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Metoclopramide inhibits plasma cholinesterase

To the Editor:

We read with interest the paper by Kambam *et al.* noting the inhibition of plasma cholinesterase by metoclopramide *in vitro*.[1] However, we feel that their observations may not justify their conclusions concerning the clinical relevance of this interaction. Their experimental method was based on creating specific concentrations of metoclopramide in the cholinesterase reaction mixture[2] and they succeeded in demonstrating increasing inhibition of enzyme activity with increasing metoclopramide concentrations. Unfortunately they appear to have confused *in vivo* therapeutic levels of metoclopramide with the *in vitro* concentrations used in their study. To produce concentrations in plasma similar to the *in vitro* metoclopramide concentrations described by the authors the concentration would need to be 30 times that stated in the reaction mixture since only 0.1 ml of plasma was used in a total reaction volume of 3 ml. Thus a plasma concentration of 0.14 $\mu g \cdot ml^{-1}$ (their quoted normal peak plasma level of metoclopramide after a 10 mg dose) would produce such a low concentration in the reaction mixture (0.005 $\mu g \cdot ml^{-1}$ approximately) that enzymatic inhibition would be insignificant. We feel that this pharmacological phenomenon is unlikely to be of clinical significance at normal clinical doses of metoclopramide, although the larger doses used in counteracting the emetic effects of cancer chemotherapy may result in some degree of plasma cholinesterase inhibition.

If this interpretation is correct, it would also cast doubt on the interpretations in an earlier paper by the primary author describing the inhibitory effect of procainamide on plasma cholinesterase activity *in vitro* with an identical protocol, and extrapolating this to clinical situations.[3]

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REPLY

We previously reported the in vitro *effect of metoclopramide on plasma cholinesterase (PCHE) activity.[1] Our data showed that PCHE activity was significantly reduced by metoclopramide at all concentrations studied ($P < 0.001$). We recommended caution when succinylcholine and/or ester type local anaesthetics are administered to patients who are also receiving metoclopramide, especially in high doses. A recent study by Kao and Turner using an entirely different PCHE assay showed a similar decrease in PCHE activity by metoclopramide.[2] Kao and Turner also showed a significant prolongation of succinylcholine action by metoclopramide in their patients.*

We used a kinetic method described by Zapf and Coghlan in the determination of PCHE activity and dibucaine numbers.[3] Metoclopramide was added to the reaction mixture to give a final concentration of 0.05, 0.1, 0.5, 1.0, 2.5, and 5.0 $\mu g \cdot ml^{-1}$. The reaction was started with the addition of 0.1 ml of plasma and the resulting PCHE activity was expressed as units $\cdot ml^{-1}$ of plasma. Our in vitro *concentrations of metoclopramide were designed to reflect the* in vivo *concentrations of metoclopramide to which the PCHE is exposed. When the effect of inhibitors on PCHE activity is studied* in vitro, *it is the final concentration of the inhibitor in the reaction mixture that is commonly reported. For example the effects of dibucaine (Dibucaine number) and fluoride (Fluoride number) are studied and expressed in this manner.[3–4] An* in vivo *study presents a somewhat different problem with dilution. The small amount of plasma taken from the patients receiving metoclopramide is diluted several times in the reaction mixture. This in turn yields a spuriously higher than expected PCHE activity and would not reflect the* in vivo *effect of the inhibitor on PCHE activity.*

In summary we think the method we used is correct. We also believe that when the effect of drugs on PCHE activity needs to be determined, an in vitro *study is probably superior to an* in vivo *study. Finally, the significance of* in vitro *findings of PCHE inhibition can be determined clinically by studying the duration of succinylcholine action in patients receiving inhibitor drugs.*

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