Aust. N.Z. J. Med. (1977), 7, pp. 414–417

CASE REPORT

Use of a Microprocessor in the Control of Malignant Hypertension with Sodium Nitroprusside

R. V. Jackson*, J. B. Love†, W. G. Parkin‡, M. L. Wahlqvist and N. S. Williams††**

From the Intensive Care Unit, Prince Henry's Hospital and Department of Medicine, Monash University, Prince Henry's Hospital, Melbourne

Summary: Use of a microprocessor in the control of malignant hypertension with sodium nitroprusside. R. V. Jackson, J. B. Love, W. G. Parkin, M. L. Wahlqvist and N. S. Williams, *Aust. N.Z. J. Med.*, 1977, **7**, pp.414–417.

In a malignant hypertensive, steady control of blood pressure at a pre-determined level has been achieved with the continuous intravenous infusion of sodium nitroprusside. A microprocessor was programmed to assess the patient's blood pressure and adjust the rate of nitroprusside infusion so that a mean pressure of 106 mmHg was achieved. Brief interruption of the nitroprusside infusion allowed the effectiveness of changes in oral therapy to be evaluated. Thiocyanate concentrations were measured throughout as an index of potential nitroprusside toxicity. After six days, blood pressure control was maintained with oral therapy alone and papilloedema had almost resolved.

Intravenous infusion of sodium nitroprusside (SNP) is an effective method for the control of malignant hypertension.[1] One limitation of its usefulness has been the need for continuous adjustment of the infusion. The advent of relatively inexpensive microprocessors[2, 3] has made it possible to effect precise minute-to-minute control of blood pressure with nitroprusside infusion. We have employed this technique to manage a young man with malignant hypertension resistant to conventional anti-hypertensive agents. The patient's oral therapy was evaluated by brief interruptions of the nitroprusside infusion. As more effective oral therapy was introduced, the microprocessor reduced the nitroprusside infusion. Thus, the technique allows the simultaneous control of malignant hypertension and evaluation of oral therapy.

*Medical Registrar.
†Registrar, Intensive Care Unit.
‡Director, Intensive Care Unit.
**Senior Lecturer in Medicine.
††Senior Resident Medical Officer.
Correspondence: Dr. W. G. Parkin, Intensive Care Unit, Prince Henry's Hospital, Melbourne, Victoria 3004
Accepted for publication: 6 April, 1977

Case History

Mr. R.M., a 34-year-old man, was admitted for control of malignant hypertension. He had been admitted four months previously for extensive investigation of hypertension – no cause was found and a diagnosis of essential hypertension made. Renovascular hypertension, renal parenchymal disease and phaeochromocytoma were specifically excluded. Between admissions features of his illness suggested the presence of a connective tissue disorder. For this reason, hydrallazine was avoided and he was given a trial of prednisolone without effect.

On admission his lying blood pressure was 190/140 mmHg. Fundoscopy revealed bilateral papilloedema, haemorrhages and exudates. There was evidence of biventricular cardiac failure. He had albuminuria and haematuria. His serum creatinine was 0·15 mmol/l (normal 0·03–0·12) and his creatinine clearance 39 ml/min (normal 90–120). Chest X-ray showed cardiomegaly. There was evidence of left ventricular hypertrophy, right bundle branch block and ischaemic change on the electrocardiogram.

His antihypertensive drugs were progressively increased such that on the day prior to intervention with sodium nitroprusside his daily therapy consisted of: cyclopenthiazide, 500 mg, alpha methyldopa, 1·5 g, clonidine, 675 μg, propranolol, 960 mg, bethanidine, 50 mg and prazosin, 15 mg. His blood pressure on this regimen was 240–250/140–150 mmHg. He failed to respond to intravenous clonidine and intravenous propranolol. Intravenous diazoxide reduced his blood pressure to 155/95 mmHg, but this returned to pre-treatment levels in about three hours. When it was elected to treat with sodium nitroprusside, clonidine was stopped.

