CONTROLLED HYPOTENSION IN NEUROSURGERY WITH HEXAMETHONIUM AND PROCAINE AMIDE

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The two greatest difficulties with which the neurosurgeon has to contend are haemorrhage and increased intracranial tension. It is now becoming possible for the anaesthetist to give him the great advantage of working in an almost bloodless field and with a brain shrunken to an easily manageable size; but these benefits are bought at the price of certain dangers. This paper attempts to outline the methods of lowering the blood pressure, to give a list of the main dangers that may be encountered, and to suggest measures for countering them.

Methods of Controlling Blood Pressure

Hexamethonium Bromide (or Iodide).—This is the drug in common use for the induction of hypotension. Its great disadvantage is that it has a failure (or partial failure) rate of some 40%.

Procaine Amide.—This is used extensively in cardiac and thoracic surgery for the elimination of cardiac irregularities. A common side-effect is to cause a slight lowering of the blood pressure, and W. D. M. Paton (personal communication) has suggested that this may be due to a weak ganglion-blocking effect. There often follows a small decrease in the pulse rate, which connotes possibly a decrease in cardiac output. When a case fails to respond satisfactorily to hexamethonium a suitable dose of procaine amide will with a high degree of probability convert it into a successful case of hypotension. The reason for this potentiation is not clearly understood. It may be due to a simple synergistic action or to the effect of a reduced cardiac output, or to a combination of these factors.

Posture.—This plays an important part in the management of the case. Before the administration of the hypotensive drug the patient is placed in an anti-Trendelenburg tilt of 25 to 30 degrees. This will usually reduce the blood pressure by about 10 mm. Hg. The tilt is decreased during the course of the operation if the blood pressure falls too low. Post-operatively the blood pressure is prevented from rising too rapidly or from falling too low by altering the position of the patient. As an example of the delicacy of blood-pressure control by means of posture, we operated on a few cases on a table which did not have a foot-rest (to prevent the patient sliding down the table). The patients were arranged with the head slightly raised, the body almost horizontal, and the legs hanging over the end of the table. In each case when it became necessary at the end of the operation to increase the blood pressure the mere act of raising the legs to the horizontal position caused a rise of 15 to 20 mm. Hg within a few minutes. In only two cases has it been necessary to resort to methylamphetamine hydrochloride to raise the blood pressure post-operatively.

Dangers of Hypotensive Anaesthesia

1. Allowing the Pressure to Drop too Low

It cannot be said with certainty how low the pressure may be dropped with safety. Pressures below 60 mm. may result in liver damage. Still lower pressures may be associated with anoxia, thrombosis, or even death. One

fatal case probably falls into this category, but with the added results of "retractor anaemia," under which heading it is described.

2. Anoxia

Although there is no supporting evidence, it is possible that a slight degree of cerebral anoxia may be present during hypotension because of the reduced amount of blood passing through the brain. The colour of the brain and blood does not suggest that this is so. Siguier *et al.* (1951) state that the electroencephalogram shows no evidence of anoxia. During direct electroencephalographic recordings of the cortex I have deliberately produced a slight degree of anoxia (without hypotension), and the tracings have shown no changes from the normal. The claim of Siguier *et al.* would therefore seem to be valueless. Nor do tracings under hypotension show variations from the normal. There is evidence to suggest that the blood flow through the brain is less than is indicated by the brachial blood pressure, and that therefore the danger of anoxia may be greater than would appear on the surface.

A man of 20 was having his frontal lobe amputated for epilepsy. His blood pressure before operation was 126/84. An inexplicable rise to 160/120 after induction was lowered to 154 by 50 mg. of hexamethonium, and to 134 by a further dose of 50 mg. All this time, as was to be expected, a good deal of bleeding was going on and the dura was tense. At this stage 400 mg. of procaine amide was given intravenously, and within a few minutes the bleeding had stopped and the brain had retracted from the dura. Yet the blood pressure was 118.

It is hoped to obtain further knowledge on this point by taking blood pressure readings from a cerebral artery. No definite evidence of anoxia has appeared in any cases in the present series, yet its results may possibly have been masked by surgical trauma.

