Communications for this section will be published as space and priorities permit. The comments should not exceed 350 words in length, with a maximum of five references; one figure or table can be printed. Exceptions may occur under particular circumstances. Contributions may include comments on articles published in this periodical, or they may be reports of unique educational character. Specific permission to publish should be cited in a covering letter or appended as a postscript.

Digitalis-like Factors and Digoxin Pharmacokinetics.

To the Editor

King et al. have recently reported a successful reduction of fetal supraventricular tachycardia with maternal digoxin therapy. Previous reports have also described very similar observations with the same benefit, but discrepancies were observed when the digoxin concentrations were investigated in cord and maternal blood. Equal digoxin levels in cord and maternal blood have been found by Rogers et al. and Lingman et al. On the contrary, several authors have reported that the cord serum digoxin concentration was lower than the maternal serum digoxin concentration.

We are surprised to notice that, for all these contributions, no reference is made to the digitalis-like factor. Several studies using immunoassays have proved the presence of digoxin-like substance (DLIS) in the sera of premature, full-term infants and women in the third trimester of pregnancy who had not been treated with digoxin. The DLIS interference has also been recovered from patients with liver disease, renal impairment and essential hypertension. The degree of interference may vary between different digoxin immunoassay techniques and exhibit a lot-to-lot sensitivity for a same technique.

Vinge et al. have recently suggested that the interfering factor was a protein that could bind labeled digoxin derivatives supporting a non-specific interaction.

Other studies have shown that many compounds, including pregnancy steroids, bile salts, and lipids with detergent activity, cross-react, giving false-positive digoxin indications. Even if some unspecified compounds may be involved, numerous studies generally conclude the concomitant presence of a digoxin-like factor interacting with digoxin antibodies. The properties of DLIS include an inotropic action and the inhibition of the Na⁺, K⁺-ATPase, i.e., the specific receptor of cardiac glycosides.

Gruber et al. and Cusdon et al. have suggested that DLIS might be the putative natriuretic hormone. The DLIS biochemical identification remains under active investigation and peptide- vs-steroid controversy over the nature of the DLIS is not yet resolved.

Whatever the nature of analytical interference is, digoxin monitoring and pharmacokinetics using immunoassay technique on samples where DLIS is present have to be investigated cautiously. Lackner et al. and Barbarash have recently criticized the digoxin pharmacokinetic study during pregnancy of Luxford and Kellaway where they described lower post-partum serum digoxin levels as compared to concentrations during the third trimester of pregnancy. These comments can be generalized to all studies on placental transfer of digoxin.

Is digoxin level of 0.3 to 0.4 ng/mL reliable in venous cord blood when the DLIS interference reaches or overtakes this level? No efficient conclusions can be drawn from the various ratio described between human fetus and maternal digoxin levels. The efficiency of the digoxin administration in utero cannot be demonstrated by digoxin levels and other investigations should be used to adequately digitalize the fetus without incurring maternal toxic effects. The DLIS presence leads to the re-investigation of a large number of pharmacokinetic data for digoxin. Many cautions have been taken for the interpretation of digoxin level in various physiological states or diseases.

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**Erratum**

To the Editor:

I apologize for the typographical error in my paper, "Right ventricular volumes by thermodilution in the adult respiratory distress syndrome," published in the July issues of Chest (1985; 88: 34-39). The formula given on page 35 should be:

\[ K = C_0/C_1 + C_2/C_1 + \ldots + C_n/C_1 - 1 \]

n = 1

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**Optimal Use of MDIs**

To the Editor:

In his article, "Spacer devices used with metered-dose inhalers" (Chest 1985; 88:276-84), Peter König has provided an excellent review of the state-of-the-art with respect to these MDI add-on units. In table 6, which compares clinical trials using the various devices, we would like to stress the point that the device delivered to the lung using the Aerochamber plus MDI was similar to the dose delivered when the MDI was used optimally, i.e., held 3 cm in front of the widely opened mouth with the aerosol bolus inhaled from FRC to TLC, followed by a ten second breath hold. This method of using the MDI delivers about twice as much aerosolized medicine to the lung than when the MDI is discharged between closed lips. Since the latter method was used for MDI aerosol delivery in the Brethancer (tube spacer) study, it is not surprising that pulmonary deposition with the device was greater than when the unaired MDI was used. The closed mouth MDI administration technique was also used as the "gold standard" in the InspiEase study.3

As one of the co-authors of the study suggesting possibly less efficacy when steroid aerosols are administered via the Aerochamber, it should also be stressed that this information appears in abstract form only and will not be published since patients, misunderstanding the instructions for Aerochamber use, sprayed several puffs consecutively into the device before inhaling. Since 20 ml of freon and drug are ejected with each puff, substantial amounts of the total dose were lost. In a more recent study without these limitations, the beclomethasone MDI with Aerochamber was found superior to the unaired MDI in the delivery of medication with respect to both improved efficacy (twice as many patients could discontinue systemic steroid therapy while using MDI plus Aerochamber) and decreased incidence of Candidiasis infection (22 percent in the MDI only group vs no infection in the MDI plus Aerochamber group).

It appears from this comprehensive article that there is little difference in efficacy between the various devices. Selection of an MDI add-on device in clinical practice is probably best determined by ease of use, assurance of drug delivery, portability and cost. However, these considerations should not detract from the importance, in general, of spacer devices in the therapeutic regimen of obstructive airways disease for many patients. In our opinion, the major importance of MDI with add-on devices for the delivery of aerosol therapy to children continues to be grossly underestimated. Spacers are simple to use, inexpensive and independent of an external gas or power supply, unlike nebulizers, whose per treatment cost is much higher and incurs the added potential of nosocomial infection. Thus, add-on devices are neither "breakthrough nor gimmick," but a valuable adjunct to therapy in selected patients.

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To the Editor:

The letter by Newhouse and Dolovich makes a number of points. It is possible that they are correct in their explanation of better results in some studies with tube spacers because they were compared with the "closed lips" technique of MDI use. However, an equally distinguished group of investigators4 considers the "closed lips" technique better than "open lips." In my opinion, it is still not certain which method works better for adults, but in children, because of the possibility of faulty aim when holding the inhaler 3 to 4 cm in front of the mouth, I prefer to use the "closed lips" technique. With regard to the possible reduced clinical efficacy of cortico-steroids with aerochamber, the footnote in table 6 clearly stated that it was based on a single abstract, and I am grateful for their clarification of possible problems in that study.

I quite agree with Drs. Newhouse and Dolovich that spacers are underused and are useful in selected patients, as I concluded in the summary of my review article.

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