Prolongation of Succinylcholine Block by Metoclopramide

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Laboratory and clinical evidence of the inhibition of plasma cholinesterase by metoclopramide was demonstrated. When succinylcholine is used as the substrate and the product choline assayed by choline oxidase-peroxidase-quinone dye colorimetry, the rate of the choline production as optical density change was reduced to 50% by $19.5 \times 10^{-6}$ M metoclopramide at 20° C. Prolongation of neuromuscular blockade produced by concurrent administration of succinylcholine and metoclopramide was studied in 22 patients aged between 18 and 49 years undergoing elective gynecological surgery. EMG activity in the adductor pollicis muscle was recorded in response to a train-of-four (TOF) stimulus delivered every 10 s. Patients were randomly divided into two groups: A and B. In both groups, anesthesia was induced with thiopental and maintained with sufentanil and nitrous oxide. Tracheal intubation followed intravenous succinylcholine. Intraoperatively, after returning of neuromuscular function, patients in both groups received 20 mg succinylcholine for the determination of duration of neuromuscular blockade. Time from 95% suppression of baseline twitch following a 20 mg increment of succinylcholine until recovery to 25% of control activity was determined. Thereafter, in group A, patients receive metoclopramide (10 mg iv) followed by succinylcholine 20 mg iv, and patients in group B received succinylcholine 20 mg iv alone. Recovery times were again measured and found to be prolonged in patients receiving metoclopramide compared with those not receiving metoclopramide ($P < 0.05$). Metoclopramide has no intrinsic neuromuscular blocking activity, but its ability to inhibit plasma cholinesterase probably is the mechanism by which it prolongs succinylcholine block. Reducing the dose of succinylcholine may be appropriate when metoclopramide is given concurrently. (Key words: Interactions, drug. Neuromuscular relaxants: succinylcholine. Pharmacology: metoclopramide.)

METOCLOPRAMIDE, which has antidopaminergic properties, interacts with the central chemoreceptor trigger zone, producing anti-nausea and vomiting activities. It also increases the tone at the high-pressure zone (HPZ) in the lower esophagus and promotes anterograde peristalsis in the gastrointestinal tract. Metoclopramide may be used as a preoperative medication in the management of unfasted patients to reduce the risk of regurgitation and aspiration of gastric contents. It can also be given intraoperatively to reduce the incidence and severity of postoperative nausea and vomiting. Structurally, metoclopramide can be considered as a derivative of procainamide, which has been shown to be an inhibitor of plasma cholinesterase. This similarity to procainamide led us to speculate that metoclopramide might have an affinity for plasma cholinesterase. If it does inhibit plasma cholinesterase, metoclopramide might prolong the duration of action of succinylcholine by interfering with its hydrolysis.

We performed an in vitro laboratory study to determine the extent of any interaction between succinylcholine and metoclopramide, and followed this with a clinical trial to determine the clinical significance of our findings.

Methods

LABORATORY STUDY

The rate of hydrolysis of succinylcholine by plasma cholinesterase was studied using the method described by Wakid et al. Briefly, this involves the enzymatic degradation of succinylcholine by cholinesterase to form choline. The concentration of choline is determined by a colorimetric technique involving addition of choline oxidase, peroxidase, 4-aminopyrine, and phenol which, together with choline, produce a red quinone dye. The amount of dye produced depends upon the activity of cholinesterase and is quantified by measuring the optical density of the solution at 500 nm with a spectrophotometer. Plasma from a single healthy volunteer was used in our study. Metoclopramide in specific concentrations was introduced into the reaction mixture as described. Each concentration point was repeated three times. The average activity value was used in the figure. The 50% inhibitory concentration, $I_{50}$, was determined by a probit dose plot. To reduce the rate of spontaneous succinylcholine hydrolysis, the reactions were carried out at 20° C.

CLINICAL STUDY

Written informed consent was obtained from all patients and the study was approved by the Institutional Review Board of the Texas Tech University Health Sciences Center.

Twenty-two ASA physical status 1 or 2 patients weighing between 50 and 75 kg undergoing brief gynecological procedures were randomly divided into two groups: A ($n = 11$) and B ($n = 11$). The body weights of each group were 62.8 ± 7.8 kg and 64.1 ± 6.0 kg, respectively. Both groups of patients received scopolamine (0.2 mg), sufentanil (50 μg), and $N_2O$ (67%) in oxygen after induction of anesthesia with thiopental (4 mg/kg). Neuromuscular
blockade during the study was monitored with a Datex Neuromuscular Transmission Monitor (NMT—Puritan Bennett Inc., Massachusetts), which provided a record of EMG activity elicited by supramaximal stimulation of the ulnar nerve. Two stimulating electrodes were placed along the course of the ulnar nerve about 10 cm from the wrist, a grounding electrode was placed at the wrist over the median nerve, and two sensing electrodes were placed along the axis of the adductor pollicis muscle. A control twitch response was recorded after induction of anesthesia, but prior to administration of any succinylcholine. Subsequently, a train-of-four (TOF) stimulus at 2 Hz was applied to the nerve every 10 s and the electrical response of the muscle was recorded. Insertion of an endotracheal tube was facilitated by the administration of succinylcholine (1.5 mg/kg), positive pressure ventilation was begun, and end-tidal CO₂ tension was maintained between 30 and 35 mmHg by adjusting minute ventilation.