3. Thrombosis

This is an ever-present danger and may occur with even a small drop in blood pressure. Many cases have been reported under this form of anaesthesia. There were no cases of thrombosis in the present series.

4. Reactionary Haemorrhage

In general surgery, under hypotension, reactionary haemorrhage has been one of the most frequent complications. In neurosurgery it is apt to occur under any type of anaesthesia. It has occurred in only one case in this series.

A woman of 54 had an angioma removed in the morning. After an early recovery she became drowsy towards evening and showed signs of intracranial bleeding. On reopening the flap a small subdural clot, together with a quantity of blood-stained fluid, was evacuated. The surgeon felt doubtful whether this was a true haemorrhage. The patient had no further trouble and made a good recovery.

5. "Retractor Anaemia"

So far as I know this condition has not up to the present been recognized, and for that reason and because of its importance it is dealt with at some length. In the series there were three deaths attributable directly or indirectly to the anaesthetic. All three showed evidence of "retractor anaemia," two of them to a marked degree.

When hypotension is induced the brain retracts within the cranial cavity, leaving a clear space between it and the cut edge of the dura. At the same time its consistency is completely altered. It has lost all tone and behaves like soft dough. When pressure is applied it is easily compressed, and on release is slow to regain its normal conformity. Blood is forced out of those parts of the brain on which the pressure is exerted, and because of the small blood flow the vessels are only slowly replenished on removal of the pressure. It can be seen that pressure by a brain retractor may be transmitted even to comparatively

distant parts of the brain, thereby depriving those areas of their blood supply and thus causing irreversible and possibly widespread damage.

A man of 35 had a pituitary adenoma removed. He recovered well from the operation and anaesthetic and was responding within a few minutes of the end of the operation. His condition continued to be satisfactory, giving no cause whatsoever for anxiety, when suddenly, eight hours later, he died. The post-mortem findings were: "Cranium and contents: Haemorrhage had taken place around the bone-flap and no haemorrhage was present under the dura. The convolutions of the cerebral hemisphere were flattened and there was some herniation of the right hemisphere under the falx. A marked degree of tonsillar herniation through the foramen magnum had occurred. . . . Haemorrhage had taken place into the remaining portions of the tumour and into the right frontal lobe. The right frontal lobe was soft in consistency. The right cerebral hemisphere was greatly enlarged, particularly anteriorly, and herniated under the falx. . . ."

The striking part of this report is the great enlargement of the right hemisphere, particularly the anterior part of it—so great, in fact, that part of the lobe had to be accommodated under the falx. (The craniotomy was of course performed on the right side.) The enlargement is undoubtedly due to acute oedema, which, in its turn, is caused by vascular damage. Had vascular damage been caused by hypotension and anoxia due to the anaesthetic one would have expected enlargement of both hemispheres. There seems, therefore, little room for doubt that the damage was caused by retractor pressure. A second death occurred in the following case.

A man of 42 with a right frontal glioma had had his frontal lobe amputated. Post-operatively he did not regain consciousness, and died the following morning. His blood pressure, by an unfortunate chain of circumstances, had been allowed to remain too low, and at the time we attributed his death to this cause. The post-mortem examination showed: "Cranium and contents: no evidence of thrombosis was seen in the venous sinuses. The convolutions of both cerebral hemispheres were flattened and the sulci shallow. The right hemisphere was much larger than the left and had herniated under the falx cerebri. It filled the cranium, although the frontal lobe had been amputated for the removal of a calcified glioma. On the right the hippocampus herniated through the tentorium cerebelli, pushing the right communicating artery downwards, and portions of the hippocampus lay on either side of the vessel. There was no marked degree of tonsillar herniation. A large amount of blood had collected in the cisterna magna. The right frontal lobe had been amputated, but the right hemisphere filled the cranial cavity on this side and herniated to a very marked degree under the falx. . . ."

Here we have a picture very similar to the previous case. Amputation of the frontal lobe is a comparatively innocuous procedure which as a rule causes little or no upset to the patient. A persistent low blood pressure would be expected to cause more generalized changes in the brain. The pronounced changes on the right point once again to the extreme vulnerability of the brain, in the hypotensive state, to retractor pressure. A third death occurred in the following case.

