other drugs could not be assessed despite their potential contributions to hepatitis risk. Among all age groups, the definitions of “clinical hepatitis” and, very likely, the intensity of surveillance for hepatitis used in the cited studies varied. This may well account for the broad range of “clinical hepatitis” noted. It was also not possible to identify the time point in therapy when hepatitis occurred. Since INH and rifampin-containing regimens are now typically given for nine months or, when supplemented for two months with pyrazinamide, for six months, hepatitis beginning beyond those time points should be avoidable. Finally, it is essential to note that regimens that did not include both INH and rifampin still were associated with hepatitis. Indeed, many of the drugs available today for treating tuberculosis have been associated with hepatitis. For adults, in particular, the increment in hepatitis risk related to combining INH and rifampin appears quite modest. Although the risk of INH-rifampin regimens for children seems more substantial, only a handful of the studies reviewed by Steele et al involved a sizeable cohort. Moreover, the study4 with the largest population and one of the highest reported rates of hepatitis among children also used pyrazinamide, a potentially hepatotoxic drug. This study’s inclusion in the analysis may have inflated the rate of “INH-rifampin” hepatotoxicity. More information concerning how our youngest patients tolerate antituberculosis therapy is clearly needed.

How, then, should clinicians use these insights when managing patients with tuberculosis? First, clinicians must recognize that tuberculosis is an important health problem which should be treated promptly when it is diagnosed. Second, they must be informed as to the potential side effects or contraindications to the use of particular drugs and drug combinations. Clinicians should be prepared to do what they can to prevent these reactions or to identify them early on if they occur. This includes educating the patient in avoiding activities that could adversely affect treatment and in recognizing adverse reactions. It also includes efforts, like those of Steele and colleagues, to study these problems in an effort to better understand them. Ultimately, clinicians must select the most favorable balance between the risk of a particular treatment on the one hand and the potential benefit to be derived on the other. Although complications of therapy such as hepatotoxicity represent an obvious risk, failure to complete an adequate course of treatment with consequent continued or recurrent tuberculosis is a more subtle but no less important “risk.” Drug combinations that reduce that problem should be viewed as having added benefit. From that perspective, the combination of INH and rifampin looks quite attractive.

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REFERENCES

2 Centers for Disease Control. Tuberculosis Program Management in The United States 1984. Atlanta: Division of Tuberculosis Control, Center for Prevention Services, Centers for Disease Control Publication No. 00-4913

Interpretation of Pco2 in the Asthmatic Patient

In asthmatic patients, the relationship between arterial carbon dioxide tension (PaCO2) and FEV1, used as a measure of airway dysfunction, is not linear. Hypocapnia (low PaCO2) is the rule unless airway obstruction is severe, when mild hypercapnia may occur.1 The PaCO2 is an index of, and is inversely related to, ventilation. Mechanical airway obstruction ought to impair ventilation and thus CO2 elimination. The major event governing PaCO2 in asthma is then the degree of airway obstruction: PaCO2 is an index of disease severity, an interpretation of considerable importance to the clinician. Simultaneous measurement of FEV1 and PaCO2 may help us to confirm (or disprove) the correctness of the clinical impression. Hypocapnia in the asthmatic patient whose airway obstruction appears clinically to be mild or moderate is reassuring.

Ventilation alone, however, may not explain the variability in measured PaCO2. The Montreal group points out that CO2 tension is determined by three variables: CO2 production (assumed to be constant by earlier authors), central ventilatory drive as a reflection of ventilation, and physiologic dead space.2 Our recent observation that measurable increases (or decreases) of ventilation in the asthmatic patient may not be accompanied by any change of PaCO2 underscores the importance of this view.3 Small increases in ventilatory drive such as can be induced by the stimulation of a mouthpiece (or decreases induced by oxygen administration) are followed by the expected changes in.