Following tracheal intubation, neuromuscular function was allowed to recover to between 90 and 100% of control as gauged from the NMT trace. Atropine (0.2 mg iv) was given if the pulse rate was less than 70 beats/minute, and this was followed by a 20-mg increment of succinylcholine, which produced 100% block in all patients. Duration of block was calculated by measuring the interval from onset of 95% block to a point corresponding to 25% recovery of twitch height (75% block), and this was designated "Ts." The interpretation and compilation of the EMG record were done blindly.

Once again, the patients' neuromuscular function was allowed to recover to between 90 and 100% of control, and then patients in group A were given metoclopramide (10 mg iv) and, 1 min later, a further 20-mg increment of succinylcholine. Measurements of time from 95% block until spontaneous recovery to 25% recovery of the twitch height were again made, but the interval was designated "Tms." After recovery from the first increment of succinylcholine, patients in group B received an additional 20 mg of succinylcholine (iv) but no metoclopramide, and their time interval to 75% block was designated "Tss."

An independent t test was used to compare the mean Tms/Ts ratio in group A with the mean Tss/Ts ratio in group B.

**Results**

**LABORATORY STUDY**

The in vitro study confirmed our hypothesis that metoclopramide inhibits PACHÉ (fig. 1). A metoclopramide concentration of $19.5 \times 10^{-4}$ M inhibited PACHÉ catalyzed hydrolysis of succinylcholine by 50%.

**CLINICAL STUDY**

Metoclopramide prolonged the duration from 95% block after succinylcholine to 25% recovery as monitored by twitch response in all patients tested (table 1). Ratios of Tms/Ts show that recovery time after metoclopramide and succinylcholine was between 135 and 228% of the recovery time following succinylcholine alone.

In group B, recovery times after repeated boluses of succinylcholine are not appreciably different (74–113%). The means of the ratios in group A and B were found to be significantly different at the $P < 0.05$ level.

**Discussion**

The administration of metoclopramide to surgical patients by anesthesiologists has evolved around two indications. Metoclopramide promotes gastric emptying and decreases the lower esophageal sphincter tone, and is widely used as a preanesthetic medication in patients with a "full stomach" or delayed gastric emptying to reduce the risk of perioperative regurgitation and aspiration. However, metoclopramide also interacts with the chemoreceptor trigger zone at the floor of the fourth ventricle. By central action, it reduces nausea and vomiting from many different causes and intramuscular metoclopramide up to 20 mg intraoperatively may be used to reduce postoperative nausea and vomiting. The pharmacokinetics of intravenous metoclopramide has been extensively evaluated. Immediately after a 10-mg iv infusion, the plasma level of metoclopramide was found to be $305–464 \times 10^{-9}$ M. Thirty minutes after infusion, the concentration was reduced to $120 \times 10^{-9}$ M.

The relatively small change in concentration occurred because of
the relatively short distribution half-life (4 min) and long elimination life (4 h). The peak level of metoclopramide after 5 mg im reach about 100 × 10⁻⁶ M. Theoretically, a 20-mg im injection would produce a peak concentration at 400 × 10⁻⁹ M, a value similar to that seen immediately after a 10-mg iv infusion. Therefore, the potential interaction between succinylcholine and metoclopramide in clinical practice becomes a real possibility, both quantitatively and qualitatively. Neuromuscular blockade induced by 20 mg succinylcholine may be prolonged only 2–3 min by metoclopramide. However, a larger dose of succinylcholine might be followed by a much more pronounced prolongation of effect if preceded by metoclopramide. Therefore, our experimental design correlates with a clinical situation that may precipitate an unexpected drug interaction.

To ensure that prolongation of the neuromuscular block was not caused by a cumulative effect of succinylcholine, we monitored the neuromuscular response to a second increment of succinylcholine (group B). There was little difference between the times to 25% recovery after the first and second increments of succinylcholine (Ts/Ts: 74–113%), indicating that differences between the means in groups A and B are a result of metoclopramide.

In a prior study, we found that when acetylcholine was used as the substrates for PACHE (Galli et al.⁷), 50% inhibition of pseudocholinesterase activity was produced by 1.7 × 10⁻⁶ M metoclopramide. In the present study, in which succinylcholine was used as a substrate, 110 times as much metoclopramide (19.5 × 10⁻⁶ M) was required to reduce PACHE activity by 50%. This discrepancy may be attributable to the more indirect method used for the current assay. The sequential nature of this assay as described in Methods, and different substrates may account for the differences of the measured reaction kinetic constants. As the rate of a reaction is determined by the association constants between enzyme and substrate, and also by the activation energy of the reaction, these factors will vary depending on the substrate used. The effect of metoclopramide on cholinesterase and peroxidase was unknown.

The cholinergic properties of metoclopramide in the gastrointestinal tract are well known. Hay and Man⁷ found that pretreatment of guinea pig antrum with hemicholinium prevented the normal excitatory responses to metoclopramide, and they concluded that the contractile activity of the antrum to metoclopramide depended upon maintenance of intrinsic stores of acetylcholine. It follows that the cholinergic properties of metoclopramide may be mediated through an action on anticholinesterase, which will serve to augment the acetylcholine released from intrinsic stores. In addition, in the present study we have shown that the laboratory evidence of plasma cholinesterase inhibition by metoclopramide may be of clinical importance. Prolonged paralysis following succinylcholine might occur if the succinylcholine is preceded by parenteral metoclopramide. In conditions where plasma cholinesterase activity is low, the duration of action of succinylcholine may be further prolonged by concurrent administration of metoclopramide, which might, in turn, increase the chance of conversion to a phase II block.

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References