PAPERS AND ORIGINALS

Intraoperative management of phaeochromocytoma with sodium nitroprusside

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Summary and conclusions

Sodium nitroprusside (SNP) is a powerful, peripherally acting hypotensive agent with a rapid onset but short duration of action. It is highly effective for hypertensive episodes in patients with a phaeochromocytoma and may be used safely with adrenoceptor-blocking agents. Two cases are described that illustrate its effectiveness in this condition, even in the presence of exceptionally high circulating concentrations of catecholamines. A simple and reliable regimen for preparing these patients for surgery may be based on oral adrenoceptor-blocking medication (phenoxybenzamine and propranolol) to provide "background" hypotensive and antiarrhythmic cover. SNP by infusion is then used as the principal intraoperative hypotensive agent, dysrhythmias being controlled with additional intravenous propranolol if required.

Introduction

The management of patients with a phaeochromocytoma is designed to avoid extremes of blood pressure, particularly during general anaesthesia. Ross *et al*¹ described an effective regimen by which such patients may be prepared for surgery but it does not eliminate hypertensive episodes. These crises are generally controlled with short-acting adrenoceptor-blocking drugs² or ganglion-blocking agents,³ but both classes of drug may produce unwelcome and possibly prolonged hypotension. Sodium nitroprusside (SNP), a powerful, peripherally

acting hypotensive agent,⁴ is rapidly metabolised and its effects are short lived. It is therefore suitable for controlling hypertensive episodes during anaesthesia in patients with a phaeochromocytoma.⁵ Its effects are exerted despite the high circulating catecholamine concentrations that occur during surgery in these patients. We report its use during general anaesthesia three times in two patients and give details of blood pressure recordings and simultaneous plasma catecholamine measurements.

Patients and methods

The two patients had a typical history of phaeochromocytoma, with high 24-hour urinary vanillylmandelic acid concentrations. The tumour was initially localised by excretion urography, with confirmation in case 1 by selective adrenal arteriography. Blood samples were collected at times of severe hypertension and at critical moments during the operation. Plasma was separated at once, by centrifugation at 2000 rpm for three minutes, and transferred by decanting into cooled glass tubes containing 0.1 ml 5% sodium metabisulphite solution (an inhibitor of plasma catechol-*o*-methyltransferase). It was frozen immediately pending analysis.⁶ In addition to these samples blood was withdrawn continuously, using an apparatus described,⁷ precautions being taken to prevent the degradation of adrenaline and noradrenaline.⁸ Analysis of these samples provided measurement of integrated concentrations over the periods of collection, which were arranged as follows: (1) between leaving the ward and arriving in the operating theatre, (2) between the induction of anaesthesia and surgical exposure of the tumour; (3) during manipulations of the tumour, up to the time of its removal. Blood pressure was recorded automatically with a transducer system connected to an indwelling cannula in the right radial artery, which was inserted after the induction of anaesthesia. The infusion of SNP was controlled with a microdrip arrangement calibrated in ml/min.

Results

CASE 1

Adrenal arteriography was performed under general anaesthesia after seven days of preparation with oral phenoxybenzamine 10 mg thrice daily and propranolol 20 mg thrice daily. On arrival in the

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x-ray department the patient's blood pressure was 140/80 mm Hg and pulse 60/min, but induction of anaesthesia with thiopentone, pethidine, and nitrous oxide and oxygen (by mask) caused the blood pressure to rise to 150/100 mm Hg. With the temporary addition of 0.5% halothane it settled to 110/50 mm Hg but, as expected, the injection of contrast into the right adrenal artery produced a sharp rise to 250/150 mm Hg. SNP 4 mg (as 0.01% solution) was then infused over eight minutes, and the blood pressure fell to 90/50 mm Hg and the pulse rate from 80 to 55/min. After withdrawal of SNP the

FIG 1—Case 1. Changes in blood pressure and integrated and "spot" (x) plasma catecholamine concentrations during operation. Rates of SNP infusion shown as arbitrary values. Conversion: SI to traditional units—Plasma catecholamines: 1 nmol/l $\approx$ 0.018 μ g/100 ml.

blood pressure rose to 200/80 mm Hg but fell spontaneously during the recovery period.