Methods

The mean blood pressure was recorded using a Hewlett Packard transducer type 1280C connected to a Medicut Gauge 20 radial artery cannula. The system was continuously flushed with heparinised saline using a Holter 1200 series peristaltic pump with air embolus protection at a rate designed to produce a pressure drop of less than 1 mmHg between transducer and patient. A locally designed pressure

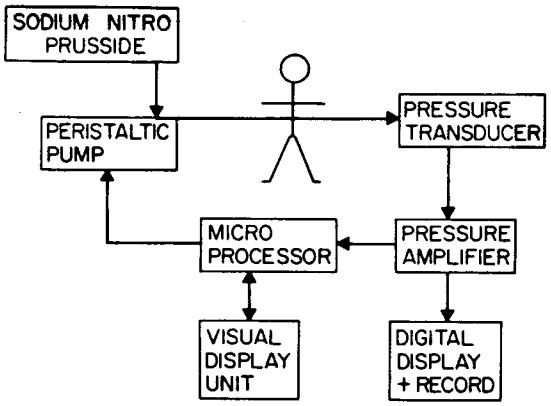

FIGURE 1. System used for controlling blood pressure with sodium nitroprusside and microprocessor.

amplifier allowed digital readout of systolic and diastolic or, alternatively, mean arterial pressure. An analog voltage, obtained from the amplifier was digitised for introduction into the microprocessor (Fig. 1). The microprocessor was a Fairchild F8 8 bit device consisting essentially of a chip-mounted central processor unit and programme storage unit addressing 2000 locations of random access memory. Microprocessor instructions were altered by way of a visual display unit (VDU) or teletype. The teletype allowed generation or loading of paper tape program. Programming was in machine code, simple mathematical operations requiring user-generated subroutines.

The digitised mean blood pressure reading was loaded into a memory register every two seconds via a microprocessor input/output port. Comparison of the actual blood pressure with a desired blood pressure, entered via the VDU, allowed the creation of an error term used in the control algorithm below.

The calculated infusion rate was generated as an 8 bit number (R) where $0 < R < 256$. Rate control of the nitroprusside pump (McLennan type PP 210) was achieved by altering the "on" time according to the value of R above. The pump was switched on every two seconds and remained on for R/256 of this time. The constant pump speed setting was arranged so that, with 100 mg of sodium nitroprusside in 500 ml of 5% dextrose, appropriate control ranges were achieved. In operation, infusion rates of sodium nitroprusside were of the order of 1 μg/kg/minute, similar to those described by other authors.[4]

The rate of infusion of SNP was given by the term $R = K_1 + K_2e$. The signed error term (e) represents the difference between the desired blood pressure and the actual blood pressure (mmHg), and K_2 is the constant of proportionality or gain. A value of five, obtained experimentally, was used for K_2. K_1 represents the infusion rate corresponding to the desired mean blood pressure when stable control has been achieved. In this situation the proportional term K_2e approaches zero. Initially an approximate value for K_1 was entered into the control algorithm. A signed integral term of the type $K_3\int_{i_0}^{i_n} edt$ was then used to modify the value of K_1 after each n blood pressure samples. K_1 was incremented or decremented according to whether the value of the actual blood pressure tended to exceed or not attain the desired value. In practice sampling occurred each two seconds and K_3 was set to unity. A value of 15 was chosen for n, K_1 thus being modified each 30 seconds. The upper limit for a single integral modification of K_1 ($0 \leqslant K_1 < 256$) was set at 64, that is one quarter of the control range. In this way the system tended to an appriate value of K_1.

The signed proportional term K_2e was used to enable a fast response to changes in the blood pressure. In summary the combination of proportional and integral control allowed both a rapid response to transients (proportional term) and a more gradual (adaptive) response (integral term). The latter allows the error term to equal zero in the stable control case.

A mathematical description of the way in which the blood pressure responds to SNP was not attempted. This was because of uncertainty about biological variables such as circulation time, dose response to SNP between individuals and SNP pharmacological half-life. An analysis of the step response and stability of the system at various gains is envisaged.

