Attention is drawn to the need to inquire carefully for signs of previous allergy before penicillin is prescribed.

My thanks are due to Dr. J. McGregor Robertson, consultant venereologist, Western Regional Hospital Board, for permission to publish this case and for helpful criticism, and to Dr. A. L. K. Rankine, physician-superintendent, Belvidere Infectious Diseases Hospital, Glasgow, for reading the manuscript. I would also like to thank Dr. W. A. J. Crane, of the pathology department, Glasgow Royal Infirmary, for carrying out the post-mortem examination.

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COMPARISON OF VASOACTIVE DRUGS IN MAN

BY

P. R. BROMAGE, M.B., B.S., D.A.

*Consultant Anaesthetist, Chichester and Portsmouth
Hospital Groups*

The assessment of vasopressor drugs is commonly carried out in experimental animals under controlled conditions. Clinical trials follow, and if these are satisfactory the drug under investigation is added to the list of those already in use, and its properties are defined in terms of the results obtained by animal and human experiment. But, while the experiments in animals are fully controlled, those in the human involve many variables, and results in the latter tend to be coloured by findings in the former, regardless of the possibility of species differences.

In human trials it is desirable, therefore, to eliminate as many variables as possible, and at some stage in the investigation to try to reproduce the clinical conditions under which the drugs are most likely to find their greatest therapeutic application. Since individuals differ widely in their response to pressor drugs, this will involve comparing both of the drugs under trial in the same subject, unless very large numbers are concerned, as in a study by Dripps and Deming (1946) in which 2,500 patients were used to compare the effects of four drugs.

Under normal conditions homeostatic vascular reflexes are at work which diminish the effects of injected pressor drugs, making it necessary to use relatively large doses in order to obtain a small response (Moe, 1948). Taylor and Page (1951) have shown that powerful components of these compensatory reflexes arise from chemoreceptors in the brain and have their efferent pathway in the sympathetic outflow.

In the experimental animal, stable conditions are efficiently obtained by destructive procedures on the central nervous system which eliminate vasosensory reflexes. Crimson and Tainter (1939) compared the effects of several pressor drugs in cats, in the normal state and in decerebrate shock, and found greatly augmented pressor responses after destruction of the central vasomotor

mechanisms. Page and Taylor (1950) showed that a similar augmentation of vasoactive substances occurred after ganglionic blockade with tetraethylammonium chloride (T.E.A.C.), an effect which was intensified when elimination of T.E.A.C. was prevented by preliminary nephrectomy. The same authors found that pre-ganglionic denervation between the sixth cervical and sixth thoracic segments produced the greatest pressor augmentation by local neural destruction.

In man temporary chemical interference with the compensatory vasomotor mechanisms can be obtained either by blocking the sympathetic outflow at the ganglion synapses, with drugs of the methonium group, or by the application of local analgesic to the appropriate sympathetic nerves. The methonium drugs are simple to administer but variable and evanescent in their effects, and are therefore unsuitable for providing a constant base-line of vascular hypotension against which the pressor effects of the test drugs can be measured. Of the nerve-blocking techniques available, subarachnoid and extradural spinal block are the most practical for routine use. Subarachnoid spinal block has a higher morbidity rate and a shorter duration of action than extradural block when administered by the single-dose method, and so the latter was preferred as providing the desired experimental conditions.

In this study conditions provided by depressed vaso-sensory reflexes have been illustrated by a comparison of the pressor effects of the two optical isomers of methyl amphetamine. The dextrorotatory (D-) form of methyl amphetamine is known as "methedrine" in English-speaking countries and as "pervitin" in Germany, and it is used extensively as a vascular and cerebral stimulant. The laevorotatory (L-) isomer is inferior to the D-isomer as a cerebral stimulant in animals and man (Hauschild, 1938), but little work has been done on the vasopressor properties of the L-isomer in man.

Method

Measurements were carried out on patients during routine surgical operations in which some degree of controlled vascular hypotension was thought desirable. No departure was made from the anaesthetic technique which would have been chosen irrespective of the investigation, and there was no question of treatment becoming subordinate to experiment.