A man of 39, with a pituitary adenoma, was one of the early cases in the series; we were then not seriously concerned if the blood pressure fell to below 60. In this case it dropped to 40, and, in spite of reducing the tilt, did not rise more than a few points. He failed to come round after the operation, developed decerebrate rigidity, and died the following day. A post-mortem examination revealed the following: "On removing the skull vault the dura was under marked tension and the underlying brain obviously swollen. . . . On cutting the brain there was marked oedema throughout both hemispheres. . . . Pathological report: " . . . Examination revealed a haemorrhage 2 cm. in diameter situated at a low level in the right cerebral peduncle. . . ."

Bilateral enlargement of the hemisphere suggests generalized brain damage by too low blood pressure. The haemorrhage into the peduncle may have been caused by retractor pressure. Several of the earlier cases were operated on under very low pressure without obvious ill effects, and, while this is no argument that the patient did not die as a result of the damage due solely to low blood pressure, retractor pressure cannot be entirely dissociated as an additional factor.

An interesting comparison with the preceding examples is provided by a case which terminated fatally, a result for which the anaesthetic could in no way be held responsible.

A woman of 56 was being operated on for removal of a sphenoid wing meningioma. In the course of the operation the surgeon accidentally opened a big vessel, causing a profuse and rapid loss of blood. In due course the haemorrhage was arrested by clipping two large arteries. During this period the condition of the patient had been fairly satisfactorily maintained by rapid replacement of blood and, of course, by levelling the table. By the end of the operation she was responding well and her general condition was quite good. However, she gradually deteriorated, and died the same day. The necropsy report was as follows: "The cerebral convolutions of both hemispheres were flattened. The right cerebral hemisphere was enormously enlarged and had herniated under the falx cerebri. The adjacent sides of the fronto-temporal lobes had been removed. The fronto-parietal part of the hemisphere was very soft in consistency. Clips were present on the right middle and right anterior cerebral arteries. A considerable degree of hippocampal herniation had taken place on the right side. . . . An extensive infarction was present in the region supplied by the right middle cerebral artery. . . . The hypothalamus on the right side did not appear to be infarcted. . . ."

This picture is strikingly reminiscent of the previously described cases. Each shows the result of widespread ischaemia of the brain, in one case by clipping arteries, in the other cases by retractor pressure on the brain.

Two cases of pituitary adenoma show post-operative signs which may have been due to retractor pressure. As a rule these patients proceed to an uneventful recovery.

A man of 49 made a good immediate recovery, but had a stormy convalescence. On discharge the final note read: "This man has made an excellent recovery following aspiration of a cystic chromophobe adenoma; however, he remains retarded and still has pathological extensor plantar responses. Post-operatively he has some ataxia of his gait and left arm."

A man of 64 was in coma for two hours after operation. He remained drowsy and incontinent after initial improvement. The final note said: "He is alert, fully orientated as regards time, place, and person. He remains, however, quite still, a little sleepy, more than normal."

Technique

Premedication consists of atropine only, given half an hour to an hour before operation. The patient is induced with thiopentone, 0.5 to 1 g., followed by a short-acting relaxant and 50 to 100 mg. of pethidine intravenously. An endotracheal tube is then introduced and anaesthesia is maintained on a nitrous oxide and oxygen mixture with periodic injections of 15 to 20 mg. of pethidine. Rarely, very small quantities of trichlorethylene are added.

Of the relaxants I prefer gallamine triethiodide to succinylcholine chloride, as the duration of action of the latter is so short that introduction of the endotracheal tube will often start a bout of coughing. Gallamine triethiodide allows time for the pethidine to come into action, so that one is rarely bothered by this disturbance. Succinylcholine chloride has the advantage so far as relaxation of the cords is concerned.