Thiocyanate levels in blood were measured by the method of Bowler.[5]

Results

The fast onset and short time of action of an intravenous infusion of SNP is illustrated in Figure 2. Whilst on oral antihypertensive medication the infusion of SNP at a rate designed to achieve a mean blood pressure of 100 mmHg, resulted in an overall calculated mean of 106 mmHg (SD 14) as recorded by intra-arterial measurement. With the introduction of diazoxide and labetalol decreasing amounts of SNP were required and it was finally discontinued (Fig. 3). No rebound rise in blood pressure was seen. Thiocyanate levels ranged between 0·19 and 0·53 mmol/l. Toxic features have not been reported below thiocyanate levels of 0·8 mmol/l.[4]

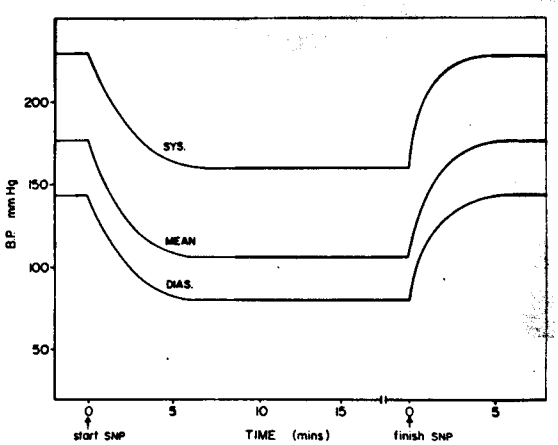

FIGURE 2. Acute change in blood pressure with commencement and cessation of sodium nitroprusside infusion (SNP); here a microprocessor has been programmed to achieve a mean arterial blood pressure of 100 mmHg.

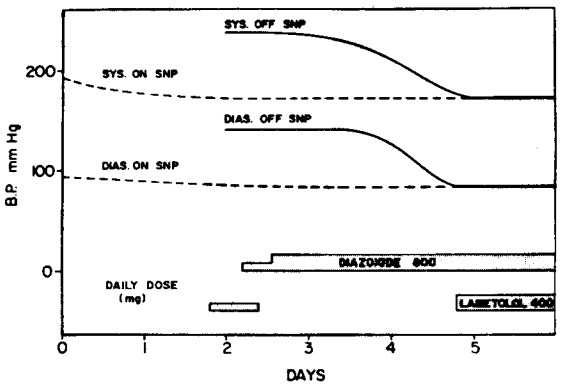

FIGURE 3. Effect of sodium nitroprusside infusion and of additional oral agents (diazoxide, labetalol) on blood pressure during five days of microprocessor control. The area of hatched bars is proportional to the daily dose of diazoxide (upper bar) and of labetalol (lower bars). The other oral agents were continued during this time (see text). Pressures shown were those recorded by a sphygmomanometer.

After stopping SNP, the patient's anti-hypertensive therapy was progressively reduced and he remained normotensive on daily doses of oral diazoxide, 800 mg, labetalol, 400 mg and amiloride, 5 mg.

Discussion

The immediate control of malignant hypertension in a way that allows the evaluation of oral maintenance therapy, would appear to be of considerable value. At least, the patient's hospital stay is shortened. At best, the patient is spared periods of high blood pressure and related organ damage. According to Koch-Weser[6] a few days of effective blood pressure control can restore therapeutic responsiveness to more conventional anti-hypertensive drugs. Such control is easily achieved with our approach. In addition, we were able to stop clonidine when it seemed ineffective and avoid the risk of withdrawal hypertension.

The minimal requirements for our system would be a pressure transducer and amplifier, a microprocessor, a teletype and ideally a visual display unit. It should be noted, however, that relatively simple machine operations may require considerable programming time. Developmental work is in hand to improve the control aspects of the present system. The stability and accuracy of the system as described were within clinically acceptable limits.

