Iseganan Failure Due to the Wrong Pharmaceutical Technology

To the Editor:

We read the recent review by Craven in CHEST (July 2006),1 entitled “Preventing Ventilator-Associated Pneumonia in Adults.” We enjoyed the article as it was up to date and balanced. In particular, we welcomed Dr. Craven’s conclusion on the iseganan failure that “these results raise several questions about iseganan efficacy and why it failed” as the original investigators did not attempt to explain their negative randomized controlled trial (RCT) findings.2 Iseganan did not impact pneumonia because the solution failed to decontaminate the oropharynx, as “there were no differences in reductions in total Gram-negative organisms and Staphylococcus aureus between test and control groups.”3 The failure to eradicate the oropharyngeal carrier state of these potential pathogens is probably due to the short contact time between iseganan in solution and the potential pathogens. Stoutenbeek et al3 were the first investigators to decontaminate the oropharynx of ventilated patients using a mucosa-adhesive paste (Orabase; Colgate; New York, NY) with 2% polymyxin E/tobramycin.

The major weakness of the iseganan RCT was its design because the control patients received placebo,4 which is unethical as they were put at unnecessary risk of pneumonia. The iseganan maneuver should have been compared with the best available clinical evidence, selective digestive decontamination.5,6 Two of the iseganan trial authors published selective digestive decontamination RCTs,5,6 demonstrating pneumonia reduction. We believe that clinical trials with end points of pneumonia/mortality should be preceded by a microbiological trial with an end point of clearing the abnormal carrier state. Obviously, regular surveillance (ie, daily or, minimally, three times per week) is essential to assess the efficacy of a 2% iseganan gel as decontaminating agent. Throat surveillance in the iseganan RCT by Kollef et al4 was limited to swabbing at the start and end of the study, and when pneumonia developed in the patient.

We hope that iseganan will get another chance as this trial by Craven5 was ill-advised.

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Methamphetamine and Idiopathic Pulmonary Arterial Hypertension

Role of the Serotonin Transporter

To the Editor:

In a recent article in CHEST (December 2006),1 Chin et al reported that methamphetamine (METH) abuse significantly increases the risk of developing idiopathic pulmonary arterial hypertension (IPAH) [odds ratio, 11.6]. Their findings add IPAH to the list of serious medical complications associated with METH abuse.2 The data, while requiring confirmation by a larger epidemiologic investigation,3 raise interesting questions as to what pharmacologic mechanism might underlie the link between METH and IPAH. We suspect at least two critical factors contribute to such a mechanism: (1) the preferential interaction of METH with serotonin transporters (SERTs) in vivo; and (2) the high doses of illicit METH that are typically self-administered.

Our previous work4 has demonstrated that medications known to increase the risk of IPAH (ie, fenfluramine, d-fenfluramine, and amphetamine) reduce serotonin transporter density in vivo; and that METH increases methylation of serotonin transporter RNA.5 These observations suggest that METH increases the probability that the SERT substrate may be of the metabolically unstable form (NADPH oxidase).6 However, the potential importance of METH-induced SERT upregulation remains to be explored.

We hope that the recent findings by Chin et al will stimulate further investigation of the complex pharmacologic mechanisms that may be involved in METH’s influence on SERT expression and, hence, SERT-mediated neurotransmission.

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