VASOPRESSOR ACTIVITY OF ERGOMETRINE MALEATE IN ANAESTHETIZED PARTURIENT WOMEN

BY

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The alkaloids of ergot have occupied a prominent place in medical literature for a great many years. The writings concerning ergometrine are largely and rightly contained in obstetric publications and have dealt, in the main, with the oxytocic properties of the drug. Its ability to control post-partum bleeding has won for this agent a firmly established role in modern obstetric practice.

Relatively little study has been devoted to the systemic effects of ergometrine, particularly its vasopressor activity; indeed, some current textbooks attribute little or no such action to it within the therapeutic range. An exhaustive search of the literature has revealed few papers that record changes in blood-pressure following the intravenous injection of ergometrine to a large series of patients, and those that have appeared bear little or no relationship to present-day obstetric practice in Great Britain.

Several factors prompted the present study. Firstly, it has been noted for some time that a rise in blood-pressure after intravenous administration of ergometrine is a more frequent occurrence in hypertensive than in normotensive patients. Secondly, despite this general tendency, the appearance of a significant pressor response in some normotensive women and the lack of it in other hypertensive subjects seemed to merit investigation. In recent years, too, we have seen a rise in the dose of ergometrine employed intravenously from 0.125 mg. to 0.5 mg., sometimes repeated or supported by an intramuscular injection of the same order. Moreover, vasodepressant anaesthetic techniques such as nitrous oxide, oxygen, and diethyl ether have been largely displaced in this country by the thiopentone, muscle relaxant, nitrous oxide, and oxygen sequence with endotracheal intubation and intermittent positive-pressure insufflation of the lungs.

It is not the intention of this paper to discuss the place of ergometrine in modern obstetric practice but rather to assist in the selective administration of this life-saving, yet potentially dangerous drug.

Method of Study

A study was made of 272 patients requiring general anaesthesia for delivery by forceps or caesarean section, and for the purposes of the investigation the anaesthetic technique employed was standard. Pre-anaesthetic medication consisted of 0.6 mg. of atropine sulphate only. After intravenous induction of anaesthesia with 200–250 mg. of thiopentone sodium, suxamethonium 60–70 mg. was given for tracheal intubation. Thereafter intermittent positive-pressure insufflation of the lungs was carried out with nitrous oxide and oxygen, the suxamethonium being repeated to maintain apnoea and muscular flaccidity. Increments of suxamethonium were of the order of 20 mg., not only because of the risk of cardiac irregularity or standstill, but also because it was found early in the investigation that increments

in excess of 20 mg. of this depolarizing agent produced spikes of temporary rise in blood-pressure.

The dose of ergometrine maleate was 0.5 mg. in all but the six patients from whom the drug was withheld. In recording the systemic blood-pressure the auscultatory method was employed, the basal pressure being taken as that pressure found on admission, in the case of emergency procedures, or as the pressure recorded in the ward preoperatively, in the case of elective operations.

Early in the investigation it was found that patients exhibiting a vasopressor response did so within one to two minutes and that after the third minute no further elevation occurred. As a result, only the rise in systemic blood-pressure three minutes after ergometrine is recorded below, although in all patients the readings were charted throughout the operation.

The only cases excluded from the series were patients who required active resuscitation to render them fit for operation and those whose rapid deterioration due to operative haemorrhage rendered them valueless so far as this study was concerned.

Results

In the 266 patients to whom ergometrine was administered the blood-pressure was recorded at three specific stages in the procedure: (1) pre-operatively or on admission, (2) at the time of intravenous injection of the drug, and (3) three minutes after the injection. For the purpose of analysis of the results the cases were arranged in order of ascending basal diastolic blood-pressure.

A basal diastolic pressure of less than 90 mm. Hg was accepted as normal, and 173 patients presented in this normotensive category (see Table I). Of these, 24 (13.9%) showed a rise in systolic pressure of at least 10 mm. Hg and 6 (3.5%) a rise of at least 20 mm. Hg after the intravenous injection of 0.5 mg. of ergometrine. One of the six normotensive women who showed a significant response had a twin pregnancy and another an accidental haemorrhage.

