would caution, however, that if an ECG electrode other than the one tested is used, an initial period of close observation may be warranted.

With the use of disposable pregelled surface electrodes, we have found the study of neuromuscular function during anesthesia to be as safe, simple and convenient as routine ECG monitoring.

Tachyphylaxis to Sodium Nitroprusside

L. AMARANATH, M.D.,* AND W. F. KELLERMeyer, JR., M.D.†

Rapidly developing tolerance to the hypotensive effects of ganglionic blocking agents, when administered repeatedly and at short intervals, is well known.1 Similar pharmacologic behavior (i.e., acute tolerance) has not been reported to occur with sodium nitroprusside.2,3 However, cases in which initial high doses of sodium nitroprusside were needed have been reported.4 Even though the pharmacologic mechanisms of tachyphylaxis to sodium nitroprusside are not clear, the following case report describes the development of acute progressive tolerance to the administration of sodium nitroprusside.

REPORT OF A CASE

A 41-year-old Caucasian woman who had Legg-Calvé-Perthes disease was scheduled for left total hip replacement. Medical, surgical, and anesthetic history was unremarkable. The patient weighed 82 kg and was normotensive. According to cardiology and anesthesiology consultation, the patient was in good general health (ASA Physical Status I). The general laboratory work-up was within normal limits.

The patient was premedicated with morphine sulfate, 8 mg, and seconobarbital, 100 mg, im. In the operating room, after iv administration of atropine, 0.6 mg, the heart rate was 80 beats/min and blood pressure 120/80 torr. Induction and maintenance of general endotracheal anesthesia and sodium thiopental, 300 mg, iv, 70 per cent nitrous oxide, 30 per cent oxygen, morphine sulfate, 20 mg, iv, and d-tubocurarine, 48 mg, iv, were uneventful. Controlled ventilation via an Air-Shields respirator was adjusted to maintain arterial PaO₂, 30–35 torr. Esophageal heart sounds, lead II electrocardiogram, direct radial arterial pressure, arterial blood gases, and hourly urinary output were monitored.

After the fascia lata was incised, sodium nitroprusside (0.005 per cent solution in 5 per cent dextrose in water) was infused iv via microdrip to achieve controlled hypotension.5 Response to the drug was prompt, and systemic arterial blood pressure was easily maintained at 80/60 torr for approximately 30 minutes with 200 μg/min sodium nitroprusside. During the following 30 minutes the heart rate increased from 80 to 100 beats/min and the dose of sodium nitroprusside had to be increased to 500 μg/min to maintain systolic pressure around 90 torr. At this stage the pupils were constricted. Even though there was no sign of “light” anesthesia, morphine sulfate, 10 mg, and thiopental, 600 mg, iv, were administered in incremental doses, with no appreciable effect on heart rate or on the sodium nitroprusside dosage. The systolic blood pressure kept rising, necessitating a further increase in nitroprusside dosage (fig. 1). At this time we decided to use a fresh, more concentrated solution of nitroprusside (0.01 per cent in 5 per cent dextrose in water). During the next 45 minutes the nitroprusside dosage had to be progressively increased to 1,200 μg/min (approximately 15 μg/kg/min). Arterial blood-gas analysis at the peak of tolerance to nitroprusside showed pH 7.35, PaO₂ 35 torr, and PbO₂ 100 torr. The hypotensive technique was abandoned and samples of blood and urine were obtained for catecholamine and renin activity estimation. The remainder of the operative procedure was completed with blood pressures ranging from 180/100 to 160/90 torr and heart rates from 110 to 100 beats/min. Total anesthesia time was 4 hours, 15

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minutes. Estimated operative blood loss was 1,200 ml, and total blood and fluid replacement consisted of 1,000 ml of whole blood, 1,200 ml of 5 per cent dextrose in lactated Ringer’s solution, and 1,000 ml of 5 per cent dextrose in water. During anesthesia the urinary output averaged 75 ml/hr. Intraoperatively arterial blood gases were normal throughout the procedure.

At the end of the operation the residual d-tubocurarine was reversed with atropine and neostigmine, iv, and the trachea extubated. In the recovery room, blood pressure and heart rate returned to preoperative levels, and the patient did not require any narcotic for the first 12 hours postoperatively. Arterial blood-gas analysis in the third postoperative hour, during spontaneous breathing (oxygen by mask), showed pH 7.36, Po2 37 torr, and Pco2 120 torr. The rest of the hospital course was uneventful.

Plasma and urinary catecholamine levels were measured by the Anton and Sayre method and plasma renin activity was analyzed by radioimmunoassay. Urinary and plasma norepinephrine and epinephrine, urinary vanillylmandelic acid, and plasma renin activity at the peak of tolerance to nitroprusside were within the normal ranges.

