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The Action of Phenacetin on Tremorine-Induced Cholinergic Effects (33765)

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In laboratory animals, tremorine is a potent analgesic agent. In addition, it possesses profound cholinergic activities which include the peripheral effects of diarrhea, chromodacryorrhea, salivation, and centrally-induced tremors. It has been shown by Kocsis and Welch (1) and Cho *et al.* (2) that tremorine is metabolized into oxotremorine which is many times more potent than tremorine. This conversion, which occurs in the liver, was shown to be blocked by the liver microsomal enzyme inhibitor SKF 525-A (3). In addition, phenothiazines act similarly to SKF 525-A in that they block the tremors in mice induced by tremorine but not those induced by oxotremorine (4). Anticholinergic compounds block the effects of both tremorine and oxotremorine and probably do not enter into the biological conversion mechanism.

During the course of investigating potentially active analgesic agents, various amounts of APC (aspirin, phenacetin, and caffeine) were used in conjunction with the agents in an attempt to augment their analgesic activity. It was shown previously (5) that the addition of APC to analgesic agents enhances their activity by an unknown mechanism.

Preliminary experiments in our laboratory showed that the administration of APC compound not only augmented the analgesic effect of tremorine but also markedly reduced the cholinergic effects. Further investigation revealed that neither aspirin nor caffeine altered the tremorine-induced cholinergic effects, whereas phenacetin tended to delay the onset of tremorine action. This report concerns the interaction of phenacetin with tremorine and oxotremorine particularly with respect to the cholinergic effect of the latter two compounds.

Material and Method. The tremorine effects of diarrhea, chromodacryorrhea, salivation and tremors were quantitatively measured in 100 mice. A dose of 5 mg/kg i.p.

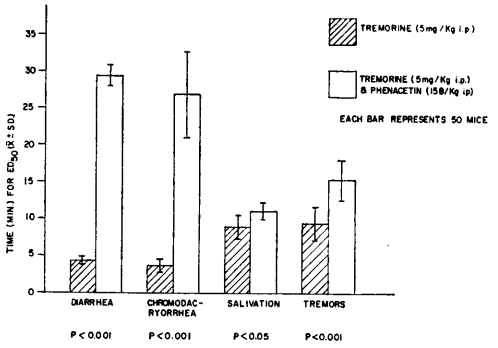

FIG. 1. The response of phenacetin on tremorine-induced cholinergic effects.

of tremorine was used in which 50 of the 100 mice were pretreated (30 min) with phenacetin at a dose of 158 mg/kg i.p. A similar experiment was carried out using oxotremorine at a dose of 0.125 mg/kg i.p. The onset time for each of the four effects was noted in the mice and the time in minutes at which 50% of the mice showed the effect (ED_{50}) was calculated ± SD.

Results. The delay in onset of tremorine-induced diarrhea and chromodacryorrhea after phenacetin is shown clearly in Fig. 1. The delay in onset time of salivation was small though significantly different from the control value ($p < 0.05$). The onset time of tremors after tremorine was also significantly delayed by pretreatment with phenacetin. The percentage delay in onset of the four parameters were: diarrhea, 655%; chromodacryorrhea, 671%; salivation, 12% and tremors, 63%.

Figure 2 shows the results of similar exper-

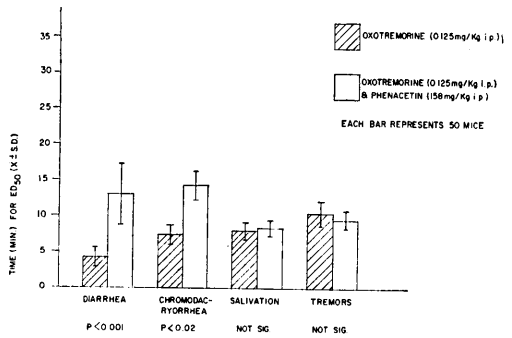

FIG. 2. The response of phenacetin on oxotremorine-induced cholinergic effects.

TABLE I. A Comparison of Atropine Sulfate, SKF 525-A, and Phenacetin on Various Pharmacologic Procedures.

Procedures	Effect on procedures by: Atropine sulfate Effect	Dose	SKF 525-A Effect	Dose	Phenacetin Effect	Dose
Hexobarbital sleep time (mice)	No effects	1 mg/kg i.p.	Prolong	20 mg/kg i.p.	Prolong	158 mg/kg i.p.
Sodium barbital sleep time (mice)	No effect	1 mg/kg i.p.	No effect	20 mg/kg i.p.	No effect	158 mg/kg i.p.
Tremorine cholinergic effects (mice)	Block	1 mg/kg i.p.	Block	20 mg/kg i.p.	Block	158 mg/kg i.p.
Oxotremorine cholinergic effects (mice)	Block	1 mg/kg i.p.	Sl. block	20 mg/kg i.p.	Sl. block	158 mg/kg i.p.
Methacholine cholinergic effects (mice)	Block	1 mg/kg i.p.	Sl. block	20 mg/kg i.p.	No effect	158 mg/kg i.p.
Acetylcholine vasodepressor effects (dog)	Block	1 mg/kg i.v.	Sl. block	3 mg/kg i.v.	No effect	200 mg/kg i.v.
Acetylcholine contraction of guinea pig ileum (*in vitro*)	Block	10^{-8} *M*	Sl. block	10^{-4} *M*	No effect	10^{-4} *M*

iments using oxotremorine as the tremoragenic agent. As shown phenacetin antagonized the cholinergic effects of oxotremorine to a much lesser extent than that observed with tremorine. There was no significant antagonism of the induced salivation and tremors, while the effect on diarrhea and chromodacryorrhea was much less than that observed with the combination of tremorine and phenacetin.

Discussion. The fact that phenacetin produced a much greater antagonism of the tremorine-induced cholinergic effects than the oxotremorine effects suggested the possibility that phenacetin produced a blockade of the liver microsomal enzymes necessary for the conversion of tremorine to oxotremorine. For this reason a comparison was made to the classic liver enzyme inhibitor, SKF 525-A, in other test systems (Table I). Phenacetin produced a prolongation in the anesthetic period following hexobarbital sodium in a fashion similar to SKF 525-A. This activity did not follow atropine sulfate administration.

Further, if phenacetin prolonged the anesthetic period of hexobarbital by a mechanism of addition to CNS depression, then the same effect would be expected to occur following sodium barbital. No effect on sodium barbital sleep time followed either phenacetin or SKF 525-A. In addition, the general failure of phenacetin to behave as a typical anticholinergic agent against methacholine and acetylcholine (Table I) is evidence that some other mechanism is involved.

From the evidence presented, it appears that phenacetin may inhibit liver microsomal enzymes that are responsible for the detoxification of certain agents and thus may be added to the list of compounds which include the phenothiazines and SKF 525-A. By this mechanism phenacetin may increase and/or prolong the activity of various agents to which it is added.

Summary. The effect of phenacetin on the cholinergic response of tremorine and oxotremorine were described. Phenacetin delayed the onset of the cholinergic effects observed after tremorine to a greater degree than those effects observed after oxotremorine. The effect from phenacetin was similar to that of SKF 525-A.

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