tion, could explain their finding of no effect on theophylline clearance.

The level of cytochrome P-450 activity is another factor which may be a determinant of the theophylline-erythromycin interaction. May et al. made the interesting observation that no interaction occurred in three of four cigarette smokers compared to only one of 13 non-smokers. It is possible that sufficient enzyme activity is present in cigarette smokers to compensate for the hypoxactivity induced by standard doses of erythromycin.

Thus, we conclude that the duration of erythromycin therapy and the peak erythromycin serum concentration (a function of dose, extent of absorption, and clearance) are important determinants of this interaction, and variability in these factors between studies accounts for the discrepant results. Furthermore, it is possible that the interaction may not occur with conventional erythromycin doses in patients whose microsomal enzyme systems are stimulated by smoking or other drugs.

To avoid the interaction, an alternative antibiotic should be prescribed, if possible, for patients taking theophylline in doses producing therapeutic serum levels. When there is no good alternate antibiotic (ie, Mycoplasma pneumonia in children or Legionnaires' disease) the theophylline dose should be reduced 25 percent and subsequent dosage adjustments guided by serum level measurements obtained at least six days after initiation of erythromycin therapy.

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To the Editor:

The article by Maddux et al demonstrated no apparent effect of 1 g/day of erythromycin stearate during five days of administration to 14 adult volunteers. These conclusions are based upon clearance derived from six serum concentrations with intervals as wide as three hours over a six hour dosing interval during the two periods of the study and elimination rate constants that could only reliably have been based on three serum concentrations at most. The authors discount other studies showing alteration of theophylline elimination by erythromycin with the consequent potential for toxicity and find support for their conclusions from two previous publications. In point of fact, the two studies which they cite in support of their findings included one which examined the effect of erythromycin on theophylline after only 25 hours of the antibiotic; the other consisted of a letter to the editor without presentation of data. In contrast, three studies utilizing healthy adult volunteers reported varying degrees of statistically significant decrease in the rate of theophylline elimination with courses of erythromycin for seven to ten days. Similar effect was observed in children with asthma treated with erythromycin for one week as part of a study protocol and not because of concomitant illness. Only a more recent study on this subject, one not referenced by Maddux et al, could be criticized on the grounds of patient selection and even that study presents a sufficient argument for an interaction to warrant caution when the two drugs are used together. Moreover, the study by Prince et al showed a significant correlation between peak serum erythromycin levels and decrease in theophylline clearance.

While the interaction between theophylline and erythromycin therefore justifies appropriate caution if the combination is essential in some patients, the accompanying editorial by Jenne may paint a gloomier picture than necessary regarding the clinical problems of using theophylline. For example, while it is apparent that unusual extremes of diet can affect theophylline elimination, the study by Feldman et al discussed by Dr. Jenne suffered from a serious error in the method of determination of half-life of elimination. The more validly calculated clearance value in that study showed only about a 25 percent change in clearance associated with the extremes of diet studied.

The methodology of these various studies has to be examined carefully before their conclusions are uncritically accepted. In contrast to Dr. Jenne’s conclusion that these various effects on theophylline are "unpredictable," I find a high degree of predictability, and studies by Dr. Jenne in adults and by my colleagues and me in children have suggested that clearance and consequent serum concentrations generally remain acceptably stable. While I share Dr. Jenne’s concern regarding the potential risks of "pushing" all serum concentrations to the upper limit of the "therapeutic range," a current survey of 1,000 of our patients indicates that a mean peak serum concentration of 14 µg/ml (with a range of 10 to 20 µg/ml) is well tolerated with no serious adverse effects, and only about 2 percent of the children treated with theophylline for chronic asthma had any complaints of adverse effects at the time serum concentrations were measured. Moreover, persisting intolerance of the drug has been seen in only about 1 percent of children. While intolerance to theophylline may be somewhat higher in adults, the most common reason for complaints is the failure to use the clinical titration procedure included in the current FDA approved package insert prior to final dose determination guided by measurement of serum concentration.

