The inhibitory effect of metoclopramide on plasma cholinesterase activity

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The in vitro effect of metoclopramide on plasma cholinesterase (PCHE) activity was studied to investigate a mechanism for metoclopramide-induced prolongation of succinylcholine action. The mean PCHE of the control samples was 0.86 ± 0.02 unit·ml⁻¹. PCHE activity in the presence of metoclopramide, at concentrations of 0.05, 0.10, 0.50, 1.0, 2.5 and 5.0 µg·ml⁻¹, was reduced to 0.78 ± 0.02 , 0.69 ± 0.04 , 0.50 ± 0.03 , 0.39 ± 0.02 , 0.24 ± 0.01 and 0.15 ± 0.01 unit·ml⁻¹, respectively. Our data demonstrated that PCHE activity was significantly depressed by metoclopramide at all concentrations studied ($p < 0.001$). Our data also show that the concentration of metoclopramide required to inhibit 50 per cent of PCHE activity (I_{50}) was $0.8 \mu\text{g}\cdot\text{ml}^{-1}$ (2.4×10^{-6} M). We recommend caution when succinylcholine and/or ester type local anaesthetics are administered to patients who are also receiving metoclopramide, especially in high doses.

Metoclopramide is one of the most commonly used drugs in the perioperative period. It is especially used by anaesthetists as an antiemetic and to facilitate gastric emptying, thus reducing the risks of aspiration.¹ Metoclopramide is also used frequently in the preoperative period by radiologists to aid in radiological examination of the stomach and small intestine.²

The chemical structure of metoclopramide is very

similar to that of procainamide.³ We demonstrated recently the inhibitory effect of procainamide on PCHE activity.⁴ We have also observed prolongation of succinylcholine action in patients receiving metoclopramide suggesting the possibility of depressed PCHE activity. Many patients with a full stomach who undergo regional anaesthesia for emergency surgery receive metoclopramide preoperatively. It may be important for anaesthetists to know the effect of metoclopramide on PCHE activity, especially when they use multiple doses of succinylcholine and/or ester type local anaesthetics in patients receiving metoclopramide. Therefore, we studied the effect of metoclopramide on PCHE activity.

Methods

With the prior approval of our Institutional Review Board for the Protection of Human Subjects, we included 12 healthy American Society of Anesthesiologists (ASA) physical status I and II patients (ages 25–40, both sexes). Informed consent was obtained from all patients. Ten ml of venous blood was drawn into a heparinized syringe from each patient. The plasma was immediately separated and stored in a refrigerator at 4°C and used within five days for cholinesterase assay. A kinetic method described by Zapf *et al.* was used in the determination of PCHE activity and dibucaine numbers (DN).⁵

The reaction mixture contained 1-naphthyl acetate as substrate in phosphate buffer with a pH of 7.50. The total volume of reaction mixture was 3 ml. Metoclopramide was added *in vitro* to the reaction mixture to give a final concentration of 0.05, 0.1, 0.5, 1.0, 2.5, and 5.0 µg·ml⁻¹. After determining a baseline absorbance at 321 nm in a Beckman Model 24 recording spectrophotometer, the reaction was started with the addition of 100 µmol of plasma. The absorbance change was recorded and PCHE activity was expressed as units·ml⁻¹ of plasma. One unit corresponds to the liberation of 1 µmol of naphthol per minute under conditions of assay.

In addition to linear regression analysis, data were analyzed for statistical significance using a randomized block analysis of variance within treatment levels and multiple comparison testing by the Dunnett's test was

Key words

PHARMACOLOGY: metoclopramide; ENZYMES: plasma cholinesterase (PCHE), pseudocholinesterase.

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FIGURE Inhibitory effect of metoclopramide on plasma cholinesterase activity (PCHE). ($I_{50} = 0.8 \mu\text{g}\cdot\text{ml}^{-1}$ or $2.4 \times 10^{-6} \text{ M}$).

used to compare the drug effects against the control. A difference was considered significant if $p < 0.05$.

Results

Results are shown in the Table. All the values reported were the average means of duplicate determinations of plasma cholinesterase activity. The mean PCHE activity of all the plasma samples was $0.86 \pm 0.02 \text{ units}\cdot\text{ml}^{-1}$. PCHE activity in the presence of metoclopramide at concentrations of 0.05, 0.1, 0.5, 1.0, 2.5, and $5.0 \mu\text{g}\cdot\text{ml}^{-1}$ was 0.78 ± 0.02 , 0.69 ± 0.04 , 0.50 ± 0.03 , 0.39 ± 0.02 , 0.24 ± 0.01 and $0.15 \pm 0.01 \text{ units}\cdot\text{ml}^{-1}$, respectively. There was 10, 20, 42, 55, 73 and 83 per cent depression of PCHE activity in the presence of metoclopramide at concentrations of 0.05, 0.1, 0.5, 1.0, 2.5 and $5.0 \mu\text{g}\cdot\text{ml}^{-1}$, respectively. The Figure shows a plot of per cent inhibition of PCHE activity against plasma metoclopramide concentrations. Linear correlation is evident, as indicated by a correlation coefficient (R) of 0.99. The

concentration of metoclopramide required to inhibit 50% of PCHE activity (I_{50}) was found to be $0.8 \mu\text{g}\cdot\text{ml}^{-1}$, or $2.4 \times 10^{-6} \text{ M}$.

