Nitrous Oxide-Curare Anesthesia: Reappraisal*

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Of the many inhalation drugs available today, nitrous oxide is the only one which is both non-explosive and non-toxic. Although the compound is rarely listed as a primary agent, it is used on almost every patient. The usefulness of nitrous oxide tends to be dismissed because it is considered to be relatively weak. However, with the continuing trend toward lighter anesthesia seen during the past quarter century, this viewpoint is no longer reasonable. The fact that MAC for halothane can be reduced to one third by the addition of 70% nitrous oxide attests to the drug's potency.

The experience of many practicing anesthetists throughout the United States indicates that anesthetic administration currently is more striking in its similarities than in its differences. It may even be said that a universal modern anesthetic sequence has evolved (fig. 1). First, almost everyone uses thiopental or some other barbiturate for induction, as a social necessity. Second, nitrous oxide in a concentration of 50% to 70% is invariably employed during the maintenance phase of anesthesia. Third, a muscle relaxant is used in most major cases, both to facilitate intubation and to produce surgical relaxation. Deep anesthesia is almost never relied upon. Finally, some other drug, perhaps halothane, ether, or Innovar may be adopted—in conjunction with nitrous oxide—for the maintenance of anesthesia. According to tradition this is called the primary agent. But with the aforementioned trend toward very light anesthesia, more often than not, this agent is adjunctive in nature. In fact, in some instances, an adjunctive drug is not used at all.

MODERN ANESTHETIC SEQUENCE

1. THIOPENTAL INDUCTION
2. NITROUS OXIDE
3. MUSCLE RELAXANT
4. (ADJUNCTIVE AGENT)

Fig. 1—Modern anesthetic sequence.

In the 1950's the British developed a technique in which very large doses of curare were used in combination with nothing more than nitrous oxide to produce the condition of anesthesia. No other adjunctive drug was used for maintenance. In this way, explosive agents were avoided. The process became known as the "Liverpool Technique" (Geddes and Gray, 1959). Part and parcel of the Liverpool Technique was the intentional production of respiratory alkalosis by hyperventilation. It was felt that alkalosis increased the depth of anesthesia. In recent years, however, the depressant effects of this condition have been questioned and, indeed, alkalosis itself has been shown to be not without its hazards.

During the past four years, we at Roosevelt Hospital have been increasingly interested in avoiding not only explosives but also potentially toxic agents. We have adopted essentially the Liverpool Technique (that is, nitrous oxide without supplementation, and curare) and modified it in two major aspects: we have employed normal ventilation, and we have modified the curare dosage. To date this technique has been applied to approximately 3,200 patients.

Technique. Figure 2 is a step-by-step description of the technique as we have employed it. Premedication has been variable, but we prefer a narcotic in the usual clinical doses. Thiopental is used for the induction of anesthesia in a dosage sufficient to abolish the lid reflex. One hundred percent oxygen is administered by mask for about two minutes, either prior to or immediately after the thiopental, and then after intravenous succinyl-

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1. PREMEDICATION: NARCOTIC PREFERRED
2. THIOPENTAL, 4-8 mg/kg
3. O_2 100% 2 MIN.
4. SUCCINYLCHOLINE 1 mg/kg
5. INTUBATION
6. N_2O 3.5 L, O_2 1.5 L.
7. VENTILATOR, MV = 90 ml/kg
8. CURARE: BY DOSAGE SCHEDULE
9. REVERSAL: NEOSTIGMINE 2.5 mg
   ATROPINE 1.0 mg
10. DECISION TO EXTUBATE

Fig. 2—Roosevelt Hospital's adaptation of the Liverpool Technique.

choline, endotracheal intubation is carried out. Immediately after intubation, nitrous oxide 3.5 liters and oxygen 1.5 liters are allowed to flow into the partial rebreathing circle system. This flow is then maintained throughout the remainder of the operation. A mechanical ventilator is employed in all instances promptly after intubation. The ventilator is set to deliver a calculated minute volume of 90 ml per kg. A relatively slow respiratory rate, approximately 8 to 10 per minute, with a relatively large tidal volume is preferred. The minute volume is routinely checked with a Wright ventilometer. With signs of returning muscle power following succinylcholine, curare is administered by a dosage schedule described in figure 5. Full curarization is maintained throughout the procedure. At the termination of the surgical procedure, reversal of curare is accomplished with the use of neostigmine 2.5 mg and atropine 1 mg given simultaneously intravenously and repeated once if necessary. Finally, a decision to extubate is made by clinical means. If the patient is capable of coughing vigorously on the endotracheal tube and of using his upper intercostal muscles to take a deep breath, and can lift his head off the table, the endotracheal tube is removed. If not, the patient is taken to the recovery room where mechanical ventilation is continued until full motor power returns spontaneously.

