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. Such documentation is not available for lower dose combination therapy; only bronchodilatation after single doses has been examined. Oral beta, agonists, although having little potential for serious toxicity, cause much less 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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REFERENCES

To the Editor:
We appreciate the comments by Drs. Jonkman, Hendele and Weinberger. Despite a careful review of the literature, the explanations offered by Jonkman and Hendele 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 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. 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. Hendele and Weinberger failed to detect any change in the metabolic degradation of theophylline in subjects receiving erythromycin. 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. 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 (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. 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
any theophylline-erythromycin interaction remains questionable, particularly in view of the already wide interpatient variability intrinsically associated with theophylline pharmacokinetics. If such an interaction really exists, it appears to be minimal when compared to other recently characterized drug-drug interactions (eg, digoxin-quinidine). Until an effect of erythromycin on theophylline pharmacokinetics is more rigorously established, empiric recommendations for dosage adjustment in patients receiving concomitant erythromycin may be premature.

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Beryllium Disease

Necessity for Continuing Surveillance

To the Editor:

Three cases of chronic beryllium disease diagnosed between 1978 and 1980 were recently reported to the Beryllium Case Registry (BCR) of the National Institute for Occupational Safety and Health (NIOSH). All these were machinists who fabricated beryllium metal parts for missile guidance systems in a large aerospace manufacturing plant in California. A review of environmental survey data suggests that levels of exposure to beryllium dust exceeded prevailing occupational exposure standards during the 1960s and early 70s, and were likely responsible for the subsequent development of the disease.

Acute beryllium disease was first reported in the European literature in 1933. In the United States, hundreds of cases of acute and chronic beryllium disease were documented during the 1940s and 50s. After recognition of the serious health hazard associated with beryllium, control of exposure led to a reduced number of both acute and chronic cases. During the period of 1973 through 1977, 55 cases were added to the Registry, for an average of 11 per year. During the five years which followed (through 1982), only ten cases were added, making the current number 897.

Beryllium phosphor was once used in fluorescent lighting tubes. Although this major use was discontinued in 1949, beryllium's many industrial uses and the resultant opportunities for toxic exposure still exist. Major consumption occurs in the nuclear and aerospace industries, in electrical applications, and in the manufacture of many electronic devices.

Recently, Balmes et al reported four cases of chronic beryllium disease among workers in a secondary smelter in Connecticut where scraps of beryllium-copper alloys were melted to reclaim copper. The four cases were documented over a period of eight years, and all resembled sarcoidosis. Exposure to beryllium oxide in the melting process was probable.

The similarities between sarcoidosis and beryllium disease have been well established. Differential diagnosis of sarcoidosis requires the consideration of beryllium disease and a careful review of occupational history. In vitro lymphoblast transformation test and T-lymphocyte count from bronchoalveolar lavage have been advocated as useful aids for the differential diagnosis. Chemical assays for beryllium in lung tissue, lymph node and urine are useful in evaluation of the individual's exposure.

While the number of beryllium disease cases appears to be waning, its potential still exists in certain industries, as amply illustrated by these clusters. Physicians can play a role in the continued control of beryllium disease by reporting any suspect cases to the U.S. Beryllium Case Registry. Inquiries and reports should be addressed to:

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4676 Columbia Parkway
Cincinnati, Ohio 45226
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