In all craniotomies an intravenous drip is put up; in cases in which excessive haemorrhage is anticipated the drip is duplicated. The patient is placed on the operating table, which is then put into an anti-Trendelenburg tilt of 25 to 30 degrees. The head is cleaned and draped, and at this point the hexamethonium compound is injected. If a local analgesic is used, adrenaline must of course be omitted, as it antagonizes the action of hexamethonium.

In certain operations—namely, hemispherectomy or excision of an epileptic focus—the actual operation of ablation is preceded by direct electrical stimulation of the motor cortex and electroencephalographic tracings. Since these investigations involve a considerable amount of time the hexamethonium is withheld until these procedures have been completed.

Neither pethidine nor hexamethonium has any effect on the electroencephalogram, in contradistinction to thiopen-

tone, which, in small doses, potentiates epileptic waves and is given when it is desired to produce this effect.

Enderby and Pelmore (1951) suggest initial doses of 40 to 50 mg. of hexamethonium. Guiot and Damoiseau (1952) postulate a maximum of 50 mg. I have found these doses to be on the low side, and originally my practice was to start with at least 100 mg. in a robust patient, and I have at times increased this to as much as 250 mg. When using procaine amide in addition for resistant cases I am now giving rather smaller initial doses of hexamethonium—40–75 mg. for an elderly patient, 50–100 mg. for a young adult.

Within a few minutes of the injection the blood pressure will begin to fall and in a favourable case will reach a point between 60 and 70 mm. Hg, where it will remain. At the same time the pulse pressure shows a considerable decrease with only a few points marking the difference between the systolic and the diastolic pressure.

As a general rule bleeding is minimal when the pressure is dropped to 70 or lower. This is surprising, as one would expect that in order to obtain what would appear to be this critical point in bleeding it would be necessary to produce a lower blood pressure in a patient with an initial low pressure than in a patient with an initial high pressure. A blood pressure below 60, we now know, may result in liver degeneration. Our aim should therefore be to keep the pressure between 60 and 70.

Frequently, following the injection of hexamethonium, the initial fall in blood pressure, which may reach a point well below 60, is quickly followed by a rise which, favourably, will be held below 70. If the pressure should remain below 60 for more than a few minutes the foot-down tilt must be decreased until this pressure is attained. If, on the other hand, the pressure should continue to rise beyond 70, increasing the tilt will not check the rise. Nor will an additional dose of hexamethonium as a rule have the desired effect. Yet again hexamethonium may fail to give a satisfactory response in the first place, and the pressure may drop by only a few points.

The cases in which hexamethonium fails to give an adequate reaction or in which the action is of extremely short duration constitute a fairly high proportion of the total number—in the neighbourhood of 40%—and until recently they were therefore written off as failures. With procaine amide at our disposal we are now able to “rescue” the majority of them.

The dose of procaine amide is judged according to the previous effect of the hexamethonium and the age and condition of the patient, and varies between 200 and 500 mg. A poor result of hexamethonium demands a high dosage of procaine amide, as does a young and robust adult.

Assuming the hexamethonium has been given, one should be able to decide within five to seven minutes whether a successful reaction is to be anticipated. If after this time the blood pressure fails to reach a satisfactory level, or, having dropped to a suitable level, immediately begins to rise and continues to do so, procaine amide should be given. The injection is made intravenously and slowly, taking ten to twenty seconds for each 100 mg. From now on there is no further tendency for the blood pressure to rise. It will remain stationary for ten minutes or so and then gradually fall. At the same time there will usually be a decrease in the pulse rate.

One cannot predict the duration of action of these compounds. A single dose will often suffice for the complete operation. On the other hand, if the blood pressure rises, causing increased bleeding, the drug will have to be given again. The second dose should be much smaller than the first.

At the conclusion of the operation Siguier *et al.* raise the blood pressure by rapidly returning the patient to horizontal, and all bleeding is then stopped. Our policy from the beginning has been to allow a slow return of blood pressure over several hours. This is carried out entirely by

means of posture. The nursing staff have clear instructions that the blood pressure must, so far as possible, be kept below 100 for several hours.

Recovery

Recovery from the anaesthetic is usually extremely good and very similar to recovery after pethidine anaesthesia. Hexamethonium, in fact, seems to have little added effect. Provided the blood pressure is over 70, consciousness is regained within a few minutes after the end of the operation and the patient will respond to simple commands and answer simple questions, albeit drowsily.