The second group (Table II) is composed of the 59 patients with basal pre-operative diastolic pressures of 90 to 99 mm. Hg. Within this range of diastolic pressure there was a marked increase in the number of cases showing elevation of systolic blood-pressure, 39 (66.1%) exhibiting a rise of 10 mm. and 12 (20.3%) a rise of at least 20 mm. Hg. Of women who failed to show a

TABLE I.—Readings Obtained in 173 Patients with Basal Diastolic Blood-pressure of Less than 90 mm. Hg

Diastolic Pressure mm. Hg	No. of Patients	No. Showing a Rise (in mm. Hg) in Systolic Pressure of						
		< 5	5–	10–	15–	20–	25–	30
60–64	4	4	0	0	0	0	0	0
65–69	9	8	1	0	0	0	0	0
70–74	48	43	3	2	0	0	0	0
75–79	16	14	0	1	1	0	0	0
80–84	73	55	6	9	1	2	0	0
85–89	23	13	2	4	0	3	0	1

TABLE II.—Readings Obtained in 59 Patients with Basal Diastolic Blood-pressure of 90–99 mm. Hg

Diastolic Pressure mm. Hg	No. of Patients	No. Showing a Rise (in mm. Hg) in Systolic Pressure of									
		< 5	5–	10–	15–	20–	25–	30–	35–	40–	45–49
90–94	45	12	5	15	6	5	1	0	1	0	0
95–99	14	3	0	4	2	2	0	2	0	0	1

marked elevation, two suffered from diabetes, two had renal disease, and two carried a pre-operative diagnosis of essential hypertension. A further two patients, both with severe toxæmia, had a significant fall in pressure.

Cases with diastolic blood-pressure of at least 100 mm. Hg but below 110 mm. are listed in Table III, and number 21 of the total. Nineteen (90.5%) patients in this group responded to ergometrine by an elevation of 10 mm. systolic or more and 11 (52.4%) by a rise of 20 mm. or more. It is worthy of note that only two patients within this range of pre-operative diastolic pressure, one of whom had chronic hypertension, showed a response of less than 10 mm. Hg to the injection.

Thirteen women presented with a very high basal diastolic pressure of 110 mm. Hg or more (Table IV), but in this group the incidence of a demonstrable pressor response was lower than in the last, 8 patients (61.5%) experiencing an elevation of 10 mm. and 7 (53.8%) an elevation of 20 mm. Hg. Chronic hypertension was diagnosed pre-operatively in three of these women, while in one pre-eclamptic patient a severe fall in blood-pressure occurred. One patient who was delivered of twins, and who had an eclamptic seizure, was deeply sedated with tribromethanol at the time of induction of anaesthesia. The intravenous injection of ergometrine caused no alteration in her level of blood-pressure.

It is noticeable from the foregoing tables that there is a tendency for the pressor response following intravenous ergometrine to increase with height of basal blood-pressure up to the region of 110 mm. diastolic; thereafter the frequency of the response tends to decrease. This tendency is demonstrated by Table V.

This decrease in frequency of response to ergometrine in the cases listed in Table IV is the result of the inclusion in this group of patients with chronic hypertension. In several patients there no doubt coexist chronic hypertension and toxæmia of pregnancy.

Five twin pregnancies occurred in the investigation. One of three falling into the normotensive group showed a significant elevation (20/14 mm.), one a rise of 12/6 mm., and the third no alteration in blood-pressure. Of the two hypertensive patients, one demonstrated a pressor response of 14/10 mm. Hg and the other, who

TABLE III.—Readings Obtained in 21 Patients with Basal Diastolic Blood-pressures of 100–109 mm. Hg

Diastolic Pressure mm. Hg	No. of Patients	No. of Patients Showing a Rise (in mm. Hg) in Systolic Pressure of									
		<5	5–	10–	15–	20–	25–	30–	35–	40–	45–49
100–104	18	1	0	4	3	5	0	1	1	3	0
105–109	3	1	0	1	0	0	0	0	1	0	0

TABLE IV.—Readings Obtained in 13 Patients with Basal Diastolic Blood-pressures of 110 mm. Hg or More

Diastolic Pressure mm. Hg	No. of Patients	No. of Patients Showing a Rise in Systolic Pressure of									
		<5	5–	10–	15–	20–	25–	30–	35–	40–44	
110–119	7	2	0	0	0	2	1	0	0	0	2
120–129	5	1	1	1	0	0	0	2	0	0	0
130–139	1	1	0	0	0	0	0	0	0	0	0

TABLE V

Rise in Systolic Pressure		Diastolic Pressure (mm. Hg)			
		<90	90–98	100–108	110+
10 mm.	..	13.9%	66.1%	90.5%	61.5%
20 "	..	3.5%	20.3%	52.4%	53.8%

was under deep narcosis with tribromethanol, showed no change.

