92**: 283-290 (March) 1948.
2. Steven, R. J. M., and Tovell, R. M.: Case Report: Efficacious Administration of Methoxamine Hydrochloride (Vasoxyl), *Hartford Hospital Bulletin*, October, 1950.
3. Kistler, E. M., and Ruben, J. E.: Methoxamine in one per cent Procaine as a Prophylactic Vasopressor in Spinal Anesthesia, *Arch. Surg.* **62**: 1, 64 (Jan.) 1951.
4. Dripps, R. D., and Deming, M. V.: Evaluation of Certain Drugs Used to Maintain Blood Pressure During Spinal Anesthesia; Comparison of Ephedrine, Paredrine, Pitressin-Ephedrine and Methedrine in 2500 Cases, *Surg. Gynec. & Obst.* **83**: 312-322 (Sept.) 1946.
5. King, B. D., and Dripps, R. D.: Use of Methoxamine for Maintenance of the Circulation During Spinal Anesthesia, *Surg., Gynec. & Obst.* **90**: 659-665 (June) 1950.
6. Fassett, D. W., and Taube, H.: Unpublished Data.
7. Stutzman, J. W.; Pettinga, F. L., and Fruggiero, E. J.: Cardiac Effects of Methoxamine ( $\beta$ -[2,5-Dimethoxyphenyl]- $\beta$ -Hydroxyisopropyl amine HCl) and Desoxyephedrine During Cyclopropane Anesthesia, *J. Pharmacol. & Exper. Therap.* **97**: 4, 385-387 (Dec.) (pt. 1) 1949.