A number of authors have described the usefulness of sodium nitroprusside in the management of malignant hypertension.[1, 5] SNP is also used to achieve controlled hypotension during surgery and in the medical management of dissecting aortic aneurysm.[4] Low cardiac output states with acute myocardial infarction have been significantly improved by SNP therapy.[7, 8] The vasodilator action of the drug has been associated with the resolution of idiopathic lactic acidosis.[9]

Caution is required in the use of SNP. This is because nitroprusside is converted to cyanide and thence to thiocyanate. Thiocyanate may be slowly oxidised back to cyanide.[1] At no stage did our patient's thiocyanate levels exceed acceptable limits. Tissue toxicity may be associated with increasing CN-ion levels and may be best monitored by plasma cyanide levels or by measuring indices of anaerobic metabolism (elevated blood lactate or increased plasma hydrogen ion concentration).

No adverse side effects of nitroprusside were noted. Acute effects are the most common and are due mainly to vasodilator activity.[1] Nausea, vomiting, diaphoresis, dizziness and headache can occur. These effects subside promptly when the infusion rate is decreased. Less common side effects include tachyphylaxis[10], hypothyroidism, methaemoglobinaemia[11], cyanide poisoning[10] and metabolic acidosis. It would be possible, should tachyphylaxis occur, for a feedback system to infuse SNP at a rate which might be associated with cyanide toxicity. A projected program development is to include a warning signal when acceptable SNP infusion rates are exceeded.

Large doses of hydroxocobalamin (vit. $B_{12}a$) are an effective non-toxic antidote for cyanide poisoning.[12, 13] Cyanide poisoning is classically treated by the administration of nitrites to form methaemoglobin.[12] The accumulation of methaemoglobin can be dangerous. Sodium nitroprusside is contraindicated in states of low plasma vitamin B_{12} levels, impaired liver function and Leber's optic atrophy.[14]

Acknowledgements

We wish to thank Drs N. Balazs and P. Dennis, Department of Chemical Pathology, Prince Henry's Hospital, for measurement of thiocyanate levels and Dr. W. Barry, Department of Medical Electronics, Prince Henry's Hospital, for most valuable technical assistance.

References

1. Ahearn, D. J. and Grim, C. E. (1974): Treatment of malignant hypertension with sodium nitroprusside. *Arch. intern. Med.* **133**, 187.
2. Dessy, R. E. (1976): Microprocessors? An end user's view. *Science* **192**, 511.
3. Arnold, J. T. (1976): Microprocessor application: a less sophisticated approach. *Science* **192**, 519.
4. Palmer, R. F. and Lasseter, K. C. (1975): Sodium nitroprusside. *New Engl. J. Med.* **292**, 294.
5. Bowler, R. G. (1944): The determination of thiocyanate in blood serum. *Biochem. J.* **38**, 385.
6. Koch-Weser, J. (1976): Diazoxide. *New Engl. J. Med.* **294**, 1271.
7. Franciosa, J. A., Guiha, N. H., Limas, C. J., Rodriguera, E. and Cohn, J. N. (1972): Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet* **1**, 650.
8. Chatterjee, K., Parmley, W. W., Ganz, W., Forrester, J., Walinsky, P., Crexells, C. and Swan, H. J. C. (1973): Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. *Circulation* **48**, 1183.
9. Taradash, M. R. and Jacobson, L. B. (1975): Vasodilator therapy of idiopathic lactic acidosis. *New Engl. J. Med.* **293**, 468.
10. Amaranath, L. and Kellermeyer, W. S. (1976): Tachyphylaxis to sodium nitroprusside. *Anesthesiology* **44**, 345.
11. Bower, P. J. and Peterson, J. N. (1975): Methemoglobinemia after sodium nitroprusside therapy. *New Engl. J. Med.* **293**, 865.
12. Posner, M. A., Tobey, R. E. and McElroy, H. (1976): Hydroxocobalamin therapy of cyanide intoxication in guinea pigs. *Anesthesiology* **44**, 157.
13. Posner, M. A., Rodkey, S. L. and Tobey, R. E. (1976): Nitroprusside-induced cyanide poisoning. *Anesthesiology* **44**, 330.
14. Leading article (1975): Sodium nitroprusside in anaesthesia. *Brit. Med. J.* **2**, 524.