High lumbar extradural spinal block was employed as part of the anaesthetic technique for 15 patients undergoing major abdominal or lower-limb surgery. A solution containing 1:600 "percarine" and 1.6% procaine was used, and injection made in any convenient space between the spines of the twelfth thoracic and third lumbar vertebrae. Dosage varied between 25 ml. and 45 ml., according to the height and age of the patient. Analgesia was carried to the upper thoracic segments so that the greater part of the sympathetic outflow was blocked, and the blood pressure fell to the region of 60 mm. Hg for a period of up to four hours (Bromage, 1951, 1952a). Alterations of blood volume were minimal, the total operative blood loss, estimated gravimetrically by weighing swabs, never exceeding 250 ml. in any one case. General anaesthesia was maintained with intermittent injections of thiopentone and inhalation of a mixture of one part oxygen and two parts nitrous oxide from a semi-open machine.

The limited time factor of a routine surgical operation made it impracticable to compare two pressor drugs of doubtful tolerance potentialities with a third drug, such as adrenaline, which is known to produce no tolerance effects on repeated injection (Chen, 1928). But errors due to tachyphylaxis were minimized by using small quantities

of drugs (Wislicki, 1949), and further control was obtained by alternating the order of administration of the isomers in successive subjects (Barger and Dale, 1910). Thirty milligrams of methyl amphetamine were dissolved in 10 ml. of distilled water, and intravenous doses of 6 mg. were employed after the blood pressure had become stabilized at a low level. Intervals of 30 minutes between injections allowed time for the blood pressure to rise and return to its base-line before administering the succeeding injection. In some cases the blood pressure did not return to its previous low level, but showed a slight increase following each injection of methyl amphetamine, the systolic base-line developing an upward drift. This may have been due to a cumulative action of the drug, or possibly to a retrogression of the epidural block, causing a progressive return of sympathetic innervation. For the purposes of this investigation errors due to drift of the blood pressure from an ideal horizontal base-line were ignored, because the slope of the drift was small (less than 15 degrees) compared with the slope of pressor response to injected methyl amphetamine (greater than 75 degrees), see Chart.

Blood pressure chart of man, aged 69, undergoing partial gastrectomy. General anaesthesia. Extradural block to T 2. $\alpha=84^\circ$. $\beta=79^\circ$. The angle of drift of the base-line (α) is small compared with the angle of response to D-methyl amphetamine (β).

Results

Pressor responses to D-methyl amphetamine were found to be between nearly 3 and 15 times greater in the anaesthetized patient subjected to high spinal blockade than in the conscious normotensive subject (see Table).

Comparison of Systolic-blood-pressure Responses to D-methyl Amphetamine in Normal and Hypotensive States

Case No.	Age	Conscious Normotensive			Anaesthetized Hypotensive			Normal/Hypotensive Ratio
		Resting B.P.	B.P. Awake 2-5 min. after 6 mg. Meth.	Systolic Response (mm. Hg. per 1 mg.)	Hypotensive	B.P. 5 min. after 6 mg. Meth.	Systolic Response (mm. Hg. per 1 mg.)	
1	65	135/65	142/70	1.16	92/55	130/80	6.3	5.4
2	70	145/95	150/95	0.83	50/30	110/80	10.0	12
3	67	125/80	130/80	0.83	55/40	122/75	10.1	13
4	40	140/80	152/85	2.0	55/35	100/65	7.5	3.75
5	60	155/80	162/80	1.16	58/40	95/70	6.16	5.3
6	65	140/70	152/80	2.0	35/?	120/?	14.16	7
7	75	160/80	162/80	0.33	55/?	85/?	5.0	15
8	70	168/80	172/80	0.66	68/40	90/65	3.6	5.5
9	61	140/90	152/90	2.0	55/25	90/55	5.8	2.9
10	38	165/85	178/90	2.16	68/40	138/80	11.6	5.4
11	31	142/80	152/85	1.66	80/?	110/70	5.0	3.0
12	65	108/80	115/70	1.16	70/50	105/75	5.8	5.0
13	69	130/60	140/65	1.66	50/25	110/50	10.0	6.0
14	48	140/85	152/85	2.0	82/50	132/80	8.3	4.1
15	49	150/95	160/95	1.66	65/35	100/55	5.8	3.5

The pressor effects of dextrorotatory and laevorotatory isomers of methyl amphetamine were compared in 15 hypotensive subjects, and a total of 50 observations made—that is, 25 observations for each drug. The following results

were obtained. *Intensity of Effect*: The L-isomer of methyl amphetamine is considerably less powerful than the D-form, the ratio of intensity being 1:2. *Duration of Effect*: The L- to D-ratio of their 50%-duration-times was 1:1.5. The absolute duration of effect of a small intravenous dose of D-methyl amphetamine under the conditions employed was of the order of 20–25 minutes.

