with regimens outlined in our article, which include prednisone at doses of 15 mg every other day or less, two have been lost to follow-up, and the two remaining women currently are enrolled in clinical trials with investigational agents other than luteinizing hormone-releasing hormone (LHRH) agonists. Consequently, we presently have no plans to use LHRH agonists in these patients.

We believe a relationship between progesterone levels and episodes of recurrent anaphylaxis remains to be established. As Slater et al.[1] state in discussing patients in their article, "It is also possible that the cause of anaphylaxis in these patients is some other substance (or substances) entirely, and that there is no causal association with medroxyprogesterone injection and conditions known to be associated with elevated progesterone levels."

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REFERENCE

1. Slater JE, Raphael G, Cutler GB, et al. Recurrent anaphylaxis in menstruating women: treatment with a luteinizing hormone-releasing hormone agonist—a preliminary report. Obstet Gynecol 1987;70;545.

Sustained-release theophylline preparations

To the Editor:

The article by Arkinstall et al.[1] concludes that their study "demonstrated that the release mechanism of Uniphyl tablets is not adversely affected when the drug is taken after a high-fat meal." In point of fact, their data demonstrated a mean 10% difference in area under the concentration-time curve (AUC) after the study dose. Moreover, the protocol indicates that the specified condition of dosage administration with regard to meals was maintained only for each study dose, and examination of the data in Fig. 1 of their article[1] indicates that the 24-hour serum concentration was rising (by about 14%) after the postprandial dose and falling (by about 23%) after the 6-hour fast. This suggests that the observed differences in AUC would have been larger had the study conditions been maintained for further doses.

Arkinstall et al.[1] acknowledge that grossly incomplete bioavailability had been demonstrated by Karim et al.[2] after an overnight fast but rationalize that "a major difference between the two studies is that our study was a multiple-dose study with the pharmacokinetic parameters measured at steady state, whereas that of Karim et al.[2] was a single dose evaluation." However, their data were not measured at steady state (since predose serum concentrations were increasing in the postprandial group and decreasing in the other), and patients of Arkinstall et al.[1] were compared after a 6-hour late afternoon fast rather than an overnight fast. Moreover, another study has confirmed results of Karim et al.[2] in both a single-dose study and under true multiple-dose, steady-state conditions in which the same conditions of administration were maintained for 3 consecutive days.[3]

Thus, it can be stated unequivocally that theophylline is substantially malabsorbed from the Uniphyl formulation when it is taken after an overnight fast, and data of Arkinstall et al.[1] are consistent with previous studies that absorption is more complete when theophylline is taken after a meal. I support the argument made by Arkinstall et al.[1] that the evening dose is preferable to a morning dose (in part because of the greater assurance of postprandial conditions that increases the likelihood of complete absorption). However, this does not belie the previous studies demonstrating gross malabsorption after a morning dose under fasting conditions. Although the evening dose strategy might minimize the clinical consequences of this quirk in the formulation, the Uniphyl formulation nonetheless differs qualitatively from products, such as Theo-dur tablets and Slo-bid Gyrocaps, two products with the same approval by the Food and Drug Administration for once-daily dosing claims as Uniphyl, but without systematic effect of food on the extent of absorption. Whatever the wisdom of once-daily dosing, it is difficult to rationalize the use of formulations, such as Uniphyl, Theo-24, or Theo-dur Sprinkle, that deliver substantially less than the administered dose under some, but not all, conditions likely to be encountered in practice.[4]

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REFERENCES

1. Arkinstall WW, Hopkinson M, Rivington RN, Calcutt L, Aitken T, Stewart JH. The clinical significance of food-induced changes in the absorption of theophylline from Uniphyl tablets. J ALLERGY CLIN IMMUNOL 1988;82:155-64.
2. Karim A, Burns T, Wearley L, Streicher J, Palmer M. Food-induced changes in theophylline absorption from controlled-release formulations. Part 1. Substantial increased and decreased absorption with Uniphyl tablets and Theo-Dur Sprinkle. Clin Pharmacol Ther 1985;38:777-83.
3. Milavetz G, Vaughan LM, Weinberger MM, Harris JB, Mullenix TA. Relationship between rate and extent of absorption of oral theophylline from Uniphyl brand of slow-release theophylline and resulting serum concentrations during multiple dosing. J ALLERGY CLIN IMMUNOL 1987;80:723-9.
4. Hendeles L, Weinberger M. Selection of slow-release theophylline products [Symposium]. J ALLERGY CLIN IMMUNOL 1986;78:743-51.

Reply

To the Editor:

Once again Dr. Weinberger has provided us with the opportunity to reply to his comments on the use of sustained-release theophylline preparations and to clarify certain points in his discussion of our study. Dr. Weinberger cer-

tainly provided a significant service to respirology by popularizing the use of sustained-release theophylline, particularly Theo-Dur. However, in our view, his continued challenge of most other sustained-release theophylline formulations on the basis of pharmacokinetic projections is becoming tedious.