Subsequently, during the two weeks before surgery the same adrenoceptor-blocking regimen was maintained, which eliminated hypertensive episodes without causing postural hypotension. Two days before operation intramuscular phentolamine (5 mg six-hourly) was substituted for the longer-acting phenoxybenzamine. Pre-medication with pentobarbitone 100 mg by mouth, perphenazine 2.5 mg intramuscularly, and papaveretum 10 mg and hyoscine 0.3 mg intramuscularly (given three, two, and one hour preoperatively respectively) produced a sedated and co-operative patient with a blood pressure of 140/80 mm Hg. Induction of anaesthesia with thiopentone, pethidine, nitrous oxide and oxygen, and tubocurarine was followed by endotracheal intubation. This caused a rise in blood pressure to 220/120 mm Hg, but the infusion of 0.01% SNP reduced it to 70/35 mm Hg. Thereafter, by varying the rate of SNP infusion the blood pressure was maintained between 80/40 and 70/30 mm Hg until the tumour was removed. During manipulation of the pheochromocytoma the blood pressure rose to 100/60 mm Hg on one occasion and to 170/80 mm Hg on another with an accompanying tachycardia of 150/min, both crises being easily resolved by increasing the SNP infusion rate. On the second occasion propranolol 1 mg intravenously was used to lower the pulse rate to 80/min. As the last vein draining the tumour was ligated the SNP infusion was discontinued; the blood pressure then rose to 190/70 mm Hg but fell over the next 20 minutes and remained stable at around 130/70 mm Hg during the postoperative period.

Fig 1 shows the relation between these events and the plasma catecholamine concentrations.

CASE 2

The same adrenoceptor-blocking regimen as in case 1 was used initially in this case, but five days preoperatively the oral phenoxybenzamine was increased to 10 mg four times daily. This was changed to intramuscular phentolamine (5 mg six-hourly) two days before surgery, premedication being similar to that in case 1. In the anaesthetic room the patient's blood pressure was 120/60 mm Hg and pulse rate 64/min. To try to prevent the increase in blood pressure often associated with endotracheal intubation the infusion of SNP (0.01% solution) was started before inducing anaesthesia, producing a fall to 65/20 mm Hg over five minutes. This low pressure precipitated catecholamine release and the pressure rose to 220/100 mm Hg with accompanying peripheral vasoconstriction. The crisis was resolved by increasing the rate of SNP infusion, and seven minutes later anaesthesia was induced with thiopentone, pethidine, nitrous oxide and oxygen, and tubocurarine. During intubation the pressure rose to 240/90 mm Hg, reverting to 110/50 mm Hg when the SNP infusion rate was increased. Adding 0.5% halothane to the anaesthetic regimen helped to stabilise the blood pressure, which was then kept between 60/25 and 50/20 mm Hg during the operation. Propranolol 1 mg intravenously was given once during surgery, as the pulse rate was consistently between 100 and 140/min despite well-controlled blood pressure. During manipulation of the tumour, increases in

FIG 2—Case 2. Changes in blood pressure and integrated and "spot" (x) plasma catecholamine concentrations during operation. Rates of SNP infusion shown as arbitrary values. Conversion: SI to traditional units—Plasma catecholamines: 1 nmol/l $\approx$ 0.018 μ g/100 ml.

blood pressure were controlled by stepping up the rate of SNP infusion and also by increasing the inspired concentration of halothane to 3.0%. After obliteration of the last vein draining the tumour the blood pressure fell, but this was counteracted by stopping the SNP infusion. The pressure then rose promptly to 150/90 mm Hg and remained stable at around this level during removal of the tumour and completion of the operation.

Fig 2 shows these events in relation to the plasma catecholamine concentrations.

Discussion

In these two cases SNP effectively controlled hypertensive episodes despite demonstrably high circulating catecholamine concentrations at these times. SNP can also prevent hypertensive crises, since the integrated concentration (which is an average of hormonal peaks and troughs) was exceptionally high during surgery when the blood pressure was well stabilised. We subsequently used SNP in other cases of pheochromocytoma and suggest that it is an important advance in the intra-operative management of such patients.

Preparation of these patients for surgery should start at least 14 days before operation with oral propranolol and phenoxybenzamine. This regimen prevents hypertensive episodes, allows the contracted plasma volume to expand,⁹ and protects against arrhythmias. A patient so prepared is not, however, completely blocked and may react adversely to stressful procedures such as intra-arterial injection of contrast or endotracheal intubation. Phenoxybenzamine should be changed to the short-acting drug phentolamine (given intramuscularly six-hourly) 48 hours before surgery, so that prolonged hypotension does not occur after removal of the tumour. The SNP infusion should be set up before anaesthesia is induced so that it may be used to control hypertension at this time. It should be adjusted to give a pressure of around 80 mm Hg systolic, and intra-arterial pressure monitoring during the operation is invaluable for this. When the last vein draining the tumour is occluded the infusion should be stopped to forestall hypotension. If the pressure begins to rise the presence of further functioning chromaffin tissue should be suspected, which is a useful diagnostic point.¹⁰ Provided that fluid replacement has been adequate during surgery (best monitored by central venous pressure measurements) hypotension will not occur after the tumour has been removed. If tachydysrhythmia develops intravenous propranolol may be safely combined with this regimen, injections of 1 mg usually being sufficient.

