TREATMENT OF CARDIAC SHOCK BY METARAMINOL

BY

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An 80% mortality has been reported in shock following acute cardiac infarction (Hellerstein *et al.*, 1952; Griffith *et al.*, 1954). However, this figure is probably an underestimate, as it is based on hospital experience alone. The early use of pressors has been advocated by Griffith *et al.* (1954): in a series of cases treated for shock within three hours of its onset only 13% died. Noradrenaline infusions have reduced the overall mortality to between 40% and 50% (Moyer *et al.*, 1953; Sampson and Zipser, 1954; Garai and Smith, 1958).

However satisfactory noradrenaline may be in hospital practice, the use of a drip in a patient's home presents many difficulties, and this drug is rarely used in domiciliary treatment of shock. This complication may therefore persist for several hours, with a consequently poorer prognosis, before the patient reaches hospital. Moreover, in some cases the shock is too severe to allow removal to hospital. The immediate requirement for such patients is a drug similar to noradrenaline, yet possible to administer by intravenous, intramuscular, or subcutaneous injections. Such a substance might be used either for continued therapy at home or to counter shock temporarily to allow transfer to a hospital.

Noradrenaline has been shown to increase the contractile force of the heart, increase coronary flow, and raise the peripheral vascular resistance without inducing arrhythmias or tachycardia (Burn and Hutcheon, 1949; Gazes *et al.*, 1953; Denison *et al.*, 1956). Other pressors such as phenylephrine work by a purely peripheral action on the systemic resistance and have been found less effective in the treatment of cardiac shock. This difference is attributed to the direct myocardial action of noradrenaline (Gazes *et al.*, 1953).

Mephentermine sulphate has been used successfully in the treatment of cardiac shock by Brofman *et al.* (1952), Hellerstein *et al.* (1952), and Garai and Smith (1958). This drug may be given by injection or by drip, and causes a rise in systemic pressure and an increased coronary blood flow. Recent experimental studies in dogs have shown that the pressor effects of mephentermine are due to its central action rather than to peripheral vasoconstriction (Welch *et al.*, 1958). Clinically the only drawback to this drug is the occasional development of tachyphylaxis: an increasing refractoriness to repeated injections necessitating larger doses of mephentermine in order to achieve a satisfactory pressor response.

Metaraminol bitartrate ("aramine"; laevo-1 (hydroxyphenyl) - 2 - amino - 1 - propanol hydrogen d-tartrate) seems to possess the properties of direct action on the heart as well as on the peripheral resistance. It may be administered by repeated injections without the development of tachyphylaxis. In experimental cardiac ischaemia Sarnoff *et al.* (1954) produced a fall of arterial pressure, of cardiac output, and of ventricular stroke work, with a rise of left atrial pressure. Subsequent intravenous metaraminol returned these values to near normal levels and increased coronary

flow. This and other experiments indicated that metaraminol produced a sustained increase of myocardial contractility without requiring increased coronary flow per unit of ventricular work. This central action, together with the peripheral effects, achieve the most desirable results—namely, increased arterial pressure and cardiac output at a low atrial pressure. No arrhythmias or tachycardia were observed.

In hypotensive human subjects metaraminol caused an increased renal and cerebral blood flow (Moyer and Morris, 1954; Moyer *et al.*, 1954). In the United States this drug has been used for the treatment of shock in a variety of conditions, both medical and surgical, and also for maintaining blood pressure during spinal anaesthesia (Poe, 1954; Weil, 1955; Moyer and Beazley, 1955). Stechel *et al.* (1956) included 16 cases of cardiac shock in a series of 250 patients with varied types of shock treated by metaraminol infusions. Only 5 of these 16 patients survived. However, no report has yet appeared on the use of this drug by intermittent injection in cardiac shock.

Indications.—Some hypotension is common in cardiac infarction, but "shock," justifying therapy, was regarded as present only when the systolic pressure fell to 85 mm. Hg. Less severe hypotension reduces the work of the heart, and attempts to restore the pressure to normal levels may impose an excessive load on the damaged myocardium. For this reason it has been our practice to initiate pressor therapy only when the systolic pressure has fallen to 85 mm. Hg or less. Furthermore, when using pressors we have tried to avoid raising the systolic pressure higher than 110 mm. Hg.

Treatment

Twelve patients have been treated with metaraminol by intermittent injection. Five of them also received other pressors: mephentermine in four, noradrenaline infusions in two. Details of these cases are shown in Table I.

The initial intravenous dose of metaraminol should not exceed 1.25 mg. Often this proves inadequate and may need to be repeated. 2.5 mg. may be given by intramuscular or subcutaneous routes and subsequent doses determined by the pressor response. However, we have never used more than 5 mg. in one injection. The pressor effects of intravenous metaraminol appear within three minutes and persist for 10 to 30 minutes. The response to intramuscular injection occurs within 10 to 20 minutes and lasts one to three hours, whereas the pressor action appears 30 to 45 minutes after subcutaneous injection and persists for two to four hours. In severe shock absorption from subcutaneous injections is poor, and intramuscular injections were used after the initial one or more intravenous injections.

