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VASICINE—A POTENT UTERINE STIMULANT—STUDIES ON HUMAN MYOMETRIUM

by

O. P. GUPTA,* M.Sc.

R. L. WAKHLOO,** M.D.

M. L. SHARMA,* B.Sc.

and

C. K. ATAL,* Ph.D.

Adhatoda vasica Nees (Vasaka) enjoys reputation in the Indian system of medicine for a number of respiratory system ailments and is included as an expectorant in many cough preparations marketed in the country. The alkaloids vasicine and vasicinone isolated from this plant are reported to possess bronchodilatory or bronchoconstrictor activities by different workers (Chopra, 1925; Amin *et al*, 1963; Cambridge *et al*, 1962; Bhide *et al*, 1974; Lahiri and Pradhan 1964) Detailed pharmacological investigations carried out in this Institute revealed that vasicine possessed appreciable bronchodilatory, hypotensive, respiratory stimulant and marked uterine stimulant and abortifacient activities (Gupta *et al*, 1977; Gupta *et al* 1977). Its uterine stimulant activity has been studied in detail on the uteri under different hormonal influences in different species of animals both in vitro and in vivo preparations. Uterotonic action of vasicine was found to be comparable to that of oxytocin and methylergometrine. Studies on the mechanism of its action and the observation that its action and abortifacient effect were more marked under the priming influence of oestrogens Gupta *et al* 1977 (known to enhance the synthesis of prostaglandins in the uterus Nayar and Poysa 1975), indicated that its uterotonic action was atleast partly mediated through the release of prostaglandins (Gupta *et al*). Acute and subacute toxicity studies have revealed that vasicine is free from any side effect (Vane and William 1973).

*From the Regional Research Laboratory, Jammu Tawi, India.

**Professor & Head, Dept. of Gynaecology & Obstetrics, Govt. Medical College, Jammu Tawi, India.

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In view of the promise on the use of vasicine as a new oxytocic agent, the present study was undertaken to study the uterotonic action of vasicine on the human myometrium.

Material and Methods

Human myometrium strips were collected in the oxygenated Ringer solution and immediately brought to the laboratory. A thin strip of 2-3 cm in length and 0.5 cm in breadth was mounted in the organ bath assembly. The bathing fluid was Ringer solution at 37°C aerated with oxygen. Uterine movements were recorded with a suitably balanced frontal writing level. Human myometrium strips were collected from operations like hysterotomy, caesarean section or hysterectomy for dysfunctional uterine bleeding. The strips were obtained from the different parts of the uterus.

Aqueous solution of vasicine hydrochloride, oxytocin (Pitocin, Parke-Davis) and methylergometrine (Methergin, Sandoz) were employed in this study.

Results

1. Myometrial strips from non-pregnant uteri either did not show any rythmic contractions of its own or the contractions were very feeble. Vasicine in 5-10 μg/ml concentration caused a marked increase in the tone and/or amplitude of contractions (Fig. 1). The response was similar when the tissue was treated with the known test drugs, methergin or pitocin.

2. Myometrial strips obtained from the pregnant uteri during first and second trimester of pregnancy either exhibited some spontaneous rythmic movements or it was quiescent (Figs. 2, 3 and 4). In the uteri showing its rythmic movements, vasicine in 5-10 μg/ml concentration caused increase in both tone and amplitude of contractions. The effect was well-sustained and tapered only after a number of washings (Fig. 2). In the uteri

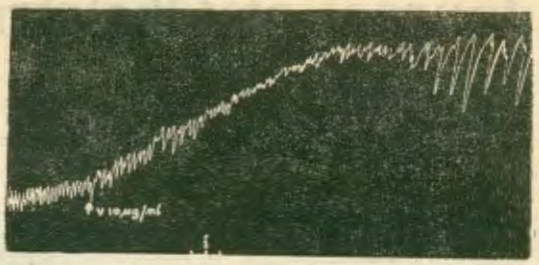

Fig. 1.
Myometrium strip (non-pregnant)—showing increase in tone followed by increase in rythmic movements with vasicine (V)

