Attenuation of Fentanyl-induced Truncal Rigidity

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Narcotic anesthesia with fentanyl has been associated with truncal rigidity. Although Stanley et al., 1 using the slow infusion rates of fentanyl for induction of anesthesia, found no incidence of rigidity, Comstock et al.2 and Waller et al.3 have reported high incidences of truncal rigidity. Varying methods have been used in an attempt to alleviate or prevent this rigidity and thereby reduce the rise in PaCO2 associated with the resultant ventilatory impairment. The site of action of fentanyl in causing rigidity has not been elucidated specifically.

Metocurine and d-tubocurarine act at presynaptic receptor sites on motor nerve terminals.4 Pancuronium, on the other hand, has predominantly a postsynaptic site of action.5 Lebowitz et al.6 have shown potentiation of pancuronium-induced neuromuscular blockade by metocurine, presumably due to their different sites of action. We investigated the effects of pretreatment with equipotent dosages of metocurine or pancuronium, administered three minutes prior to induction, on fentanyl-induced rigidity. Time to abatement of rigidity when it occurred and onset of complete neuromuscular blockade by a bolus of pancuronium following metocurine or pancuronium pretreatment also were examined.

METHODS

Studies were conducted with 27 patients scheduled for open heart surgery. Approval for the study was obtained from the institution's Clinical Research Practices Committee. Twenty-two patients were scheduled for coronary artery bypass grafting and five patients were to undergo valvular replacement. Patient age ranged from 42 to 60 years and weight ranged from 50 to 110 kg. All patients were ASA Class III.

Patients were divided into three groups of nine patients. Group 1 patients received no pretreatment and served as controls. During preoxygenation, patients in Groups 2 and 3 received an equipotent dose of pancuronium (12.5 µg/kg) or metocurine (50 µg/kg).7 Group assignment was known to the staff anesthesiologist, but was unknown to the anesthetist responsible for subjective scoring of rigidity. Three minutes after pretreatment with saline (Group 1), pancuronium (Group 2), or metocurine (Group 3), anesthesia was induced with fentanyl (50 µg/kg, iv) at an administration rate of 1 mg/min. During the study period, all patients received 100% oxygen by facemask via a semiclosed circle anesthetic system. No drugs other than fentanyl (50 µg/kg) and the muscle relaxants described were administered for induction of anesthesia. Upon loss of response to verbal command or upon development of severe truncal rigidity a pancuronium bolus (112.5 µg/kg in Group 1; 100 µg/kg in Groups 2 and 3) was administered to induce neuromuscular blockade. Relaxant doses were designed such that each patient, regardless of group assignment, received equipotent neuromuscular-blocking dosages, assuming additive effects.

After induction of anesthesia and prior to the bolus dose of pancuronium, control train-of-four response was elicited with a model MS-1 Ministim® via surface electrodes over the ulnar nerve. Train-of-four response was subsequently monitored every 10 s until the first twitch was barely discernible. Ventilation and assessment of rigidity was attempted 10 times per minute during induction after loss of response to command. If difficulty ventilating a patient was encountered, an oropharyngeal airway was inserted to rule out upper airway obstruction as the cause. Time from administration of the paralyzing dose of pancuronium to disappearance of rigidity, if it occurred, and time for onset of complete neuromuscular blockade as defined above were measured. A subjective rigidity score was assigned based on a scale of 0 to 3: 0 being no rigidity; 1 being noticeable rigidity with minimal ventilatory impairment; 2 being rigidity
with marked ventilatory impairment; and 3 being inability to ventilate due to severe rigidity.

Data were analyzed using Kruskal-Wallis one-way analysis of variance to determine statistical significance for each variable between any of the three groups. Data then were analyzed non-parametrically using a Kruskal-Wallis test for statistical significance.\textsuperscript{8}

\textbf{RESULTS}

Mean and standard error of the mean for each variable are summarized in table 1. In Group 1, eight of nine pretreated patients developed severe rigidity. This rigidity required 35 to 90 s to abate after bolus pancuronium (112.5 \mu g/kg) administration. At this point no discernible change in train-of-four had occurred. Complete neuromuscular block occurred within 105 to 260 s. One of nine patients in Group 2 pretreated with pancuronium (12.5 \mu g/kg) developed mild rigidity, three developed moderate rigidity, and five developed severe rigidity. This rigidity required 30 to 60 s to abate after bolus administration of pancuronium (100 \mu g/kg), significantly different from control (\(P < 0.05\)). Again no discernible train-of-four change was present when the rigidity broke. Complete neuromuscular block was achieved within 100 to 240 s. Only one of nine patients in Group 3 pretreated with metocurine (50 \mu g/kg) developed severe rigidity, while the other eight had only mild or no rigidity. In the patient developing severe rigidity, the rigidity was relieved 18 s after bolus administration of pancuronium (100 \mu g/kg). Complete neuromuscular blockade occurred within 75–130 s in Group III. All three variables in patients pretreated with metocurine (Group 3) differed significantly (\(P < 0.01\)) from control patients (Group 1) and those pretreated with pancuronium (Group 2).

