References

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In Reply:—Johnstone's letter concerns our Fluro-Ethyl® spray, (a nonflammable prescription topical anesthetic or skin refrigerant) and chlorofluorocarbons (CFCs) implicated in stratospheric ozone depletion.

Fluro-Ethyl contains 75% (by volume) dichlorotetrafluoroethane (114), a CFC also known as Freon® 114 or Dymel® 114, and 25% ethyl chloride. Johnstone is incorrect in stating that dichlorotetrafluoroethane is Freon 12. The chemical name for Freon 12 is dichlorodifluoromethane.

Freon 114 has been identified as a stratospheric ozone-depleting chemical. An accelerated phase-out is in progress for this chemical and for the other class I chemicals listed in the Clean Air Act Amendments of 1990, Title VI-Stratospheric Ozone Protection. The original phase-out, once set to be January 1, 2000, has been accelerated by Executive Order of President Bush. By the end of 1995, there will be no production of most class I chemicals; dichlorotetrafluoroethane is included in this phase-out. It also should be noted that this phase-out is far more strict than the United Nations-sponsored Montreal Protocol.

Johnstone states that other products, such as ethyl chloride, are available to anesthetize skin. However, ethyl chloride is flammable; Fluro-Ethyl® is not. Ethyl chloride, therefore, is sometimes not permitted in hospitals if not stored according to the recommendations of the Joint Commission on Accreditation of Hospitals.

It also should be noted that the current U. S. production of 114 is 50% of the 1986 volume, 360 million pounds. Fluro-Ethyl® uses 0.004% of this amount.

Gebauer is complying with the phase-out schedule. Regardless of the fact that we have no replacement at present for Fluro-Ethyl®, there will be no production of 114 in 1995; therefore, there will be no product.

John A. Giltinan
President
Denise Bodkin
Regulatory Affairs Manager
Gebauer Company
Pharmaceutical Preparations
9410 St. Catherine Avenue
Cleveland, Ohio 44101

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Risk of Ischemia in Patients Receiving Desflurane *Versus* Sufentanil: Sample Size and Clinical Significance

To the Editor:—Anticipating the arrival of desflurane into our clinical armamentarium, I eagerly read Helman *et al.*'s randomized trial of sufentanil *versus* desflurane in patients with documented coronary artery disease.[1] Helman *et al.* performed what appears to be a methodologically exacting study demonstrating that desflurane, like the other potent inhalational agents, can be used, with appropriate adjuncts, without unacceptable hemodynamic consequences in this patient population.

What is unclear to me as a clinical reader is their discussion directed at differences between the sufentanil and desflurane groups relative to adverse cardiac outcome. First we are informed that "our sample size was insufficient to detect a significant difference, and that even a "10-fold" increase in sample size would have been unable to detect a difference. But then the authors conclude that on the basis of a "relative risk" calculation, we should not rule out that desflurane could be associated with more prebypass ischemia than sufentanil in these patients.

What does "not significant" mean to the clinical reader? To me, it suggests that under the rules established by the investigators at the outset of the study, and subsequently validated by referees, they were unable to demonstrate a difference in the tested treatments. Clearly, Helman *et al.* were plagued with the common problem of a sample size insufficient to deal with a small "effect size" (*i.e.,* the strength of the treatment on the measured outcome). Another example of the Beelzebub of the clinical trial is, namely, does absence of evidence constitute evidence of absence?

What really disturbs me about Helman *et al.*'s paper is where it leaves us. First, the authors conclude that there was no significant

difference between the treatments. Then, through the use of the mathematically specious process of "relative risk" calculation, they deduce that desflurane is associated with 2.3 times the incidence of prebypass ischemia than sufentanil (17% *vs.* 7%).

These kinds of clinical studies have little practical moment to the ultimate consumer of them, the practitioner. Investigations that purport to test hypotheses with treatments involving insufficient subjects predictably, as in the present case, arrive at ambiguous conclusions. Rather than focusing on type I *versus* type II errors, I believe that the larger problem is one of investigators trying to do too much with too little. The investigation spanned a period of from August 1990 to April 1991—what, I ask, was the hurry? Investigators should ask themselves, if sufficient time, money, personnel, or energy are not available for the task at hand, perhaps the task should not be undertaken. Careful attention to these issues may help avoid ambiguous and confusing messages communicated to readers such as myself who depend heavily upon scientific publications for rational practice decisions.