Adrenaline.—The responses to L-adrenaline in the normal and in the hypotensive state were also compared in a small series. Single intravenous injections of 3–4 μ g. produced either no change or a slight fall of blood pressure in the normal subject. In the hypotensive state under general anaesthesia a similar quantity produced a transient rise of 15–20 mm. Hg systolic pressure.

Discussion

The vasopressor drugs are most rationally employed in states in which vasomotor tone is defective, and so it is reasonable to assess their therapeutic merits under similar conditions. These conditions are found in patients subjected to sympathetic blockade for the purpose of controlled vascular hypotension in surgery. Under such circumstances most of the efferent pathways for homeostatic vasodepressor reflexes are blocked, and a pure peripheral pressor effect is obtained in response to injected pressor amines. Thus small quantities of drugs produce easily measurable effects, and any tendency to develop tolerance is avoided.

At some point in any investigation a conflict is apt to arise between the interests of the patient and the demands of the experiment. It is felt that the technique outlined above resolves this conflict with the least interference to the patient. There is no need for a separate control series, since each patient is his own control, and the results are experimentally acceptable in a small series.

The considerable variation in degree of individual sensitization to pressor drugs in the unconscious hypotensive state, ranging from nearly thrice to fifteen times the normotensive response, may be referable to intrinsic factors of the individual response, or to the degree of anaesthetic interference with compensatory vascular reflexes, such as variations in the height of spinal block or depth of general anaesthesia. The first possibility is the most likely, since normal responses to a given dose of pressor drug vary widely from person to person. Furthermore, the upper limit of extradural block varied only between T 3 and C 8 in this series, and there seemed to be little correlation between either the initial level of hypotension or the percentage fall of blood pressure and the subsequent degree of augmentation of pressor response. However, the individual variability of augmentation is of no consequence in the comparison of two pressor drugs, since both drugs can be compared with fair accuracy in the same patient, and it is unnecessary to assess the drugs separately in two groups of patients. Indeed, if the latter were necessary the groups would have to be very large in order to reduce the statistical dispersion arising from individual variation within the groups.

The desirability of using controlled hypotensive techniques at all may be questioned. This subject is too involved to be discussed fully here, but certain remarks are relevant. The apparent harmlessness of these techniques, when used with the proper precautions and within certain limits, suggests that their use in the anaesthetized patient may not be so undesirable as would appear from experimental work on conscious hypertensive patients subjected to acute reductions of blood pressure. Kety and his fellow workers (1950), investigating cerebral blood flow in 17 conscious hypertensives, found that a 26% reduction of mean arterial pressure was accompanied by a 12% reduction of cerebral blood flow as measured by the nitrous oxide method, while cerebral oxygen consumption remained unaltered. In other words, demand exceeded supply, and the resulting cerebral oxygen deficiency was enough to cause anoxic symptoms of nausea

and vomiting in a proportion of the subjects. However, in the anaesthetized patient the situation is different. Schmidt (1950) and Wechsler *et al.* (1951) have shown that under light thiopentone narcosis cerebral metabolism is reduced by almost 40%, so that the relatively slight reduction of cerebral oxygen supply caused by hypotension is more than compensated by the greatly reduced cerebral oxygen demand. For this reason cerebral oxygenation would not appear to be jeopardized by the technique of controlled vascular hypotension, when combined with general anaesthesia, in either normotensive or hypotensive patients, provided anoxaemic anoxia is avoided.

Since this investigation was carried out observations made on the livers of anaesthetized patients suggest that the earlier recommendations for theoretically safe levels of controlled vascular hypotension are optimistic (Griffiths and Gillies, 1948). It has been found that anoxic reactions appear in the liver when the systolic pressure falls below 60 mm. Hg (Bromage, 1952b). For this reason the systolic pressure should never be allowed to fall below 60 mm. Hg except for very brief periods, and falls to the danger level should be corrected promptly by the administration of a pressor drug.