\textbf{DISCUSSION}

Stanley and Webster,\textsuperscript{4} infusing fentanyl at a rate of 50 to 100 \mu g/min during the first 4 min of induction and at 150 to 200 \mu g/min thereafter to a total dose of 50 \mu g/kg, noted no rigidity in 23 patients. More recently, Comstock et al.,\textsuperscript{5} reported that 20 of 21 patients receiving fentanyl at an infusion rate of 200 \mu g/min developed truncal rigidity impairing ventilation. Waller et al.\textsuperscript{6} noted that 12 of 12 patients receiving fentanyl (50 \mu g/kg) developed rigidity requiring succinylcholine-induced paralysis to maintain normocapnia. The use of succinylcholine was necessary prior to loss of consciousness. Stoelting et al.,\textsuperscript{7} infusing 10 \mu g/kg fentanyl or fentanyl-droperidol (10 \mu g/kg plus 100 \mu g/kg) over a 20-min period, noted severe rigidity in seven of 21 patients requiring succinylcholine administration. A statistically significant increase in central venous pressure noted in these patients was ascribed to thoracoabdominal rigidity. Using only 80 to 200 \mu g of fentanyl, Holderness et al.\textsuperscript{8} observed an 8\% incidence of muscular rigidity. Hill et al.\textsuperscript{9} reported nine of 10 patients who received 2.5 mg of fentanyl at an infusion rate of 3 \mu g \cdot kg^{-1} \cdot min^{-1} developed severe rigidity. Simultaneous administration of pancuronium (12 \mu g \cdot kg^{-1} \cdot min^{-1}) prevented the development of rigidity. Mean time to rigidity was 5 min which means approximately 60 \mu g/kg of pancuronium had been infused at a time when rigidity would be expected to occur. Although these authors did not find any evidence for it in postoperative questioning, this technique might result in noticeable weakness of patients while still conscious. Our technique, with a more rapid infusion rate of fentanyl (1 mg/min), resulted in an 88\% incidence of severe rigidity in patients not receiving pretreatment with a non-depolarizing relaxant. The incidence and severity of rigidity (Rigidity Score) was not affected by pretreatment with pancuronium. A statistically significant reduction in rigidity score was accomplished, however, by pretreatment with metocurine (50 \mu g/kg). Only one of nine patients in Group 3 had a degree of rigidity impairing ventilation by bag and mask. These pretreatment doses and the three minutes allowed prior to induction of anesthesia correspond to doses and timing commonly used prior to use of succinylcholine for tracheal intubation.

Severe rigidity, when it did occur, abated sooner if pretreatment with pancuronium (12.5 \mu g/kg) or metocurine (50 \mu g/kg) preceded fentanyl administration. Disappearance of rigidity occurred before any observable change in train-of-four response. One possible explanation is the need for a certain percentage of receptors to be blocked to relieve the rigidity. Waud and Waud\textsuperscript{10} demonstrated that 70\% receptor blockade is
necessary for any discernible change in train-of-four response. The percentage of receptor blockade necessary for relief of rigidity may be less.

Galindo\textsuperscript{13} and Glavinoc\textsuperscript{4} demonstrated that \textit{d}-tubocurarine acts predominantly at prejunctional receptors. Metocurine, due to its structural similarity to \textit{d}-tubocurarine, presumably acts primarily on prejunctional receptors as well. Bowman recently reviewed the mechanism of action of both \textit{d}-tubocurarine and pancuronium.\textsuperscript{5} Pancuronium, although able to block prejunctional sites, predominantly affects postjunctional receptors in affecting neuromuscular blockade. Lebowitz \textit{et al.}\textsuperscript{6} have shown potentiation of neuromuscular blockade by the combination of metocurine or \textit{d}-tubocurarine with pancuronium presumably due to the different sites of action. Our results are consistent with this. More rapid onset of neuromuscular blockade was observed with pancuronium (100 µg/kg) preceded by metocurine (50 µg/kg) than with an equipotent dose of pancuronium alone. Although we did not establish that a deeper neuromuscular block was produced by pretreatment with metocurine compared with pancuronium, the more rapid onset of a complete block in Group 3 compared with Group 2 suggests a more potent effect of this combination at the neuromuscular junction. Perhaps, metocurine is superior to pancuronium in attenuating fentanyl-induced rigidity because of its presynaptic effects.

In summary, rapid administration (1 mg/min) of high-dose fentanyl (50 µg/kg) for induction of anesthesia causes a high incidence (88%) of significant truncal rigidity that can impair ventilation. While pretreatment with pancuronium (12.5 µg/kg) or metocurine (50 µg/kg) facilitates abatement of rigidity, a statistically significant reduction in the incidence and severity of rigidity occurs as well with metocurine pretreatment. Metocurine pretreatment (50 µg/kg) also significantly reduces the onset time for complete neuromuscular block following bolus administration of pancuronium (100 µg/kg).

\textbf{REFERENCES}

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