Fig. 2
Myometrium strip (12 weeks pregnancy)—showing the increase in tone and amplitude of contraction with vasicine. Uterotonic effect is well sustained and tapered only after a number of washings (W)

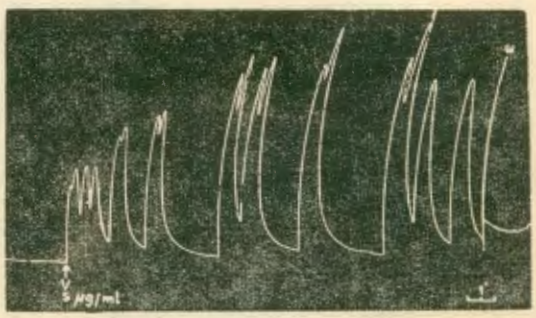

Fig. 3
Myometrium strip (20 weeks pregnancy)—showing the induction of marked uterine movement in the quiescent tissue with vasicine (V)

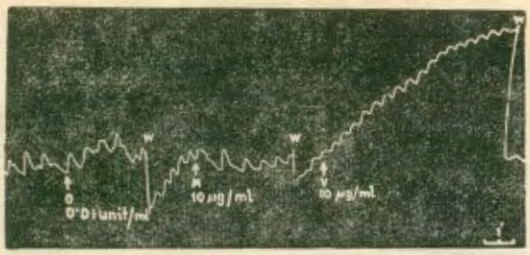

Fig. 4

Myometrium strip (20 weeks pregnancy)—oxytocin (O) and methergin (M) failing to show any effect while vasicine in a dose equal to that as tested for methergin, showed marked increase in the tone.

showing no rythmic activity, vasicine in 2.5-5 µg/ml contraction induced marked motor activity and the effect was well sustained (Fig. 3). In the uteri showing some feeble contractions oxytocin upto 0.01 unit/ml and methergin upto 10 µg/ml failed to show any response, while vasicine in 5-10 µg/ml concentration caused gradual but marked increase in the tone (Fig. 4).

3. Myometrial strips from full term pregnant uteri were taken from the upper as well as from the lower uterine segment. Uterine strips from upper segment showed feeble or no spontaneous rythmic movements. Vasicine, methergin and oxytocin in 2.5 µg/ml, 0.01 unit/ml respectively or in higher doses showed similar dose related gradual but marked

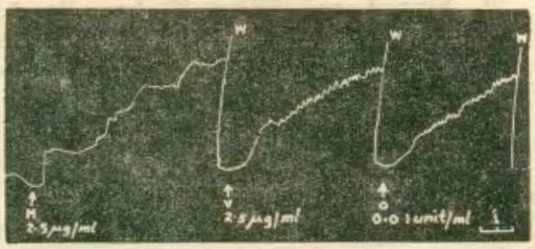

Fig. 5

Myometrium strip (full term)—showing the slowly developing increase in the tone with methergin (M) Vasicine (V) and oxytocin (O).

increase in tone (Fig. 5) or induced rythmic contractions. However, the strips obtained from the lower segment showed neither any rythmic activity nor any response to vasicine upto 10 µg/ml concentration.

4. Myometrial strips of non-pregnant uterus showed feeble rythmic movements. Vasicine in 5-10 µg/ml contractions caused appreciable increase in both tone and amplitude of contractions.