Post-operative restlessness is uncommon, owing, no doubt, to the action of pethidine, which allows a prolonged period of freedom from pain and headache and thus eliminates to a great extent the need for post-operative sedative drugs.

The patient can easily be roused, and there is no danger of confusing this drowsiness with that due to post-operative bleeding.

Contraindications

As thrombosis is one of the chief dangers with this form of anaesthesia, any pre-existing liability to thrombosis would be a contraindication to its use. Unfortunately we are unable to assess this liability, particularly in the case of coronary disease. A previous coronary thrombosis is, of course, an absolute contraindication.

Guiot and Damoiseau give hypertension and arteriosclerosis as contraindications. I should be very chary of employing the method in an advanced case of arteriosclerosis, but early cases, as one would expect, react well to the drugs and do not appear to come to harm.

I have used the method in a number of children, most of whom have reacted favourably. A child of 3 failed to give a satisfactory response, whereas a perfect result was obtained in a 7-years-old child. Comparatively large doses are required in children. The oldest patient was a man of 70.

With the danger of “retractor anaemia” in mind, it follows that this method of anaesthesia is absolutely contraindicated in any operation in which pressure is applied to a portion of the brain that is not to be excised in the course of the operation. There are occasions when it is impossible to decide in advance whether such pressure will be necessary, and in these cases it is advisable to defer the induction of hypotension until the bone flap is turned and the surgeon is quite clear about the condition he has to deal with. In this respect it is the surgeon's responsibility to decide whether hypotension is suitable or not.

When operations in the posterior fossa are carried out with patients in the prone position the same rule will apply. In this unit, however, these operations are performed in the sitting-up position, in which operating conditions are as a rule satisfactory, as regards both haemorrhage and intracranial tension. It would, of course, be foolhardy to use a hypotensive drug with a patient in this position.

Descriptive Cases

A few unusual cases are of interest.

A woman of 50 had a cerebrospinal leak from the anterior fossa. Before the opening was successfully sealed off, three operations were performed at intervals of six weeks and fourteen weeks. In each of the first two operations 150 mg. of hexamethonium produced a perfect result. In the third operation 80 mg. sufficed. The blood-pressure charts were almost identical in the three operations.

A woman of 43 with an angioma had two operations within 11 days. In the first an initial drop in blood pressure with 80 mg. of hexamethonium was followed by a slow rise which necessitated the injection of 300 mg. of procaine amide. The blood pressure fell to 66, where it remained throughout operation. At the second operation 100 mg. of hexamethonium reduced the pressure

to 50, but it rose steadily throughout the operation, which lasted only half an hour. There was a steady blood loss towards the end of the operation.

Two points emerge from these cases. First, it would seem that a patient who once responds satisfactorily to these drugs may be expected to respond in the same way on any future occasion. That being so, the converse is of course true. Secondly, hexamethonium alone may at times suffice for a short operation. If the operation is more prolonged additional hexamethonium may be given, but probably procaine amide will have the more lasting effect.

A man of 70 was being operated on for removal of a meningioma. Thirty-seven minutes after induction with thiopentone, gallamine triethiodide, and pethidine he developed an attack of asthma. Some 10 minutes previously he had been given an injection of hexamethonium, which had reduced his blood pressure to 66. Surprisingly the supervision of bronchospasm failed to cause an appreciable increase in blood pressure and the bleeding remained negligible and the colour good; but movements of the head due to laboured breathing and bulging of the brain during expiration were an annoyance to the surgeon. The condition persisted throughout the operation, clearing up within a few minutes after withdrawal of the endotracheal tube. The patient made a good recovery.

Results

The series consists of 90 cases. I have divided these into two groups, which happen to be equal in number; the first includes all those cases up to the time when procaine amide was first used, the second the remainder. The criteria of success were a negligible amount of bleeding and a good reduction in intracranial tension. Many cases, while not completely fulfilling these criteria, gave unquestionably improved operating conditions, and these I have classified as "partially successful."