It has been contended that, in some patients at least, any rise in systemic blood-pressure might well be due to an alteration in circulating blood volume as a result of uterine contraction and retraction. This argument may be ignored, since a great many cases showed no difference in pressure between the readings before and after ergometrine. In order to exclude this contention completely the administration of ergometrine to 22 women was delayed for some time after delivery and the changes in pressure were noted. These readings together with the duration of the delivery–ergometrine interval are given in Table VI. One patient with severe mitral stenosis and five patients with severe hypertension, oedema, and albuminuria received no ergometrine. All six maintained an unchanging level of systemic blood-pressure throughout operation.

TABLE VI

Pre-operative B.P.	B.P. at Delivery	B.P. at Time of I.V.I.	Alteration in B.P.	Delivery–I.V.I. Interval	Rise After I.V.I.
90/60	100/66	100/66	0/0	5 mins.	4/2
100/65	140/100	140/100	0/0	3 "	0/0
100/65	150/104	146/104	–4/0	7 "	0/0
115/70	142/98	142/98	0/0	5 "	0/0
120/70	146/86	140/84	–6/–2	6 "	0/4
120/80	150/104	146/104	–4/0	3 "	6/4
120/80	140/96	140/96	0/0	6 "	0/0
120/84	164/120	164/120	0/0	3 "	0/0
120/84	144/108	142/108	–2/0	3 "	4/8
120/85	132/94	134/94	+2/0	3 "	4/4
122/92	108/84	112/86	+4/+2	5 "	6/0
124/76	144/90	144/92	0/+2	3 "	0/2
126/90	126/90	130/90	+4/0	3 "	10/8
130/80	120/76	120/80	0/+4	3 "	10/4
130/85	140/92	140/94	0/+2	5 "	10/4
130/90	120/86	120/88	0/+2	3 "	0/2
140/90	132/90	130/90	–2/0	3 "	10/10
140/96	164/108	164/110	0/+2	6 "	16/6
140/100	148/96	148/98	0/+2	5 "	18/10
140/100	140/100	149/100	0/0	3 "	30/22
144/116	184/132	186/134	+2/+2	3 "	0/0
156/90	140/84	142/84	+2/0	6 "	10/4

Comment

That ergometrine is a drug capable of producing vasoconstriction is a fact supported by experimental evidence (Savini, 1956) and clinical experience (Dieckmann *et al.*, 1960; Schade, 1961; Forman and Sullivan, 1952; Hamilton *et al.*, 1952; McGinty, 1956).

Schade (1951) observed the changes in blood-pressure in 200 patients delivered vaginally, but the results of the investigation and his conclusions are of limited value, since 74% of the women were given spinal analgesia and 25% were anaesthetized with nitrous oxide, oxygen, and ether. Moreover, the dose of ergometrine maleate injected (0.2 mg.) was less than half the standard intravenous dose employed by many units in this country.

Hamilton *et al.* (1952), in a comparative study of naturally occurring and synthetic oxytocic agents, reported that in 166 patients who received 0.2 mg. of ergometrine intravenously a significant hypertensive response was obtained in 12–15%. None of the patients in this series had evidence of toxæmia of pregnancy and all were delivered under general anaesthesia, some with nitrous oxide and oxygen, others with nitrous oxide, oxygen, and ether. The differences in anaesthetic technique introduce an undesirable variant, but the authors concluded that "elevations in blood-pressure resulting from the use of ergonovine [ergometrine] . . . in the third stage of labour can be effectively reduced by the judicious use of premedication and anaesthesia."

Another large and more recent study is that of McGinty (1956). Of 200 patients who received oxytocic drugs as part of the management of the third stage of labour, 50 were given 0.2 mg. of ergometrine intravenously, and of this later number 10 out of 38 normotensive and 4 out of 12 hypertensive patients had a significant rise in systolic pressure. As in the two series quoted above, 20 mm. Hg was considered to be a significant elevation. It is worthy of note that in McGinty's series all patients had vaginal deliveries under pudendal block analgesia, and since the elevation in systolic pressure in the non-toxaemic cases was of a transient nature one might assume that the 1:100,000 adrenaline in the analgesic solution employed had an undesirable influence on the vascular bed, so tending to invalidate the results of an otherwise well-conducted clinical study.

