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EDITORIAL

Ethical Considerations in the Randomized Evaluation of Propofol Safety

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For more than a decade, controversy has persisted regarding the safety of propofol as a sedative agent for mechanically ventilated patients in the pediatric intensive care unit (PICU). Timpe and colleagues' comprehensive review illustrates that case reports and series, retrospective studies, and a prospective clinical trial have raised questions regarding excess mortality associated with propofol related infusion syndrome (PRIS).[1] At the same time, surveys of sedation practices in PICUs suggest that a sizable percentage of pediatric intensivists continue to use propofol, alone or in combination with other medications, as a sedative agent of choice in providing for the comfort and safety of mechanically ventilated patients.[2-4] In light of its continuing use and the persisting controversy among pediatric intensivists, further evaluation of the safety of propofol in a randomized clinical trial may be warranted. However, the ethical conduct of a safety trial requires careful consideration of two key factors: the acceptability of the risk-benefit profile of the study and the adequacy of plans for securing the informed consent of participants.

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Determining the acceptability of the risk-benefit profile of the study requires attention to several key elements. One requirement, reflected in the criteria for institutional review board (IRB) approval in the federal regulations for the protection of human subjects, is that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects."[5] Although the federal regulations do not formulate standards for determining when the risk-benefit ratio for subjects is "reasonable," it is generally agreed that the welfare of subjects should not be significantly compromised by participation in clinical trials of therapeutic interventions. In the context of a randomized comparison of alternative therapies, this moral standard requires that it not be known that the risk-benefit profile of any treatment to which subjects are randomized is significantly less favorable than any alternative treatment. In statistical terminology, it is morally acceptable to begin a randomized clinical trial (RCT) only if investigators are able to state an honest null hypothesis regarding the risk-benefit profile of the treatments compared.

ABBREVIATIONS IRB, institutional review board; PICU, pediatric intensive care unit; PRIS, propofol related infusion syndrome; RCT, randomized clinical trial

Establishing an honest null hypothesis for a propofol safety study requires careful evaluation of preliminary evidence regarding the comparative risks and benefits of using propofol and other sedative agents in mechanically

ventilated children. On one hand, a series of case reports suggests a possible link between propofol use and cardiovascular collapse, and one randomized study suggests excess mortality in the group treated with propofol compared to standard sedative agents. Any statistically significant excess of deaths from the use of propofol creates substantial uncertainty about the clinical parameters within which the drug can be safely used for sedation of mechanically ventilated children. On the other hand, the use of propofol has some significant clinical advantages over other agents. Its rapid onset of action, its dose-proportional sedative effects, and the rapid dissipation of its effects after discontinuing administration provide important clinical advantages in the management, evaluation and weaning of mechanically ventilated children. Moreover, most reports of propofol infusion syndrome suggest that specific clinical variables, including large doses, prolonged use or serious respiratory infections, may increase the probability of its occurrence. When administered in low doses and for brief periods of time, little evidence has materialized that using propofol induces the characteristic features of the infusion syndrome. These types of considerations must be weighed in determining whether it is not known that the risk-benefit ratio of using propofol for sedation in mechanically ventilated children is significantly more or less favorable than the use of other sedative agents.

Assurance that subjects are not knowingly disadvantaged by study participation also involves specifying key features of the study design in a manner that enables an honest null hypothesis to be maintained. This specification of design features must depend on preliminary information that has accrued regarding the use of propofol for sedation in mechanically ventilated children. For example, given that cases of propofol infusion syndrome have clustered in patients with upper respiratory infections, it may be appropriate that criteria for enrollment exclude such patients from participation. Similarly, given that cases of the syndrome have clustered in patients who have received doses greater than 4 mg/kg/hr and whose duration of treatment has exceeded 48 hours, it may be appropriate for the protocol to specify that propofol use must not exceed these limits. Likewise, it may be appropriate to provide adequate supplementation of carbohydrates in subjects given available evidence that propofol may impair mitochondrial fatty-acid oxidation in children without adequate carbohydrate stores. Thus, the ability to maintain that the risk-benefit ratio for subjects receiving propofol is not known to be less favorable than for subjects receiving standard sedative agents will depend crucially on specific design features of the study.

Acceptability of the risk-benefit profile involves another key component. This factor is reflected in the regulatory criterion for IRB approval requiring that "Risks to subjects are minimized…by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk."[6] This requirement is reflected in major codes of research ethics, and it suggests a series of crucial questions about the design of any RCT intended to assess the safety of propofol in mechanically ventilated pediatric patients. Perhaps the most critical issue involves defining the conditions under which sedative administration will be stopped because subjects are considered to be developing PRIS. Although frank development of the syndrome during the period of drug administration and subsequent mortality during the hospitalization may serve as appropriate data points for the safety study, minimizing risk to subjects is best served if surrogate markers for the development of the syndrome are specified. As the review by Timpe and colleagues suggests, this constellation of surrogate markers might include early clinical findings related to development of hypotension, bradycardia and arrhythmias, as well as laboratory assessments of serum lactic acid, serum lipids, serum creatinine, hepatic enzymes, and urine myoglobin. The ethical challenge is to establish criteria that allow discrimination, for scientific purposes, of patients in whom the characteristic features of PRIS may be developing, while simultaneously assuring that exposing subjects to propofol will not continue beyond the point at which the cascade of events leading to mortal danger can be reversed.