It should be noted that the above description of the nitrous oxide-curare technique contains nothing really extraordinary. Mechanical ventilation perhaps is not commonly employed, but it is generally accepted in modern anesthesia. Everything else on the list is very much a part of standard practice every day everywhere throughout the United States. Indeed, this sequence is really an example of the basic structure on which an anesthetic in this day and age is often built. What is surprising about the list, therefore, is not what is on it but what is missing from it. Note that there is no adjunctive drug listed. Or to use the more traditional terminology, there is no primary agent. Once the nitrous oxide is begun and the curare is given, no other agent is administered, either intravenously or by inhalation. Nitrous oxide is relied upon totally to produce unconsciousness, and curare is relied upon totally to keep the patient on the table.

Memory. The most significant question about this technique is whether 70% nitrous oxide by itself is enough to produce unconsciousness reliably in all patients. The only way to answer this is with the evidence of extensive experience. As mentioned earlier, we have used this technique fairly widely in all age groups on approximately 3,200 adult patients and in all types of surgery with the exception of intrathoracic procedures. Approximately two thirds of the cases were intra-abdominal. The technique has been used in operations ranging from one hour in length to well in excess of 6 hours, with an average of three hours, and it has been adopted for patients representing all grades of ASA physical status from 1 to 5, although the majority were either 2 or 3. As of this date, we know of no patient of the 3,200 who were actually receiving 70% nitrous oxide, who had any pain or any other conscious memory of the surgical procedure.

We did have five patients who remembered certain things due to a break in technique. Four of the five remembered either intubation or extubation. As a result, we have begun to use liberal amounts of induction thiopental and to continue nitrous oxide up to the moment of curare reversal. In one patient, a brief period of memory did occur during the operation. This patient remembered severe pain and a conversation which we knew did occur. On further investigation, however, we found that just before the period of memory the anesthetist had disconnected the endotracheal tube for suctioning for approximately 20 seconds. During this time the ventilator continued to operate. It emptied itself of nitrous oxide and drew air into the system through the open connector. For the next several minutes the patient received air instead of nitrous oxide.

We conclude that nitrous oxide in a concentration of 70%, does prevent memory totally and in all patients. However, the slightest break in technique

can result in memory and must be guarded against continuously.

Ventilation. A mechanical ventilator has been utilized in all cases in our experience. In addition, a Wright ventilometer is routinely used to verify the presence of proper minute volume. We have selected a figure of 90 ml per kg body weight for estimation of the minute volume on the basis of prior experience, both in the operating room and in our respiratory intensive care unit where arterial blood gas analysis revealed a $PaCO_2$ of between 35 and 45 mm Hg in most patients. This fact has also been documented in a study independent from ours (Ocbo and Terry, 1969).

Our real concern, however, was whether, with normocapnea, adequate arterial PO_2 levels could be reliably produced. We found in our early studies on healthy patients undergoing abdominal surgery, that PO_2's in excess of 100 mm Hg were produced routinely. However, in an attempt to look at the worst possible circumstance, we also studied 16 patients undergoing abdominal aortic graft procedures with 70% N_2O-curare anesthesia. Serial blood gas determinations during surgery yielded the results listed in figure 3. In no case was the PO_2 ever below 60

Abdominal Aortic Grafts
Mean Age 68 – 7 (S.D.)
ASA Status 2 – 4

Lowest PaO_2	Number
Under 60	0
60 – 69	4
70 – 79	6
80 – 89	1
90 – 99	3
100 +	2
Total	16

Fig. 3—Serial blood gas determinations during surgery with N_2O-curare anesthesia.

mm Hg, and in 12 of the 16, the lowest PO_2 recorded was above 70 mm Hg. While this does not indicate lush oxygenation, these PO_2 values probably do represent the normal levels for this age group. The average PCO_2 in this series was 38 mm Hg. It is worth repeating that a very slow ventilatory rate, 8 to 10 per minute with a relatively high tidal volume, was employed. It has been our experience that this ventilatory pattern yields consistently higher PO_2 values than a rapid, shallow pattern.