In the first group of 45 cases 26 (58%) were successful, 9 (20%) were partially successful, and 10 (22%) were failures. In the second group 38 (85%) were successful, 5 (11%) were partially successful, 2 (4%) were failures.

It will be seen from these figures that procaine amide is a useful adjunct to this form of anaesthesia, as it converts many of the potentially failed and partially failed hexamethonium cases into successful ones.

Three deaths due directly or indirectly to the anaesthetic have occurred. In the light of our experience two at least of these cases are considered to have been unsuitable for this type of anaesthesia.

There was one case of reactionary haemorrhage.

Summary

The advantages of controlled hypotension in neurosurgery are listed.

The dangers of the method are discussed, with special reference to "retractor anaemia."

A method is described of reducing the failure rate of hexamethonium by potentiating with procaine amide.

The results of a series of 90 cases are given.

REFERENCES

- Enderby, G. E. H., and Peimore, J. F. (1951). *Lancet*, 1, 663.
 Guiot, A., and Damoiseau, B. (1952). *Rev. Prat.*, 2, 172.
 Sigulier, F., Damoiseau, B., and Guiot, G. (1951). *Bull. Soc. méd. Hôp. Paris*, 67, 1201.

The *Hebrew Medical Journal* (Harofé Haivri) recently completed its twenty-fifth year of publication. Although it has been edited and produced in the United States, much of its contents have been published in Hebrew. It is a remarkable achievement on the part of those concerned that they have succeeded in adapting so ancient a language to the needs of modern medicine and have created a medical terminology and literature in Hebrew. The present editor is Dr. Moses Einhorn.

AN OUTBREAK OF DIPHTHERIA: INFLUENCE OF IMMUNIZATION

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During 1951 an outbreak of diphtheria of unusual size for the present time occurred in and around Coseley. Coseley, with a population of 34,414 at the 1951 Census, is an urban district in the Administrative County of Stafford between the county boroughs of Wolverhampton and Dudley and almost surrounded by other industrial districts. Wolverhampton and Dudley were not included in the investigation here considered, but it is understood that Wolverhampton had five cases of diphtheria during the year and that Dudley had 11 (all during the first two quarters). The total population of the seven surrounding districts included in this report was 232,836, and together they had 50 confirmed cases during the year, while Coseley had 58. These 108 cases were 15.5% of the 699 (provisional) corrected notifications for England and Wales in 1951. There has in the past been a steady and at times surprisingly high incidence of diphtheria in the neighbourhood. In Fig. 1, the figures for which were obtained from the annual reports of the medical officers of health of Coseley, the number of notifications and deaths and the population for the years 1908-51 are given.

The incidence of diphtheria in Coseley in recent years compares unfavourably with the national incidence and that of non-county boroughs and urban districts (England only, excluding London), as is shown by Fig. 2, which is based on figures published in the Registrar-General's statistical reviews 1912-49.

Bacteriology

The bacteriology of diphtheria in the Administrative County of Stafford is of interest.

Menton *et al.* (1935) reported the results of 500 swabs from 500 individual patients classified according to the type of diphtheria organism; their figures showed a marked predominance of mitis diphtheria. For 1941-4 the published data of the Stafford Public Health Laboratory showed a change to the gravis and, to a lesser extent, to the intermedius types. Comparable figures for 1946-50 show that the intermedius type exceeded the gravis type, which, however, still almost equalled the mitis type in number. In 1951 the outbreak was due to gravis diphtheria. The data are set out in Table I.

TABLE I.—Relative Incidence of Types of *C. diphtheriae*—Administrative County of Stafford (Based on the Number of Cases Shown in Parentheses)

	Reported in 1935	1941-4	1946-50	1951
Gravis ..	3.8% (19)	56.9% (1,230)	27.0% (98)	98.7% (78)
Mitis ..	68.6% (343)	6.7% (144)	27.5% (100)	1.3% (1)
Intermedius ..	19.8% (99)	36.4% (787)	45.5% (165)	0% (0)
Irregular ..	7.8% (39)	— (—)	— (—)	— (—)