Chuck Biddle, Ph.D., C.R.N.A.
41 Nottingham Circle
Lebanon, New Hampshire 03756

Reference

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In Reply:—We thank Biddle for his comments regarding our paper and would like to respond to several of the comments made in his letter.

First, Biddle stated that we demonstrated that "desflurane, like the other potent inhalational agents can be used, with appropriate adjuncts, without unacceptable hemodynamic consequences in this patient population." This is an incorrect statement. In contrast, we concluded that during anesthetic induction, desflurane, when used with sodium thiopental as an adjunct, was associated with *more* hemodynamic changes and myocardial ischemia, when compared with sufentanil anesthesia. During anesthetic maintenance, however, the risk of myocardial ischemia was not significantly increased with desflurane (used as a *sole* anesthetic agent) when compared with sufentanil anesthesia when attempts at strict hemodynamic control were employed.

Second, Biddle commented on "the differences between the sufentanil and desflurane groups relative to adverse cardiac outcome" and then went on to abstract multiple sections from the manuscript to reach the conclusion that "these kinds of clinical studies have little practical moment to the ultimate consumer of them, the practitioner." In making these statements, Biddle appeared to be rather confused about the outcome measurements and the purpose of our study. To reiterate, the purpose of our study was to determine whether the risk of myocardial ischemia was increased in patients with coronary artery disease receiving desflurane as a primary anesthetic. We believed that this was an important question because desflurane, having a low blood solubility, would likely be used for rapid induction, emergence, and recovery in noncardiac surgery. Since a substantial proportion of patients undergoing noncardiac surgery have or are at risk for coronary artery disease, proving that desflurane is safe in this patient population is critical.

We chose patients undergoing coronary artery bypass graft (CABG) surgery as a model because these patients have known coronary artery anatomy and hemodynamics are already invasively monitored. Thus, the primary end-point in our study was myocardial ischemia as measured by electrocardiogram or echocardiography (precordial or transesophageal). Our assumption is that if the risk of myocardial ischemia is not increased under desflurane anesthesia, then it is unlikely that the risk of adverse cardiac outcomes such as myocardial infarction will be increased since myocardial ischemia is usually a harbinger of myocardial infarction. If our study had demonstrated an increased risk of myocardial ischemia associated with desflurane, then further studies examining adverse cardiac outcomes would be necessary. This type of study design is more feasible since outcome studies examining hard end-points such as death or infarction are generally very large in size. The inclusion of adverse cardiac outcome data (cardiac death, myocardial infarction, and ventricular failure) in our report was performed for completeness. Comparison of adverse outcomes between the two anesthetic groups would be inappropriate (as discussed in the limitation section of the manuscript) since the study sample size was calculated based on previous incidences of myocardial ischemia and *not* myocardial infarction rates.

To clarify issues regarding sample size calculation, we based our sample size calculation on previous studies of patients undergoing CABG surgery who received isoflurane anesthesia.[1] The sample sizes were calculated to give an 80% chance of detecting a 50% difference in the incidence of myocardial ischemia with a level of significance at 5%. Using a known incidence of myocardial ischemia of 20% (as detected by Holter electrocardiogram or transesophageal echocardiography), the sample sizes were 81 patients in each of the two treatment groups, for a total of 162 evaluable patients for the study. In anticipation of unevaluable data, the final sample size was 200 patients. In designing the study *a priori,* we chose not to perform multiple looks at the data before the conclusion of the study to avoid committing a type I error. Also, this type of approach would mandate adjusting the level of statistical significance required, necessitating larger sample size if the study were to be modified. Thus, in contrast to Biddle's charge of us "trying to do too much with too little," we have adhered to the study design and the *a priori* sample size calculation.

In our discussion of the potential limitations of this study, we indicated that our study could not exclude the possibility of a small difference in echocardiographic evidence of ischemia between the two anesthetics during the prebypass period since there was a trend