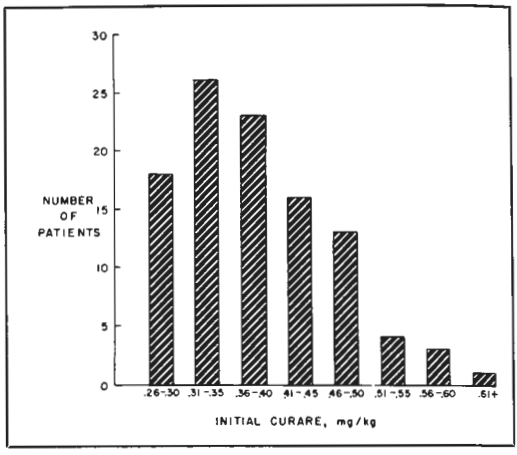

Fig. 4—Graph showing study of curare dosage necessary to produce paralysis.

We conclude that with normocapnea, adequate oxygenation can be produced, so long as the ventilatory pattern is proper, and so long as patients with severe intrapulmonary shunting, such as occurs in intrathoracic surgery, are avoided.

Curare Dosage. Traditionally, a clinically effective single dose of curare is said to be in the range of 0.5 to 0.6 mgm per kg body weight. In a series of 100 cases of patients undergoing elective surgery with thiopental-N_2O-O_2 anesthesia, we found that a dose of 0.3 mg per kg produced a clinically adequate degree of paralysis in about half the patients, as seen in figure 4.

From this experience we developed the curare dosage schedule outlined in figure 5. A dose of curare is calculated on the basis of 0.3 mg per kg and is administered to each patient. If this is not sufficient to

CURARE DOSAGE SCHEDULE

1. INITIAL
   a) 0.3 mg/kg
   b) IF INSUFFICIENT, 1 ml INCREMENTS
2. SUBSEQUENT DOSES
   a) GIVEN $\bar{q}$ 20–40 MIN
   b) EACH DOSE = $\frac{1}{2}$ PREVIOUS DOSE

Fig. 5—Outline of curare dosage schedule.

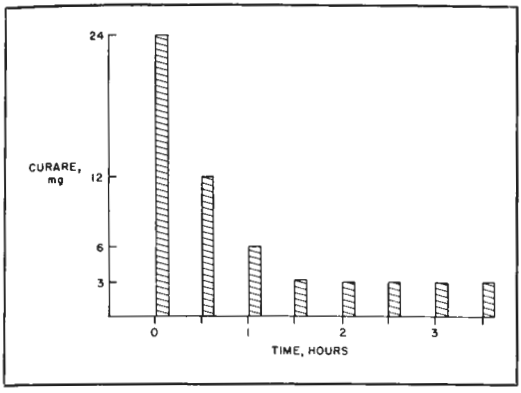

Fig. 6—Dosage schedule of curare administration.

abolish all coughing and respiratory activity, additional curare is administered in 1 ml (3 mgm) increments until all gross motor activity ceases. The total amount of curare is noted at this point, and becomes the basis for all subsequent doses. Each subsequent dose needs be only one half its previous dose, and it is required every 20 to 40 minutes when signs of returning muscle activity occur. When a dose of 3 mgm is reached, it is repeated, without halving, as necessary. An example of a dosage schedule in a typical case is shown in figure 6.

Using this dosage schedule, we have been able to reliably produce adequate continuous curarization with reasonable total curare doses. Figure 7 is a plot of the total curare dose in one hundred consecutive cases against the total duration of anesthesia. Total dose was clearly related to time. More important, the average dose was approximately 0.7 mg per kg which, for the average patient, represents a total of 50 mgm curare during a 3-hour anesthetic. This compares very favorably with the experience of the British.

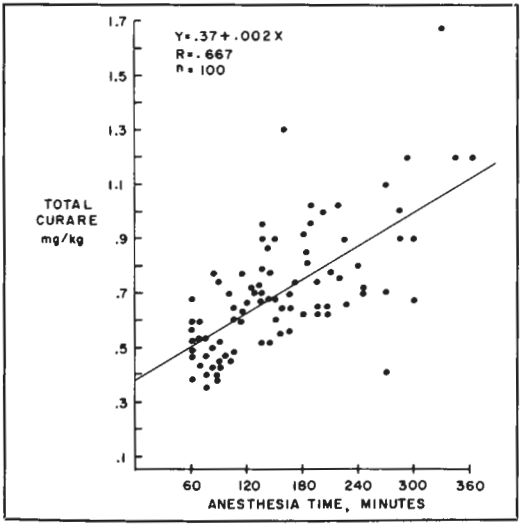

Fig. 7—Graph showing total curare dose as measured against duration of anesthesia in 100 cases.