At the time our study was designed, the major issue surrounding food-versus-fasting administration of the theophylline formulations was the dramatic increase in both rate and extent of theophylline absorption ("dose dumping") that occurred when Theo-24 was administered with a high-fat meal.[1] Accordingly, our study was primarily designed to determine whether or not evidence of "dose dumping" might occur with Uniphyl tablets. The results revealed no evidence of "dose dumping" and indicated that the difference in bioavailability between food and fasting administration of Uniphyl was approximately 10%.

Since our rigid dosing conditions were maintained for only one dose, Dr. Weinberger has suggested the possibility of a much larger difference in the food-versus-fasting bioavailability of Uniphyl if the dosing conditions had been maintained for a longer period of time. This is a valid question, which we have recently addressed in a crossover study in which Uniphyl was administered for 14 days, 7 days with food and 7 days under fasting conditions.[2] The difference in serum theophylline concentrations between the two 7-day periods was similar to differences observed in the present study and therefore confirm, even with prolonged fasting administration, that the difference between food and fasting bioavailability of Uniphyl is limited to approximately 10%.

Dr. Weinberger has referred to the study of Karim et al.[3] as evidence of substantial malabsorption of Uniphyl, when it is administered under fasting conditions, but has not compared the magnitude of this difference with that reported in his own single-dose study, which demonstrated only a 15% decrease in bioavailability of Uniphyl when it was administered under fasting conditions.[4] Moreover, Dr. Weinberger's study demonstrated that under multiple-dose conditions, the bioavailability of Uniphyl, when it is administered in the morning with food, was 86%. In two other studies[5, 6] in which Uniphyl was administered with food in the evening rather than in the morning, its bioavailability was found to be 100%. Since we have previously reported[7] that morning administration of Uniphyl results in approximately 10% reduction in bioavailability compared with evening administration, we believe that the difference between Dr. Weinberger's estimate of bioavailability and the 100% reported in our studies is due to the effect of morning dosing in Dr. Weinberger's study.

We note that Dr. Weinberger agrees that Uniphyl should be administered in the PM, albeit for the wrong reason. We have repeatedly stressed evening administration of Uniphyl with food, not only to optimize bioavailability but also, more importantly, when administered in the PM, Uniphyl has been clearly demonstrated, in a double-blind clinical comparison, to be superior to twice-daily Theo-Dur, particularly in controlling early morning symptoms and improving spirometry.[8] It is our strong contention that too much emphasis has been given to the position, frequently expressed by Dr. Weinberger and his colleagues, of the necessity of maintaining constant theophylline concentrations around the clock. The benefit of once-daily evening dosing of Uniphyl occurs because peak theophylline concentrations are maintained in the early morning, therefore providing maximum bronchodilation at the time of greatest need, during the characteristic early morning increase in airway resistance. Achieving a stable theophylline concentration around the clock may be satisfying to the clinician, oriented to pharmacokinetics, and is of much less importance to the patient whose primary need is addressed by stabilization of symptoms and spirometric values.

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REFERENCES

1. Hendeles L, Weinberger M, Milovetz G, Hill M III, Vaughn L. Food-induced "dose dumping" from a once-a-day theophylline product as a cause of theophylline toxicity. Chest 1987;8:758-65.
2. Arkinstall WW, Brar PS, Stewart JM. Multiple dosing of Uniphyl tablets under food and fasting conditions: comparison of serum theophylline levels, pulmonary function, and asthma symptoms [submitted].
3. Korim A, Burns T, Wearley L, Streicher J, Palmer M. Food-induced changes in theophylline absorption from controlled-release formulations. Part 1. Substantial increased and decreased absorption with Uniphyl tablets and Theo-Dur Sprinkle. Chin Pharmacol Ther 1985;38:77-83.
4. Milovetz G, Vaughn LM, Weinberger MM, Harris JB, Mullenix TA. Relationship between rate and extent of absorption of oral theophylline from Uniphyl brand of slow-release theophylline and resulting serum concentrations during multiple dosing. J ALLERGY CLIN IMMUNOL 1987;80:723-9.
5. Welsh PW, Reed CE, Conrad E. Timing of once-a-day theophylline dose to match peak blood level with diurnal variation in severity of asthma. Am J Med 1986;80:1098-1102.
6. Mangura BT, Maniatis T, Rahman MSA, Bartholf R, Lavietes MH. Bioavailability of a once-daily administered theophylline preparation. Chest 1985;90:566-70.
7. Rivington RN, Calcutt L, Child S, MacLeod JP, Hodder RV, Stewart JH. Comparison of morning versus evening dosing with a new once-daily oral theophylline formulation. Am J Med 1985;79(suppl 6A):67-72.
8. Arkinstall WW, Atkins ME, Harrison D, Stewart JH. Once-daily sustained-release theophylline reduces diurnal variation in spirometry and symptomatology in adult asthmatics. Am Rev Respir Dis 1987;135:316-21.

Essential acquired cold urticaria

To the Editor:

I would like to comment on "Essential (acquired) cold urticaria," which is part of a recent article by Casale et al.[1] in THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY. One of the diagnostic tests advised by the authors is "hand