Mephentermine was used first in four patients. In two cases an immediate pressor response occurred, but subsequent injections proved ineffective. Thereafter noradrenaline and metaraminol were used in one and metaraminol alone in the second case: in both a pressor response was obtained, but both patients died later. The other two patients showed no pressor response to intramuscular mephentermine: intramuscular metaraminol was then used with success and eventual recovery.

Noradrenaline infusions were used only twice. In one case it was employed after mephentermine had

proved ineffective and the pressure was maintained for 40 hours (Case 1, Table II). During the period of pressor response intermittent intravenous metaraminol was substituted for the noradrenaline, a total of 1.3 mg. being required over a period of 45 minutes to maintain the pressure at the same level as that obtained with noradrenaline, 20–24 µg./minute. In the other patient profound shock was present, refractory to both noradrenaline and metaraminol. Metaraminol was used alone in the remaining seven patients, three of whom died.

Results of Metaraminol Therapy (Table II)

Six Fatal Cases.—Case I was treated with noradrenaline; metaraminol was used over 45 minutes to demonstrate that it could substitute an equally effective pressor action. In three of the remaining five fatal cases shock was present before admission to hospital and had lasted four hours or longer. The other two patients were treated within half an hour of the onset of shock, which occurred in hospital. In Cases 3 and 4 the blood pressure was sustained until death. Two other patients (Cases 2 and 6) exhibited initial pressor responses but died in a state of terminal irreversible hypotension. Only one patient (Case 5) was absolutely refractory to treatment from the onset of shock. All these five deaths occurred within six hours of the onset of shock. Acute left ventricular failure was present at some stage in four cases and

congestive heart failure had appeared in three of them. All were promptly digitalized with lanatoside C. Arrhythmias were present in two: atrial fibrillation and atrial flutter. The ventricular rates were controlled by lanatoside C. Permission for necropsy was obtained in only one case (No. 4): widespread infarction was found involving the left ventricle and the entire septum.

Six Survivors.—All the surviving cases developed shock after admission to hospital and were therefore treated within 15 to 30 minutes of the onset. With one exception pressor therapy had to be maintained for a minimum of 12 hours: three required metaraminol for 24 to 36 hours, and one for nearly six days. The average hourly dose of metaraminol was found to be 1.3 mg. in three cases and 0.3–0.9 mg. in the remaining cases. Congestive failure was present in three of these survivors, atrial fibrillation occurred in one, and transient complete heart-block in another.

Discussion

When cardiac shock is due to extensive infarction, pressor therapy is bound to be useless. However, treatment has reduced the mortality of this complication to 50%. The value of immediate therapy has already been noted by Griffith *et al.* (1954), and in the present small series there was a 25% mortality in those cases treated promptly as opposed to a 100% mortality in the four with shock of some hours' duration before treatment. Once pressors are given, some encouragement

TABLE I.—Clinical Features of 12 Patients (not numbered chronologically)

No.	Sex	Age	Duration of Previous Angina Pectoris	Site of Present Infarction	Onset of Shock after Infarction	Arrhythmia	Failure	Previous B.P.	B.P. at Start of Treatment	B.P. after Recovery	Duration of Shock before Death	Result
1	M	64	2 years	Ant.	4 hours	0	0	140/70	75/45		3 days	Died
2	M	49	2 "	Ant.-sept.	Immediate	0	+	180/110	60/40		6 hours	"
3	M	54	2 "	Post.	7 hours	A. fib.	+	120/80	85/50		1 hour	"
4	F	73	None	Post.	Immediate	0	+	Unknown	85/60		6 hours	"
5	M	60	5 years	Ant.-sept.	11 hours	0	0	170/85	Unobtainable		2 "	"
6	M	48	4 "	Post.	Immediate	A. flutter L.B.B.B.	+	190/110	70/50		6 "	"
7	M	58	5 "	Ant.	12 hours	R.B.B.B.	+	150/90	80/55	125/85		Survived
8	M	56	None	"	18 "	0	0	Unknown	75/55	90/60		"
9	F	63	1 year	"	2 days	0	+	140/100	85/60	110/80		"
10	F	58	None	Post.	12 hours	C.H.B.	+	Unknown	70/40	170/95		"
11	F	76	7 years	Ant.	3 days	A. fib.	0	295/135	80/60	140/90		"
12	M	60	4 months	Post.-lat.	24 hours	0	0	Unknown	80/55	140/80		"

