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AstraZeneca's Response to the Review by Wysowski and Pollock Regarding Deaths Reported in Association with Propofol Use

To the Editor:—In response to the review by Wysowski and Pollock[1] regarding deaths reported in association with propofol use, AstraZeneca would like to make a few comments.

Although we acknowledge that it is difficult to tell from the original articles cited by Wysowski and Pollock, the five patients referred to in the 1992 Parke *et al.* article are also included in the 1998 article by Bray. Hence Wysowski and Pollock's total numbers of such events should be reduced by 5.

AstraZeneca's recommended maximum Diprivan dose rate for adult intensive care unit sedation is 4 mg · kg^{-1} · h^{-1}; it is of note that all of the patient groups reviewed received dose rates higher than this. Although pediatric intensive care unit sedation is a licensed indication in one country and the dose recommendations are higher than for adult intensive care unit sedation, those reports of pediatric propofol infusion syndrome events also received dose rates higher than AstraZeneca's maximum recommended rate.

It is of note that the indications for Diprivan/propofol use in a large proportion of the patients cited in this review were for the treatment of status epilepticus and the reduction of intracranial pressure. These are not licensed indications for Diprivan. Although the use of (higher dosage) Diprivan/propofol may be efficacious in these indications, the safety of such treatment regimens has not been established in clinical trials.

AstraZeneca has not and does not support the use of its products for unlicensed indications or at dose rates significantly outside the recommended dosages. (The recommended range for intensive care unit sedation was based on efficacious clinical trial dosages and includes the mean dose rate ± 2 SDs; therefore, there may uncommonly be a need to *modestly* exceed the maximum recommended dose rate.)

Having observed that a high proportion of cases involved patients with serious respiratory infections, status epilepticus, and head injuries, AstraZeneca is disappointed that Wysowski and Pollock did not discuss the possibility that disease and/or treatment-related factors, other than the use of propofol, common to these patients may have at least contributed to the development of these serious scenarios. AstraZeneca has produced an article documenting the facts regarding these events, discussing the likely causes together with suggestions for prevention and management strategies.[2] We recommend it to your readers.

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Propofol Infusion Syndrome: Is There Any More Information?

To the Editor:—With great interest, we read about the reports of death by Wysowski and Pollock[1] regarding the use of propofol for long-term sedation in pediatric and adult patients. In this article, the authors present factors contributing to the so-called propofol infusion syndrome[2] in a larger number of patients. Regarding these analyses, it is obvious that high doses of propofol (especially in children) and/or long-term administration are risk factors for development of propofol infusion syndrome. However, the incidence and pathophysiology[3] of this syndrome are still controversial.

The major problem regarding the incidence and etiology of propofol infusion syndrome is the lack of well-designed, systematic studies. Most previous studies were not adequately designed to give more insight into these issues.

For example, Martin *et al.*[4] investigated nine children receiving low doses of propofol (1–4 mg · kg^{-1} · h^{-1}) for a limited duration (48 h) after cardiac surgery. They concluded that propofol may be used safely in the recommended doses and in combination with an opioid. However, the number of patients included in this study was too small to draw any conclusions about safety.

In a second retrospective study, a total of 198 pediatric patients were included, from which 106 received propofol and 92 received other sedative agents.[5] The propofol doses ranged between 0.4 and 30.0 mg · kg^{-1} · h^{-1}, and the duration of treatment was between 30 min and 156 days. Regarding these large differences, a definite conclusion with respect to safety is impossible. The authors of a further retrospective analysis also concluded sedation with propofol might be safe[6]; however, 102 of 142 children received propofol for less than 24 h, and 133 for less than 48 h. Furthermore, maximum doses were limited to 3 mg · kg^{-1} · h^{-1}.

With respect to previous investigations, Wysowski and Pollock[1] concluded that additional studies may be warranted to compare the risks and benefits of propofol with other sedative agents. However, this study has already been performed some years ago (trial 0859IL-0068), but the results were not presented adequately until now.* In this study, a total number of 327 mechanically ventilated pediatric intensive care unit patients were allocated to one of the following groups: sedation with 2% propofol (n = 113), 1% propofol (n = 109), and standard sedative agents (lorazepam, fentanyl, ketamine, pentobarbital, and so on; n = 105). The Pediatric Risk of Mortality scores for the three groups were not different. In the standard sedative agents group, mortality was 4%; patients treated with 1% propofol had 8% mortality; and those receiving 2% propofol had 12% mortality. Interpretation of these results is difficult because (1) no statistics are given, (2) information regarding the study design is limited, and (3) nearly half of the deaths came from one participating center.

* Available at: http://an.hitchcock.org/PediSedation/. Accessed January 11, 2007.