A randomized block analysis of variance within treatment levels indicated a significant drug effect ($p < 0.001$). A Dunnett's test clearly demonstrated a statistical difference of all treatment levels from the control ($p < 0.01$).

Discussion

Metoclopramide (4-amino 5-chloro-N [2-(diethyl amino) ethyl] 2-methoxy benzamide monohydrochloride monohydrate) and procainamide (p-amino-N [2-(diethyl amino) ethyl] benzamide monohydrochloride) possess very similar chemical structures.^{3,5} We have previously shown that procainamide, an antiarrhythmic drug, inhibits plasma cholinesterase significantly.⁴ Unlike procainamide, metoclopramide has no known antiarrhythmic properties. Like the phenothiazines, metoclopramide produces sedation and occasionally may cause extrapyramidal reactions. Some phenothiazines are also known to inhibit the PCHE activity.⁸

Metoclopramide is being used increasingly by clinicians for the control of nausea and vomiting associated with narcotic analgesic therapy, radiation therapy, chemotherapy, pregnancy, and surgery and anaesthesia.⁷ Metoclopramide in doses of 10–20 mg is used by anaesthetists to facilitate gastric emptying in the preoperative period. A 10 mg dose in adult patients weighing 50–70 kg gives a peak plasma concentration of up to $0.14 \mu\text{g}\cdot\text{ml}^{-1}$.⁸ A dose of $1\text{--}3 \text{ mg}\cdot\text{kg}^{-1}$ of metoclopramide has been used for chemotherapy induced nausea and vomiting, and doses up to 1000 mg per day have been tried as an antipsychotic agent.^{9,10} Peak plasma concentrations after administration of these high doses of metoclopramide have not been studied. We believe one should use caution when succinylcholine is administered in these patients especially in those who receive high doses of metoclopramide.

PCHE is a glycoprotein produced mainly in the liver and is responsible for the metabolism of the depolarizing muscle relaxant, succinylcholine, and all ester type local anaesthetics. Pregnancy is associated with a significant decrease in PCHE activity.¹¹ Metoclopramide has proved efficacious in the treatment of vomiting and reflux esophagitis associated with pregnancy.^{12,13} Since both pregnancy and the administration of metoclopramide are associated with a decrease in PCHE activity, one should use caution when succinylcholine and/or ester type local anaesthetics are administered in pregnant patients who are also receiving metoclopramide.

Some of the other side effects of metoclopramide that are of particular interest to anaesthesiologists include

TABLE Effect of metoclopramide (MCP) on plasma cholinesterase (PCHE) activity

MCP $\mu\text{g}\cdot\text{ml}^{-1}$	PCHE Activity $\text{units}\cdot\text{ml}^{-1}$ Mean $\pm$ S.D.	% Inhibition
0 (control)	0.86 ± 0.02	—
0.05	$0.78 \pm 0.02^*$	10
0.10	$0.69 \pm 0.04^*$	20
0.50	$0.50 \pm 0.03^*$	42
1.00	$0.39 \pm 0.02^*$	55
2.50	$0.24 \pm 0.01^*$	73
5.00	$0.15 \pm 0.01^*$	83

* $n = 12$; $p < 0.001$ (randomized block analysis of variance); significance of difference from control, $p < 0.01$ (Dunnett's test).

hypotension, hypertensive crisis especially in patients with pheochromocytoma, arrhythmias, drowsiness, interference with absorption of orally administered drugs, and extrapyramidal symptoms.^{9,14-20}

In conclusion, our present study demonstrated that metoclopramide has a significant inhibitory effect on PCHE activity when tested *in vitro*. Our data also show that the concentration of metoclopramide required to inhibit 50 per cent of PCHE activity (I_{50}) was $0.8 \mu\text{g}\cdot\text{ml}^{-1}$. We recommend that neuromuscular paralysis be monitored with a peripheral nerve stimulator in patients receiving metoclopramide and succinylcholine. In addition, we suggest the combination of metoclopramide and ester type of local anaesthetics be avoided in pregnant patients and others, who already have diminished PCHE activity.

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Résumé

L'effet *in vitro* de la métoclopramide sur l'activité de la cholinestérase plasmatique (PCHE) a été étudié afin d'investiguer le mécanisme de la prolongation de l'action de la succinylcholine induite par la métoclopramide. La valeur moyenne des échantillons de contrôle de PCHE était de $0.86 \pm 0.02 \text{ unités}\cdot\text{ml}^{-1}$. L'activité du PCHE en présence de métoclopramide à des concentrations de 0.05, 0.10, 0.50, 1.0, 2.5 et $5.0 \mu\text{g}\cdot\text{ml}^{-1}$, a été réduite à 0.78 ± 0.02 , 0.69 ± 0.04 , 0.50 ± 0.03 , 0.39 ± 0.02 , 0.24 ± 0.01 et $0.15 \pm 0.01 \text{ unités}\cdot\text{ml}^{-1}$ respectivement. Nos données ont démontré que l'activité de la PCHE était significativement diminuée par la métoclopramide à toutes les concentrations étudiées ($p < 0.001$). Nos données ont aussi démontré que la concentration de métoclopramide requise afin d'inhiber 50 pour cent de l'activité de la PCHE (I_{50}) était de $0.8 \mu\text{g}\cdot\text{ml}^{-1}$ ($2.4 \times 10^{-6} \text{ M}$). On recommande la précaution quand la succinylcholine ou anesthésique local type ester est administré aux patients qui reçoivent aussi la métoclopramide, spécialement à hautes doses.