Clearly certain manoeuvres, notably endotracheal intubation, are particularly associated with severe hypertension. This is not prevented by the adrenoceptor-blocking regimen, which protects only in non-stressful conditions. SNP is effective in these episodes, but case 2 illustrates the dangers of lowering the blood pressure too far, which may provoke catecholamine release and result in a rapid rise in blood pressure. The effectiveness of SNP in controlling the intra-operative blood pressure

despite exceedingly high integrated concentrations of catecholamines suggests that its action is unrelated to an effect on adrenal medullary hormone synthesis, such as may occur with other adrenolytic agents.¹¹ Thus the pressure rose rapidly in case 1 when this peripheral action was removed by stopping the infusion. Interestingly, a similar effect did not occur in case 2, the blood pressure remaining normal despite greatly increased catecholamine concentrations. Fluid replacement had been adequate, and hypovolaemia was probably not contributory. The explanation may lie with the phenomenon of tachyphylaxis to catecholamines¹²—that is, tolerance to very high circulating concentrations. The sudden lowering of these concentrations when the tumour is removed may contribute (with fluid depletion) to a fall in blood pressure.¹³

SNP is a useful hypotensive agent and may be used safely in patients with a pheochromocytoma.¹⁴ It is potentially toxic, however, since in high dosage the normal metabolic pathways may become overloaded. Free cyanide is then formed, with its ability to destroy cytochromes.¹⁵ Hence we recommend that the total dose should not exceed 0.5 mg/kg during any one acute administration and that the infusion rate should not exceed 800 µg/minute. A preparatory adrenoceptor-blocking regimen allows the doses to be kept within these limits.

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ONE HUNDRED YEARS AGO At a recent meeting of the Edinburgh Meteorological Society, Mr Buchan read a paper on weather and health in London and New York. It was illustrated by charts, so arranged as to show a comparative view of the mortality of the two cities as influenced by the weather, on an average of the seven years ending with December 1877. The mean annual temperature of London and New York was, he said, exactly the same, about 57 deg Fahr; but New York had a summer temperature, during July and August, ten degrees in excess of that of London, while the winter temperature was ten degrees lower. Along with the great heat of the New York summer, there was considerable dryness of air; for, although the rainfall was more than that of London, the excess came in the form of heavy thunder-showers. In winter, too, a low temperature was accompanied by great dryness. The most important effect of the difference of climate was seen in the effect of the summer heat. At New York, in July and partly in August, when the temperature was so high, there was an enormous rise in the death-rate from nervous diseases, which did not occur in London to any extent. This increase was observed in the case of all nervous diseases, but particularly in sunstroke caused by the direct effect of sunheat. In 1871, the temperature in New York did not rise as high as usual, and the number of deaths from sunstroke was only twenty-one; while the following year was exceedingly hot, and the deaths from sunstroke were three hundred and twenty. Similar facts were noted in other years. This feature largely gave its character to the curve for nervous diseases. Of deaths from convulsions, London showed a slight rise in the end of July and the middle of August; in New York, the rise was much more pronounced. The facts were similar in regard to inflammation of the

brain. Suicides followed the same rule, New York showing a greater excess. A good many of the deaths from convulsions arose from complication with bowel-complaints. Now the higher temperature of New York in summer was very much felt in regard to bowel complaints. It was observed that, for three weeks, the London curve for these complaints was very high—300 per cent above the average. But for New York, in the month of July, the curve rose nearly 100 per cent above that of London; and what was very singular, there was a rise of 200 per cent in mortality of persons above five years of age, to which London showed nothing like. The deaths from tabes mesenterica and scrofula showed an enormous rise in New York, as compared with London, during the summer months. Taking the whole population, and all diseases whatever, it was found that, of those under one year of age, the London mortality for one week went about 90 per cent above the average; while in New York, for a whole month, it was 140 per cent above the average. Of children from one to two years old, the mortality in New York showed a great rise in the summer months, this arising almost exclusively from bowel-complaints. In London, the curve would probably not reach one-third of the height. Of children from one to five, the mortality in London rose a little in the summer months, but very little; in New York, the rise was five or six times greater. The old age curve in London reached its maximum in the winter months and its minimum in the warmest season; in New York, its maximum occurred in the spring months, and there was also a rise in the hot months of summer. It thus appeared that the great heat of New York was more fatal, not only to children, but also to very old people. (*British Medical Journal*, 1878.)