In spite of the potential for some drugs, dietary factors, and physiologic abnormalities to slow theophylline elimination as described and well referenced in the editorial by Dr. Jenne, asthma is a disease with a relatively high prevalence in otherwise healthy children and young adults, most of whom maintain normal diets, do not require medications for other medical problems, and find cigarette smoking intolerable. I therefore would argue against the routine use of combined bronchodilator therapy, as suggested by Dr. Jenne, rather than optimally using one drug before adding a second drug. Patients with mild disease may be managed adequately just with an inhaled beta agonist, but maintenance therapy with theophylline is indicated when symptoms still interfere with sleep and/or normal activities. Control of chronic asthma with decreased symptoms, improved sleep, better tolerance of activity, and decrease
in the frequency with which intervention with courses of prednisone is needed have been well documented for theophylline at serum concentrations in the therapeutic range.\textsuperscript{11,12} Such documentation is not available for lower dose combination therapy; only bronchodilatation after single doses has been examined. Oral beta\textsubscript{2} agonists, although having little potential for serious toxicity, cause much fewer adverse effects than theophylline when appropriately dosed, and tremor is increased synergistically from the combination. Moreover, patients prefer and thus are likely to comply better with fewer medications. Thus, let us be aware of the potential for drug interactions, choose alternatives to optimal therapy with theophylline in selected patients at high risk for altered theophylline elimination, and avoid the routine and generally unnecessary use of multiple drugs that often cause more harm than benefit.

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To the Editor:

We appreciate the comments by Drs. Jonkman, Hendeles and Weinberger. Despite a careful review of the literature, the explanations offered by Jonkman and Hendeles remain quite speculative for several reasons. First, while the interaction of erythromycin with the cytochrome P-450 system of the rat is interesting, the implications of these data\textsuperscript{1} are unclear. A closer analysis of this interaction reveals that erythromycin not only forms an inactive complex with the cytochrome P-450 enzymes, but induces production of additional cytochrome P-450 as well. This results in no net change in levels of uncomplexed (active) cytochrome P-450 after exposure to erythromycin.\textsuperscript{1} Hence, it is possible that the actual level of net enzyme activity is not altered by erythromycin. These data may be more meaningful if further animal studies are able to document impaired theophylline metabolism by cytochrome P-450 during erythromycin administration. We are unaware of any studies demonstrating such an effect, and certainly there is no direct evidence that erythromycin complexes with the human cytochrome P-450 system. Indeed, a recent study co-authored by Drs. Hendeles and Weinberger failed to detect any change in the metabolic degradation of theophylline in subjects receiving erythromycin.\textsuperscript{2} The study concludes that erythromycin apparently does not interact with any specific enzymes involved in theophylline metabolism.

Second, an association between duration of erythromycin administration and altered theophylline clearance has not been convincingly demonstrated. Although our investigation detected no change in theophylline clearance following five days of concurrent erythromycin therapy, other studies have reported reduced theophylline elimination after similar courses (six-seven days) of erythromycin.\textsuperscript{2,3} We believe it is unlikely that the course of erythromycin utilized in these studies is significantly different from the course employed in our study, and therefore doubt that our inability to detect any change in theophylline clearance can be attributed to the duration (five days vs six or seven days) of antibiotic exposure alone.

Third, we instructed all subjects in our study to take the erythromycin stearate preparation on an empty stomach (at least one hour before or two hours after meals) in order to avoid potential bioavailability problems. In retrospect, measurement of serum erythromycin concentrations would have resolved any questions regarding bioavailability and probably should have been included in our original study design.

Dr. Weinberger's concern regarding the reliability of pharmacokinetic parameters generated from a minimal number of serum concentrations is well-founded. However, due to an error in proofreading, our manuscript failed to mention that theophylline serum concentrations were also obtained at eight hours following the theophylline dose in each subject. Therefore, elimination rate constants are based on at least four serum concentrations occurring within the study period. In fact, the mean sample coefficient of determination (\textsuperscript{2}R) obtained from regression analysis was 0.94, indicating a high degree of correlation among the serum concentrations measured after each dose.

Dr. Weinberger correctly cites another recent study reporting an apparent theophylline-erythromycin interaction.\textsuperscript{4} Briefly, this investigation noted a significant reduction in theophylline clearance in asthmatic patients receiving concurrent erythromycin. However, the study groups were not well-matched, with over twice as many patients receiving theophylline alone (31 patients received only theophylline while 15 were treated with a combination of theophylline plus erythromycin). Furthermore, this study detected no significant alteration in theophylline clearance in a similar analysis of patients with chronic airflow obstruction. Hence, these data substantiate our experiences in normal subjects and suggest that this "interaction" may indeed be linked to disease state.

Finally, it should be emphasized that the clinical significance of