Summary

The sensitization to vasopressor drugs, arising from the blockade of central vascular control, has been studied in man by the use of general anaesthesia and high extradural spinal block.

It has been shown that a drug known to produce tolerance in moderate doses and even reversal of effect in large doses can be used effectively in the induced hypotensive state in repeated doses small enough to avoid the production of tolerance.

It is suggested that herein lies a valid method for comparing pressor drugs directly in man without the necessity for employing large series of cases. Such a comparison is illustrated by the pressor effects of the enantiomorphous isomers of methyl amphetamine.

I am indebted to Dr. W. A. R. Thomson for originally suggesting this investigation to me, and for his help in preparing this report. Supplies of D- and L-methyl amphetamine were kindly provided by Boots Pure Drug Company, Ltd.

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The waiting-lists for hearing-aids under the National Health Service are being steadily broken down, Miss Hornsby-Smith, Parliamentary Secretary to the Ministry of Health, stated at the annual meeting of the National Institute for the Deaf in London on July 4. She said: "I am glad to say that for some months past we have been able to supply the 48 distribution centres with all the aids they can handle, and more. There have, I know, been delays, but the shortage is now reduced to one of handling capacity and not supply. Some people have the strange idea that you can hand a deaf aid over the counter, as you would hand out a wireless set, but the fitting of a hearing-aid is a skilled and individual process, as there is immense diversity between the needs of the patients."

KARTAGENER'S SYNDROME

BY

S. KARANI, M.B., B.S., M.R.C.P., D.P.H.

Consultant Physician, St. Nicholas and Brook General Hospitals

Although isolated cases had been reported by Siewert (1904), Oeri (1909), and Guenther (1923), Kartagener (1933a) was the first to call attention to the association of bronchiectasis and sinus maldevelopment with transposition of the viscera. He described four cases illustrating the triad. Later he reported seven further cases (Kartagener, 1933b; Kartagener and Horlacher, 1935) and since then the syndrome has been associated with his name. So far 82 cases have been reported in the literature, some of them having occurred in twins and siblings. These hereditary and familial tendencies of the syndrome were first noted by Guenther (1923), who reported the triad in two sisters among four siblings, and later emphasized by Kartagener and Horlacher (1935), Adams and Churchill (1937), Lopez (1944), Trogersen (1947), and Bergstrom *et al.* (1950). The cases described below occurred in two sisters with a strong family history of weak chest, and, although isolated cases have been reported, this, so far as I know, is the first time the syndrome has been observed in members of one family in this country. The father suffers from chronic bronchitis, and one brother, who could not be traced, is known to have a weak chest and when young was told that his heart was on the wrong side.

Case 1

A married woman aged 29 gave a history of recurrent upper respiratory tract infection followed at times by bronchitis for many years. Lately her cough had been much more troublesome and she brought up foul-smelling sputum, sometimes copiously. She had had pneumonia twice, and in 1940 a polyp had been removed from her nose.

Examination showed that she was a small woman of low mental grade, with short limbs and small hands and feet. There was no clubbing. She had dextrocardia, and the liver dullness was on the left side. Her lungs showed diffuse bilateral rales and rhonchi. The central nervous system was normal. A plain x-ray film of the chest was suggestive of bilateral bronchiectasis. An x-ray film of the sinuses showed that both the frontal sinuses were much smaller than normal. There was no evidence of infection. Situs inversus totalis was confirmed by barium meal. Unfortunately, the patient's husband objected to further investigations, and so neither E.N.T. examination nor bronchography was carried out.

Case 2

A married woman (sister of Case 1) aged 41 had always had a weak chest and had been subject to recurrent attacks of sore throat, nasal colds, and anosmia all her life. She had an attack of pleurisy at the age of 16, and in spite of the chronic chest trouble had been able to lead a normal life until recently, when her cough became more troublesome and the sputum more copious; the latter was blood-stained on two occasions. She also gave a history of increasing dyspnoea and swelling of the ankles in recent months. She had one normal healthy son.

On examination she was seen to be a small woman of low mental grade with adenoid facies, short limbs, and small hands and feet. There was moderate finger-clubbing. She had dextrocardia, and the liver dullness was on the left side. The lungs showed diffuse bilateral rales and rhonchi. The central nervous system was normal. Situs