One of the most striking features of the present study is the fact that a high percentage of women with hypertensive toxæmia of pregnancy will respond to the intravenous injection of 0.5 mg. of ergometrine by producing a significant elevation in systemic blood-pressure. That there is in toxæmia of pregnancy an abnormal sensitivity of the vasoconstrictor mechanism has been shown by de Valera and Kellar (1938), Mukherjee (1941), and Dieckmann (1941). These authors found that in pre-eclampsia, as compared with normal pregnancy, a marked response to intravenous injection of a standard dose of a pressor substance is produced. Browne (1946) had the opportunity of noting the difference in pressor response to "tonephin" 0.66 ml. intravenously in two patients who developed pre-eclamptic toxæmia in late pregnancy, and found that after developing toxæmia these women, previously normal, had an abnormal increase in sensitivity of the vascular bed.

It would appear from Table I that the well-integrated vasomotor mechanism of the normal parturient woman is relatively unresponsive to the pressor activity of ergometrine, while the vascular bed of the toxæmic patient reacts by constriction. This is in keeping with the findings of the authors quoted above in respect of other vasopressor agents and suggests that the constrictor response in pre-eclamptic toxæmia is a synergistic one. It is recognized by pharmacologists that the alkaloids of ergot, in very small doses, sensitize the vascular bed to the action of adrenaline, and Jang (1942) reported that other adrenergic blocking agents act in a similar manner. These findings have been endorsed clinically by the work of Casady *et al.* (1960) on post-partum hypertension after the combined use of a sympathomimetic agent and an oxytocic drug. Evidence was brought forward by this team to show that ergometrine, administered to patients who had been delivered under caudal block analgesia and to whom methoxamine had been given to counteract any fall in blood-pressure, combined with the latter drug to produce hypertension, sometimes severe.

The intravenous injection of ergometrine in three patients with severe pre-eclamptic toxæmia coincided with the development of a sudden drop in pressure by 20, 30, and 50 mm. Hg respectively. To one woman only, methoxamine was administered with a satisfactory response. In the other two the drop did not give rise to anxiety, and in these severely toxæmic patients the dangers associated with administration of a vasopressor agent seemed to outweigh the advantages. The reason for the relative hypotension is open to argument, the depolarizing muscle relaxant employed throughout the series is known to affect cardiac rate and rhythm

(Bullough, 1959). Sinus bradycardia, depression of the excitation and conduction of cardiac impulses, and even complete arrest may be produced by suxamethonium (Lupprian and Churchill-Davidson, 1960). The size of the incremental dose of suxamethonium and not the frequency of administration seems to be the important factor. Six out of seven patients who developed ventricular standstill in the report by Lupprian and Churchill-Davidson did so after a repeated dose of at least 50 mg., twice the magnitude of the increments employed in this investigation.

Women who suffer from chronic hypertension, but who are free from the clinical features of pre-eclampsia, appear to react little to intravenous ergometrine. Seven of the patients investigated bore an antenatal diagnosis of chronic hypertension and in none was the response significant. Furthermore, one woman with hypertension of chronic nephritis retained her pre-ergometrine level of blood-pressure. This finding can be associated with the fact that the systemic blood-pressures of toxæmic patients and of women with hypertensive cardiovascular disease differ in spontaneous behaviour. Wërko and Brody (1953) found that the blood-pressure in hypertensive cardiovascular disease did not share the spontaneous diurnal variability of the blood-pressure in pre-eclampsia. Hammarström (1947) had shown that the absence of variability of the blood-pressure in hypertensive cardiovascular disease was also characteristic of chronic nephritis.

Practical Implications

From time to time there appear in the literature reports of post-partum eclamptic convulsions, sometimes in patients who had no evidence of toxæmia before delivery (Stander *et al.*, 1946; Schade, 1951; Hamilton, 1953; McFadyen, 1960). The fact that ergometrine is capable of eliciting an elevation of blood-pressure of up to 46 mm. Hg in this series cannot be ignored, and is undoubtedly a serious threat to the patient with severe pre-eclampsia. It would be interesting to compare the results of a similarly conducted investigation in patients who received only 0.125 mg. of ergometrine, the oxytocic dose advised for intravenous use by several standard textbooks of pharmacology.

Casady *et al.* (1960) have given fresh emphasis to the risk of subarachnoid and cerebral haemorrhage in hypertensive women and cite nine cases of post-partum hypertension with cerebral haemorrhage following a vasopressor agent, an oxytocic drug, or a combination of the two.

