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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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Contamination of syringes

To the Editor:

The recent article by Lessard *et al.* showed the risk to the patient of bacterial contamination with multiple use of syringes to be negligible but emphasized the risks from viral contamination.[1] A questionnaire was distributed to all members of anaesthesia departments of the Universities of Pittsburgh and Michigan in the general adult, paediatric and obstetric divisions (five hospitals total) to quantitate the frequency of common syringe techniques. Anonymous responses were collected and evaluated from 139 personnel: 48 anaesthetists, 48 CRNAs, 31 residents and 12 student CRNAs. Respondents indicated that they routinely, frequently, rarely or never used common syringe techniques 30.9, 41.7, 17 and 10 per cent of the time, respectively. Almost all personnel (98 per cent) reuse multiple dose vials opened by unknown persons and 75 per cent refill common syringes from multi-dose vials without discarding them subsequently. Common syringes were used by 18 per cent, when blood products were given through the IV line.

In the 1950's it was recognized that reusing common syringes on multiple patients could transmit diseases and that changing needles was quite ineffective in lowering the danger of crossinfection.[2,3] During needle removal from the syringe, the needle contents are aspirated up to the syringe tip before the air lock is broken at the needle hub. The lumen of intravenous lines is frequently and occultly contaminated with blood and 10^{-7} to 10^{-9} ml of blood can transmit hepatitis.[4,5] The reuse of these needles or syringes clearly presents a danger to patients and the health care providers themselves, who may acquire hepatitis from them during use or recapping. The contamination of IV tubing can only be excluded when the IV is started and continuously observed and manipulated by one person alone. Hepatitis is transmitted via transfusion and/or operation as independent factors: 3.3 per cent of non-transfused patients acquire hepatitis from unknown sources versus 5.6 per cent of transfused patients.[6–9]

Viral transmission may additionally occur when using multi-dose vials in conjunction with common syringe techniques. Hepatitis virus is stable on dry surfaces for one week and may survive longer in suitable aqueous states.[10] Bacteriological studies of multi-dose vials or syringes are not useful in documenting contamination, as contained bacteriostatic agents rapidly eliminate bacteria.[11] There is no evidence that bacteriostatic agents will destroy all introduced pathogenic virus and manufacturers recommend that only sterile equipment is used to enter multidose vials.

Although high rates of common syringe technique utilization may not be encountered in all institutions, widespread practice is likely, in spite of recommendations to the contrary.[12] These techniques violate guidelines which exist to protect hospital workers from exposure to blood-borne infections.[13,14] The Center for Disease Control, however, has no specific policy regarding common syringes. Universal precautions guidelines are apparently needed to preclude nosocomial infection of *patients*.

Until research proves that the use of common syringe techniques is safe they should be abandoned.

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