TABLE II.—Details of Pressor Therapy

No.	Duration of Shock before Treatment (Hours)	B.P. at Time of Treatment	Average Maintained B.P.	Mephentermine		Noradrenaline		Metaraminol		Duration of Pressor Therapy (Hours)	B.P. Immediately before Death	B.P. 24 Hours after Stopping Treatment	Average Dose of Metaraminol Required (mg/hr.)
				Dosage mg.	Duration of Response		Duration of Response	Dosage mg.	Duration of Response				
1	4	75/45	105/60	15 I.V. 15 I.V. 15 I.M.	1 hour None	+	40 hours	1.3 I.V. in 45 mins.	48 mins.	48	Unobtainable for 5 hours 60/40		2.0
2	4+	60/40	80/55					5 I.M. 2.5 S.C.	2½ hrs.	2½			3.0
3	½	85/50	100/70					2.5 S.C.	1 hour	1	100/70		2.5
4	6+	85/60	100/80					2.5 I.M.	4 hrs.	4	100/80		0.6
5	½	Unobtainable				+	None	7.5 I.M.	None	2	Unobtainable 65/40		
6	4	60/40	70/40	75 in ½ hr.	½ hr.			2.5 I.M.	½ hr.	2			5.0
7	½	80/55	90/60					182.5 I.V., I.M. (56 doses)	137 hrs.			100/70	1.3
8	½	70/55	95/65					10 I.M.	3 hrs.			110/70	1.4
9	½	85/60	105/70					22.5 I.M.	20 "			100/70	0.6
10	½	70/40	110/70	30 I.M.	None			7.5 I.M.	26 "				
11	½	80/60	100/75					7.5 S.C.				115/70	1.3
12	½	80/55	90/60	15 I.M.	None			5 I.V. 20 I.M. 12.5 S.C.	30 "				
								0.5 I.V. 2 I.M.	24 "			140/100	0.3
								5 S.C. 12.5 I.M.	14 "			100/70	0.9

can be felt if the blood pressure is sustained for longer than four hours. Only one death in this series followed a prolonged pressor response.

Intermittent injection of metaraminol has proved successful in maintaining the blood pressure for several days if necessary. Unnecessarily frequent injections of small doses were used initially in order to avoid the hazard of a severe pressor response. With more experience, fewer doses of larger amounts have been used. The frequency of injection has been determined by repeated blood-pressure estimations at 10- or 15-minute intervals, metaraminol being given whenever the systolic pressure fell to 85 mm. Hg or less.

No tachyphylaxis has occurred with this drug as was met with in two patients receiving mephentermine.

In a further two cases metaraminol proved effective when mephentermine had failed to raise the pressure. This study was not intended as a comparison of the pressor effects of these two drugs, but solely to assess the value of metaraminol. No doubt the use of increasingly large doses of mephentermine would have achieved a pressor response in these patients. However, the repeated efficiency of identical doses of metaraminol has proved of great value.

It would appear that metaraminol is the drug of choice for intermittent parenteral use in cardiac shock and should therefore be of particular benefit in the domiciliary treatment of this condition.

Coincident heart failure or arrhythmias should be treated immediately: four of the survivors had suffered from one or more of these additional complications.

No undesirable side-effects have accompanied the use of metaraminol.

Summary

Results are presented of the use of metaraminol in 12 patients suffering from cardiac shock. This drug has a similar action to that of noradrenaline but has the advantage that it may be given by subcutaneous, intramuscular, or intravenous injection. For this reason it should prove of value in the domiciliary treatment of cardiac shock.

The 50% mortality in this series included all the patients with shock of four or more hours' duration. This observation is in accord with the experience of others, and demonstrates the need for early treatment of this complication of cardiac infarction.

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A COMPARISON OF THE RESPONSES OF 100 INFANTS TO PRIMARY POLIO-MYELITIS IMMUNIZATION WITH TWO AND WITH THREE DOSES OF VACCINE

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In previous investigations (Perkins, Yetts, and Gaisford, 1958, 1959) it was shown that in only a small proportion of infants under the age of 10 weeks could a satisfactory basal immunity be established by the injection of two doses of poliomyelitis vaccine. This was evident not only from the responses to primary immunization but also from those obtained when a booster dose was given 10 to 12 months later. It was concluded that two factors were responsible for the poor responses—namely, the inhibiting effect of maternally transmitted antibody and the necessity for highly potent antigens in early infancy. In view of these findings, two further studies were made. The first, with 1-week-old infants, was designed to determine whether the inhibiting action of maternal antibody could be overcome by increasing the number and size of the doses. The second study, with 16-week-old infants, was made in order to determine whether infants of this age had reached a stage at which their immunological activity would overcome the inhibiting effect of passively acquired antibodies and also to investigate whether a more substantial basal immunity could be established by three doses than by two. By analogy with pertussis and diphtheria immunization in infants it might be expected that poliomyelitis would require a similar course, and that, if the vaccine was comparable in antigenicity to pertussis vaccine and diphtheria toxoid, results might be similar.

Procedures

One-week-old Infants.—In this group there were 45 infants, of whom 36 received three doses and 9 received only two. The vaccine was given at intervals of four weeks, and all infants were 1 week old at the time they received the first injection. Each dose was 2 ml., which was double the normal, and was given by injecting 1 ml.