It is clear, therefore, that the post-partum period is one of great practical importance to the hypertensive patient, especially to the woman to whom ergometrine has been administered. Great care should be taken in the accurate and frequent charting of the systemic blood-pressure and attention must be paid to the patient's symptoms, especially headache. Despite the fact that chlorpromazine has proved to be a valuable compound in the control of the hypertension and convulsions of eclamptic patients, it does not appear to enjoy the popularity it might have in the reduction of severe post-partum hypertension, morphine tending to be the drug of first choice in many obstetric units. A satisfactory method of treatment is the intravenous injection of chlorpromazine 12.5 mg., diluted to 10 ml. in saline and injected slowly over the course of two minutes, the decline in pressure being observed on the other arm by an assistant. In recent years it has been

the practice to return patients from the operating suite to a cool bed in order to avoid peripheral vasodilatation and consequent hypotension. We have found that a little warmth is a useful adjunct to the treatment of hypertension post-operatively.

Much attention is given, and rightly so, to urinary output in the post-partum period, especially in patients who present with an accidental haemorrhage. One is led to wonder how great or significant an effect the administration of ergometrine exerts on the renal blood-vessels of such patients. Byrom and Pratt (1952) state that "as long as the causation of renal cortical necrosis in pregnancy remains obscure, all vasoconstrictors . . . must be suspect."

The choice of anaesthesia exerts considerable influence on the pressor response to ergometrine. One severely toxæmic patient who was delivered of twins and was deeply sedated with tribromethanol showed no elevation of pressure following ergometrine. A study being conducted in this department at the moment shows that the hypertensive response to ergometrine in pre-eclamptic women is modified greatly by ether or halothane anaesthesia.

Summary

A study was made of 266 pregnant patients requiring general anaesthesia for caesarean section or instrumental delivery who were given 0.5 mg. of ergometrine maleate intravenously as an oxytocic following delivery of the child.

A marked rise in both systolic and diastolic pressures exceeding in many cases 20 mm. Hg was noted in patients suffering from hypertensive toxæmia.

No significant vasopressor response was elicited by ergometrine in normotensive patients. Similarly, patients with chronic hypertension showed little or no response.

Attention is drawn to the possible dangers of this effect of ergometrine under modern conditions, where little use is made of depressant anaesthetics which tend to counteract this response.

The intense interest of my obstetric colleagues in this investigation has been a constant encouragement. I am particularly grateful to Dr. A. D. Telford Govan, Director of Research, Glasgow Royal Maternity Hospital, for helpful discussion and criticism of this paper.

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EFFECT OF PENICILLAMINE ON CYSTINURIA

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The diagnosis of cystinuria in this report refers to the classical condition of cystinuria with recurrent urinary calculus formation, now known to be characterized by the urinary excretion of abnormal quantities of cystine, lysine, arginine, and ornithine.

The loss of these amino-acids does not produce any known harmful effects. The only clinical features arise from the recurrent formation of stones in the renal tract, the main cause of this feature being the high excretion and urinary concentration of the insoluble disulphide amino-acid cystine.

Disulphides undergo exchange reactions with thiols and with other disulphides, and these reactions may be simply represented by the equations: $R-S-S-R + 2 R_1-S-H \rightleftharpoons 2 R-S-S-R_1$ and $R-S-S-R + R_1-S-S-R \rightleftharpoons 2 R-S-S-R_1$. The active molecular species are the ions $R-S^-$ and R_1-S^- (Kolthoff *et al.*, 1955; Ryle and Sanger, 1955; Pihl *et al.*, 1958).

The mixed disulphides $R-S-S-R_1$ have different properties from the corresponding symmetrical disulphides $R-S-S-R$ and $R_1-S-S-R_1$.

This reaction offered a possible means of converting cystine into a more soluble derivative by an exchange reaction, if a suitable thiol or disulphide could be administered. Preliminary experiments showed that the cystine which readily crystallized from the urine of cystinurics could not be crystallized from the same urines at pH 7.2 after the addition of D(-)penicillamine (D(-)-β-β₁-dimethylcysteine) *in vitro*. This report shows the effect of oral administration of D(-)penicillamine on the urine cystine excretion in two patients with cystinuria.

Case 1

The first investigation was carried out on a man aged 37 who had suffered from recurrent cystine calculi over 15 years. At the time of investigation several small calculi were situated in the left renal pelvis and there was a mild low-grade urinary infection with *Pseudomonas pyocyanea* and *Escherichia coli*. The blood-pressure was normal and there was no evidence of impairment of renal function.

The urine was collected and acidified to pH 2 with concentrated hydrochloric acid immediately. The gross urine cystine excretion was estimated by weighing the cystine isolated from a 500-ml. aliquot of each 24-hour urine collection. Isotope dilution analysis performed on 7 of the 14 urine specimens collected confirmed the results of this finding.

D(-)penicillamine (1.05 g. six-hourly) was administered orally for four days and showed a marked reduction or disappearance of cystine from the urine. The result is shown