Blood Pressure Changes. Significant hypotension incident to the administration of clinical doses of curare has been reported (Thomas, 1957). In our experience, however, this has not been a problem. Figure 8 is a compilation of the lowest and highest blood pressures noted in 100 patients, as measured by the cuff method, during the twenty minutes following the initial curare dose. While some patients responded with very low—and some with very high—blood pressures, the majority showed only mild changes, and no definite trend of clinical significance could be discerned.

Figure 9 is a plot of the degree of hypotension seen in those 55 patients in the series who suffered a fall in pressure, versus the dosage in each case. We could discern no dose-response relationship. We conclude that while curare has been reported by others to cause hypotension it does not do so to a clinically significant degree in the dosage range employed in this series.

Curare Reversal. Early in our experience we noted an occasional patient who was unable to maintain adequate spontaneous ventilation following the administration of neostigmine, even though these patients had not received excessive doses of curare. This was surprising in view of the well-documented fact that neostigmine is a highly predictable antagonist for curare (Bridenbaugh and Churchill-Davidson, 1968; Katz, 1967). However, review of these cases disclosed the fact that many had received intraperitoneal antibiotics of the type known to produce muscle paralysis (Pittinger, *et al.*, 1970), and all the others had been either hypothermic or hypovolemic at the time of attempted curare reversal. These factors have been shown to delay significantly the redistribution of curare (Dal Santo, 1964). Following this discovery we instituted the practice of omitting neostigmine reversal in those patients who had received intraperitoneal antibiotics, who were hypothermic, or in whom a hypoperfusion state was judged to be present. The endotracheal tube was left

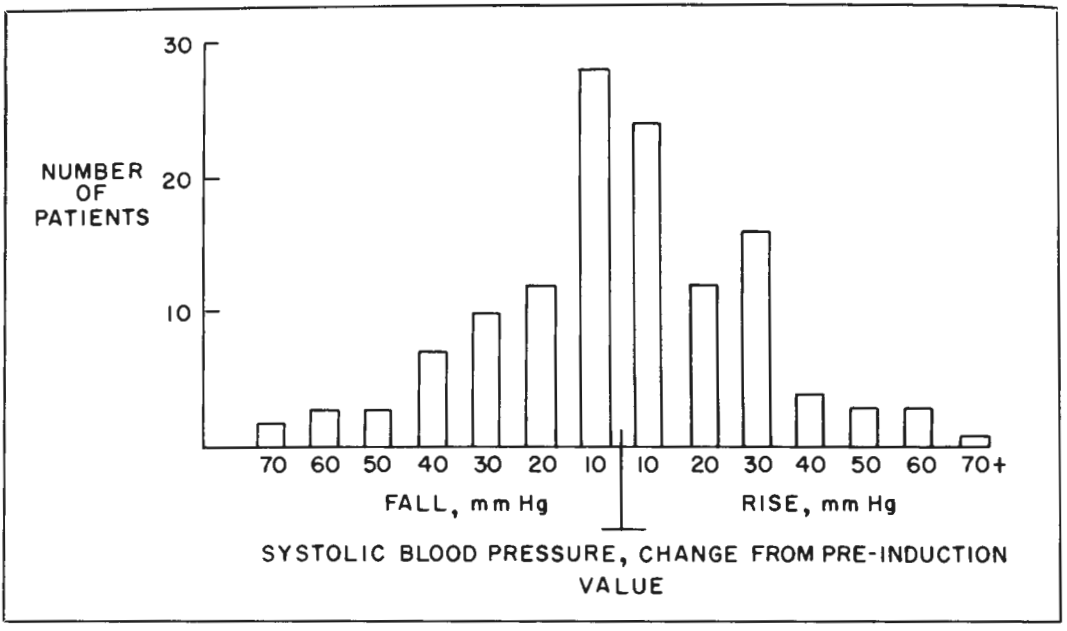

Fig. 8—Blood pressure readings of 100 patients following induction of curare.

in place, and muscle power was allowed to return spontaneously while the patient was ventilated mechanically in the recovery room. After the institution of this practice, experience in 100 consecutive patients was reviewed and is summarized in figure 10. Eighteen patients were intentionally not reversed; of these, six had undergone procedures, such as abdominal aortic grafts, in which postoperative mechanical ventilation is utilized in our institution as a matter of course. Hypoperfusion, hypothermia, the use of intraperitoneal antibiotics, or a combination of these, were present in all other instances.