Comments

The foregoing observations revealed that the uterotonic effect of vasicine on human myometrium is comparable and in some cases even more marked than that of two known oxytocics. On the myometrium strips employed from different cases in this study, vasicine either initiated rhythmic movements in the quiescent tissue or increased the tone or the amplitude of contractions or both. The response of the uterus to drugs is known to depend on its hormonal status. Therefore, variation in the uterotonic effect of vasicine on myometrium strips obtained from different cases can be attributed due to difference in their hormonal status. It has been postulated earlier that the uterotonic effect of vasicine is mediated through the release of prostaglandins, since it was observed that (i) the uterotonic effect of vasicine is more marked on the uterus employed under the priming influence of oestrogens (known to enhance the synthesis of prostaglandins); (ii) the uterotonic effect of vasicine is markedly inhibited after pretreatment of uterus with aspirin and indomethacin (the prostaglandin synthetase inhibitors) and recently it has been observed that the uterotonic effect of vasicine is blocked after pretreatment of uterus with Sc-19220 and PPP (the prostaglandin antagonists). Therefore, it seems that the

response of the uterotonic effect of vasicine of the myometrium strips obtained from different cases is probably related to the difference in the levels of circulating oestrogens in different cases influencing the synthesis of prostaglandins in the uterus.

As vasicine initiated strong rythmic movements on the myometrium strips of early and middle stages of pregnancy, it is expected to prove as an effective abortifacient like prostaglandins in human use. Since it could initiate strong rythmic movements on the myometrium strips at full term, it is also expected to find use as an oxytocic like oxytocin and methergin. Vasicine action seems to be like that of an ideal oxytocic since while it caused increase in tone and motor activity of the uterine strips obtained from the upper part of the uterus, it did not show any effect on the strips obtained from the lower uterine segment.

Vasicine is expected to be very safe for its use in human beings. Its therapeutic ratio is high and the subacute toxicity and two generations teratogenic studies in animals have shown that it is free from any such effects. Moreover, vasicine is already tried on billions of human beings upto the extent of 10 mg in the daily human dose without any side or adverse effect as it is present in a number of proprietory cough remedies and Ayurvedic preparations which contain extract of *Adhatoda Vasica* (an official preparation in Indian Pharmacopoea). Vasicine in the form of its salt as a hydrochloride forms a clear solution in water with pH near 7, which is non-irritant and stable to autoclaving.

In view of the foregoing observations it seems that after ergometrine and sparteine, vasicine is likely to prove as the next oxytocic discovered from plant source to find its use in therapeutics.

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References

1. Chopra, R. N.: Ind. J. Med. Res. **13**: 205, 1925.
2. Amin, A. H., Mehta, D. R. and Samarth, S. S.: In Proceedings, First International Pharmacological Meeting, Stockholm, Pergamon Press Ltd., **7**: 377, 1963.
3. Cambridge, G. W., Jansen, A. B. A. and Jarman, D. A.: Nature Lond. **196**: 1217, 1962.
4. Lahiri, P. K. and Pradhan, S. N.: Ind. J. Exp. Biol. **20**: 219, 1964.
5. Bhide, M. B., Naik, P. V. and Ghooi, R. B.: Studies on the Pharmacological evaluation of Vasicine and Vasicinone, Xth Scientific Seminar in Indian Medicine, Institute of Medical Sciences, Banaras Hindu University, 1974.
6. Gupta, O. P., Sharma, M. L., Ray Ghatak, B. J. and Atal, C. K.: Indian J. Med. Res. **66**: 680, 1977.
7. Gupta, O. P., Sharma, M. L., Ray Ghatak, B. J. and Atal, C. K.: Indian J. Med. Res. **66**: 865, 1977.
8. Gupta, O. P., Anand, K. K., Ray Ghatak, B. J. and Atal, C. K.: Vasicine—the alkaloid of Adhatoda vasica—a promising uterotonic abortificient, Indian J. Exp. Biol. (communicated).
9. Naylor, B. and Poyser, N. L.: Brit. J. Pharmacol. **55**: 229, 1975.
10. Vane, J. and William, K. I.: Br. J. Pharmacol. **48**: 629, 1973.
11. Gupta, O. P., Anand, K. K., Sharma, M. L., Singh, G. B. and Atal, C. K.: Pre-clinical toxicity and teratogenic studies with vasicine—the uterotonic alkaloid of Adhatoda vasica. Indian J. Med. Res. (communicated).