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ventilation; PaCO₂, however, is unchanged.\textsuperscript{1,5} Increases or decreases of V̇CO₂ (most likely representing changes in respiratory muscle oxygen consumption) counterbalance the changes in ventilation. In addition, administration of O₂ may achieve dilation of peripheral airways and thereby diminish V̇d/V̇t. Thus, serial measurements of PaCO₂ in asthma do not necessarily reflect the changes in airway function, metabolic rate, and ventilatory drive which may be occurring during therapy!

That the ventilatory stimulus of a mouthpiece seems to override the slight ventilatory depressive effect of oxygen administration has profound implications for the interpretation of clinical studies in which simultaneous measurements of ventilation and PaCO₂ are made during mouthpiece breathing. How can we evaluate the efficacy of an intervention designed to reduce breathing work (such as bronchodilatation or oxygen administration) when the mouthpiece serves to maintain an elevated ventilatory drive? An intact respiratory regulation system should be able to establish a ventilatory pattern and PaCO₂ allowing oxygenation and CO₂ elimination while minimizing breathing work. Supporting this hypothesis is a recent study which demonstrates that during mild hyperinflation, the asthmatic subject “chooses” an end-expiratory lung volume which minimizes resistive work while adding only minimally to the elastic component.\textsuperscript{6} Clearly, the ventilation observed during mouthpiece breathing does not reflect the inspiratory drive or ventilation chosen by the patient if he were unencumbered by the mouthpiece. Studies of ventilatory response to respiratory depressants such as oxygen or sedation then have little meaning when they are made during mouthpiece breathing. Finally, Georgopoulos et al\textsuperscript{7} have recently pointed out another variable confounding the estimation of ventilatory drive after changes of FIO₂, namely: the duration over which ventilation is measured.

What is the “take home” message of these observations to the practicing physician? We know that a single measurement of PaCO₂ during acute bronchospasm is helpful to verify that the patient whom we expect to maintain ventilation is in fact doing so. We must recognize, however, that subsequent PaCO₂ analyses provide limited insight into the physiologic changes which accompany convalescence in asthma.

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REFERENCES


4 Freedman AR, Mangura BT, Lavietes MH. Minute ventilation in asthma: enhancement by mouthpiece and depression by oxygen administration. Am Rev Respir Dis 1983; 129:900-05

5 Cassabian J, Miller KD, Lavietes MH. Respiratory center output and ventilatory timing in patients with acute airway (asthma) and alveolar (pneumonia) disease. Chest 1982; 81:536-43


Clinical Applications of Soluble Interleukin-2 Receptor in Granulomatous Disease

In this issue of Chest (see page 310) Takahashi and colleagues measured soluble interleukin-2 receptors in patients with lung disease and in healthy volunteers. They found higher levels in those with tuberculosis and sarcoidosis. The serum levels correlated with disease activity. This follows reports of increased soluble interleukin-2 receptors in serum and bronchoalveolar lavage fluid in patients with sarcoidosis,\textsuperscript{1,4} and is one of several recent articles that indicate how knowledge of T-cell proteins and their receptors may be applied clinically in the future.

Interleukin-2 was the first of a series of lymphocyte-trophic hormones to be well-characterized and synthesized.\textsuperscript{3} It is central to the generation and regulation of the immune response. Interleukin-2 is produced by T-cells and reacts with high-affinity receptors on the T-cell surface. After binding interleukin-2, its receptor enters the cell and initiates events leading to cell division and activation. The reaction is self-amplifying, but is checked by short lived receptor gene activity\textsuperscript{4} and further interaction with other agents. The interleukin-2 receptors are made of two chains, α and β. They have a constant region encoded by a single gene and a variable region encoded in several chromosomal domains. The domains can be combined so that millions of different conformations of the variable region are possible.\textsuperscript{5} This variability may allow for a specific marker of tuberculosis or other inflammatory lung disease, although the report in this issue does not go that far.

The study of interleukin-2 and its receptors are already telling us more about immunity to tuberculosis. In mice heavily infected intravenously with Calmette-Guerin bacilli (BCG), mitogen-induced levels