**DISCUSSION**

The prompt initial decrease in the systemic arterial pressure in response to a small dose of nitroprusside, followed by a progressive diminution in the hypotensive effect of the drug, found in this case, documents the occurrence of acute tachyphylaxis to continuous intravenous infusion of nitroprusside under general anesthesia. The mechanism of the tachyphylaxis is not clear. Several possibilities can be listed: 1) The drug may have gradually deteriorated during infusion. This possibility is not feasible because we exercised the recommended precautions, and furthermore, use of a fresh, more concentrated solution did not correct the problem. The efficacy of the drug batch in question was confirmed by Roche Company on July 30, 1975. 2) Increase in the sympathetic tone, heart rate and blood pressure during “light anesthesia” is well known. Our patient was clinically well anesthetized during the entire operative procedure. Furthermore, supplemental iv administration of narcotic and barbiturate did not help lower the drug dosage. 3) Although chemoreceptor reflex and CNS ischemic responses are known to counteract induced hypotension, these mechanisms probably did not play a major role, because the time for development of tachyphylaxis was too long, arterial oxygenation was adequate, and systemic systolic pressure was maintained at or above 90 torr. 4) The renin–angiotensin–
vasoconstrictor mechanism is known to return the lowered systemic pressure toward normal. Kaneko et al. found a significant increase in plasma renin activity when mean arterial pressure was lowered to 60–75 torr. In our patient, systolic pressure was maintained at or above 90 torr and plasma renin level was normal. 5) Asymptomatic pheochromocytoma can, under stressful conditions, discharge massive amounts of pressor amines, resulting in a hyperkinetic cardiovascular system. The normal levels of intraoperative plasma and urinary catecholamines rule out this possibility. 6) Considering the amount of blood lost and the duration of the operation, intraoperative blood and fluid administration is not a critical factor in this case. 7) Finally, there is the possibility of development of tolerance at the cellular site of drug action. Needleman and associates have shown tachyphylaxis to a variety of direct-acting vasodilators in in vitro preparations. According to their model, nitroprusside-induced tachyphylaxis can be explained in terms of the drug and tissue sulfhydryl interaction leading to the accumulation of less sensitive disulfide groups.

Overall, the baroreceptor mechanism and probably the nitroprusside-sulfhydryl interaction and accumulation of disulfide which has been reported to lower the efficacy of this drug are the best explanations for the observed nitroprusside-induced tachyphylaxis. Although blood cyanide levels were not measured in this patient, the biologic implications of tachyphylaxis to sodium nitroprusside warrant a word of caution. Nitroprusside has the potential to liberate cyanide by a nonenzymatic reaction with free sulfhydryl groups in either the erythrocytes or other cells and also by a direct nonenzymatic interaction with hemoglobin. Theoretically, nitroprusside overdosage could lead to an initial severe metabolic acidosis followed by failure of blood pressure to return to normal. Cyanide toxicity has been implicated in such cases. Due to the relatively slow rate of the nonenzymatic reaction, the liberation of cyanide and development of the metabolic acidosis may not occur for 1½–3 hours after commencement of nitroprusside infusion. In our patient there was no indication of development of metabolic acidosis during infusion of the drug or after its discontinuation. However, we still elected to discontinue nitroprusside infusion for the following reason. A study in baboons by McDowell et al. suggests that the difference between the effective and toxic doses of nitroprusside, presumably through the liberation of cyanide, may be close to 1:4, and that the lowest infusion rate associated with nitroprusside toxicity is 80 µg/kg/min. Based on these considerations, we limit the dose of nitroprusside at the present time to not more than 15 µg/kg/min in our surgical patients.

ADDENDUM

Since this paper was submitted, Davis et al. have reported a fatality associated with very high doses of sodium nitroprusside (120 µg/kg/min) during halothane, N₂O, and O₂ anesthesia. The group from the Hospital for Sick Children, Toronto, also noticed acute tolerance to sodium nitroprusside, and they suggest alternative methods if the projected nitroprusside dose for the anticipated procedure exceeds a total dosage of 3 mg/kg.

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Ankle-block Anesthesia for Foot Surgery

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Regional ankle-block anesthesia in foot surgery has the potential for decreasing anesthetic mortality and morbidity while simplifying surgical treatment. Regional anesthesia for foot surgery, as presented here, is not an original concept, but has not achieved the widespread popularity it deserves. The reason for the present in-depth description is to popularize this procedure by detailing its methods and presenting our experiences with it.

MATERIALS AND METHODS

Premedication includes a drug such as diazepam to decrease potential lidocaine toxicity and to alleviate anxiety. The patient is placed supine on the operating table, with a bolster temporarily placed under the calf to facilitate preparation.

The ankle is cleansed and the regional anesthesia is applied using 0.5 or 1.0 per cent lidocaine without epinephrine. Lidocaine, 5 ml, is injected in a fan-like manner into the posterior tibial nerve, which is approximately one fingerbreadth posterior to the medial malleolus (figs. 1, 5–7). Next, lidocaine, 3 ml, is injected into the deep peroneal nerve just proximal to the level of the tibiotaral joint (figs. 2, 5–7). Block of the sural nerve, just posterior to the distal fibula, is performed likewise (figs. 3, 5–7). Ordinarily, the saphenous nerve need not be given special attention.

After injection of lidocaine into these nerves, a subcuticular injection of 0.5 per cent lidocaine without epinephrine is made around the complete circumference of the ankle joint, just proximal to the maleoli. This anesthetizes many small but significant sensory nerves (figs. 4–7) and anesthetizes the area where the tourniquet will be applied. It has not proven important to locate the nerve precisely by production of parasthesias with the injecting needle when the individual nerve blocks are performed. With an approximate knowledge of where these nerves are, lidocaine, 3–5 ml, in each area is sufficient when given in a fan-like distribution down to the region of the periosteum. If both feet are to be operated on, the injections may be performed simultaneously in both ankles.

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