Of the 82 cases in which neostigmine was employed, only one failed to develop adequate spontaneous ventilation, and in this one case, severe hypovolemia from unrecognized surgical blood loss was noted shortly thereafter; spontaneous ventilation returned with the transfusion of two units of whole blood. We conclude that neostigmine is indeed a predictable antagonist for curare so long as the pathologic conditions noted above are excluded.

Conclusions.

1. Seventy percent N_2O, as a sole depressant agent, is adequate to prevent pain and memory in 100% of cases. There is no evidence

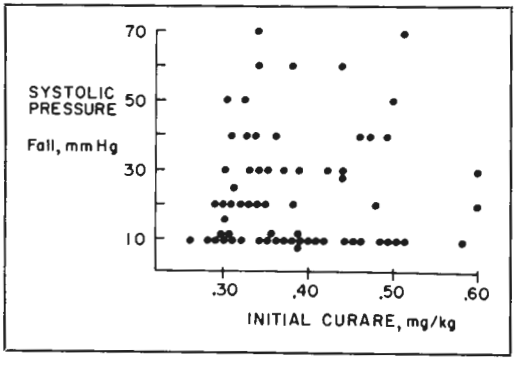

Fig. 9—Graph showing degrees of hypotension in patients as measured against individual curare dosage.

CURARE NOT REVERSED: 18 PATIENTS	
1. PLANNED POSTOP. VENTILATION	6
2. HYPOPERFUSION	7
3. HYPOTHERMIA	6
4. I. P. ANTIBIOTIC	7

Fig. 10—Results of review where curare was not reversed.

that it is ever inadequate as an anesthetic, even in deep intra-abdominal operations. Therefore, with this technique, the use of other potent depressant agents either by inhalation or by vein is unnecessary. Major organ toxicity is thus avoided, and recovery from anesthesia is prompt. Furthermore, major cardiovascular abnormalities occurring during surgery can be assumed to be due to factors other than anesthesia, since neither N_2O nor curare alter cardiovascular function significantly.

2. Curare dosage need not be excessive. When used according to the recommended schedule, it is well within the range known to be successfully antagonized with neostigmine and below the level known to produce significant hypotension.
3. Hypoxia need not occur, so long as mechanical ventilation is properly applied and meticulously measured. Whenever there is doubt, arterial blood gas analysis should be available.
4. Curare reversal has proved to be successful in all cases except in those instances in which there is some pathologic process which delays curare redistribution such as hypovolemia, or hypothermia, or in those instances in which intraperitoneal antibiotics are used. In those cases, one must be prepared to utilize postoperative mechanical ventilation.

REFERENCES

BRIDENBAUGH, P. O. AND CHURCHILL-DAVIDSON, H. C. Response to tubocurarine chloride and its reversal by neostigmine methylsulfate in man. *JAMA* 203:541–544, 1968.

DAL SANTO, G. Kinetics of distribution of radioactive labelled muscle relaxants: I. Investigations with C-14-dimethyl-d-tubocurarine. *Anesthesiology* 25:788–800, 1964.

GEDDES, I. C. AND GRAY, T. C. Hyperventilation for the maintenance of anesthesia. *Lancet* II: 4–6, 4 July, 1959.

KATZ, R. L. Neuromuscular effects of d-tubocurarine, edrophonium, and neostigmine in man. *Anesthesiology* 28:327–336, 1967.

OCBO, E. M. AND TERRY, R. N. Proposed formula for ventilatory requirements in apneic anesthetised patients. *Anesth. & Analg.* 48:455–460, 1969.

PITTINGER, C. G., ERYOSA, Y., AND ADAMSON, R. Antibiotic-induced paralysis. *Anesth. & Analg.* 49:487–501, 1970.

THOMAS, E. T. Effect of d-tubocurarine chloride on the blood pressure of anesthetised patients. *Lancet* 722, 10 October, 1957.