Once surrogate markers for the development of the infusion syndrome are specified, then several other design features essential to risk minimization can be formulated. The specific

criteria for discontinuing sedative administration in the study can be specified in terms of these surrogate markers. Similarly, the appropriate monitoring procedures and the frequency of their performance can be delineated. Appropriate rescue interventions might also be stipulated for subjects who develop signs of the infusion syndrome. Finally, a rigorous protocol can be developed for review of adverse events and study progress by a data and safety monitoring board.

In determining the acceptability of the risk-benefit ratio for a proposed study, ethical guidelines and federal regulations also require that the risks be "reasonable" in relation to "the importance of the knowledge that may reasonably be expected to result" from the study.[5] This ethical and regulatory requirement addresses the potential benefit or value of the study for society rather than the subject. From this standpoint, the potential value of a propofol safety study appears obvious. The history of pediatrics is replete with instances in which commonly used treatments have later been determined to cause unacceptable harm to patients. The basic moral injunction to "do no harm" underscores the need to establish the evidentiary basis for common practices. In the case of propofol use, numerous surveys of sedative use in the PICU underscore the fact that, despite persisting concerns about the safety of propofol for sedation in mechanically ventilated children, its use continues in a majority of PICUs. Moreover, these surveys indicate that dosages and duration of exposure are often similar to those implicated in cases of PRIS. Because of the dearth of carefully controlled trials of propofol safety, it is not known whether this widespread practice is causing serious and irreversible harm, and precise parameters for safe use of the drug remain unclear. Additional studies have the potential to circumscribe the conditions under which propofol's clinical advantages can be safely utilized in the PICU.

However, there are inherent moral tensions in the risk-benefit assessment between the interests of subjects in the protection of their welfare and the interests of society in developing generalizable knowledge about the safety of propofol. These tensions are apparent in the consideration of alternative trial design features. For example, in generating comprehensive guidelines for the safe use of propofol, it would be desirable to randomize subjects receiving propofol to different maximum dosages, e.g., one treatment arm below the dosage that preliminary evidence suggests is safe, one treatment arm at the "safe" level (such as 4mg/kg/hr), and one above the "safe" level that might produce some toxicities associated with PRIS. This type of design would enable investigators to more accurately define the upper dosage limits that might reasonably be considered safe compared to standard sedative agents. On the other hand, risks to participating subjects would be minimized by not allowing a dosage level above that which appears safe according to available preliminary evidence. Another example relates to the conditions for discontinuing administration of propofol or the comparator. If these conditions permit frank development of the infusion syndrome, then the study will be better able to define the relative risk of different dosages and duration of exposure to propofol. By contrast, if the conditions for withdrawal are specified within the narrow limits of early abnormalities in clinical and laboratory findings, then subjects will be provided with a greater measure of safety. However, precise differences in relative risk of PRIS associated with different dosages and lengths of exposure will be more difficult to establish. In these ways, study design features that can add value to the clinical relevance of the knowledge generated by the study may also increase the risks of harm faced by participating subjects. Thus, determining the overall "reasonableness" of the risk-benefit ratio of the study involves inherent trade-offs between the relative weight assigned to protection for the welfare of subjects and formulating a study design that yields the most useful clinical knowledge about safe use of propofol.

The second major factor in determining the moral acceptability of a controlled clinical trial of propofol safety involves formulating an adequate informed consent process. There is an ethical obligation to respect the broad authority of parents to make decisions for their children, and this obligation is reflected in the regulatory requirement that parental permission be obtained.[7] Although in the pediatric setting the consent process often requires the assent of the subject as well, the latter requirement is

not germane in the setting of a propofol safety study because the medical condition of eligible subjects will preclude the possibility of assent. In order to adequately respect parental decision-making authority, at least three conditions must be satisfied. The parents must receive appropriate information about the proposed study, they must comprehend this information, and their permission must be sought under conditions that permit a voluntary decision that is free from any element of coercion, duress or undue influence.

The basic criterion for information disclosure focuses on what a reasonable person in the position of the parents of a prospective subject need to know in making a decision about their child's participation. Several kinds of information are crucial to the decision making of the reasonable parent. One involves the purpose of the study. While many informed consent documents may only briefly explain the purpose of a safety and tolerability study, reasonable parents would want to know some details about the background of the propofol study. This requires an explanation of the infusion syndrome, a synopsis of the concerns that have arisen regarding its association with propofol use, and a description of the circumstances under which the syndrome seems to occur. It is also important to explain why propofol continues to be used despite these safety concerns (i.e., the advantages that it offers in managing the care of mechanically ventilated children and the lack of evidence of toxicity when it is used within narrow limits.) These items of information are essential if parents are to clearly understand the rationale for conducting a safety study.

Another category of essential information relates to the risks of participation in the study and the procedures that will be used to minimize these risks. It must be clearly explained that there is a risk of developing propofol infusion syndrome and that propofol infusion syndrome may be fatal. There must also be a description of the nonfatal harms that might be caused by the use of propofol and their significance for the recovery of the child. An estimation of the probability of occurrence of these various harms under the conditions of the study must be provided. The probability and magnitude of the risks associated with the standard sedative agents used as comparators must also be enumerated. In addition, in the context of a safety study, it will be important to explain the rigorous monitoring plans and stringent withdrawal criteria that will be used to minimize the possibility of harm to the subjects. If specific rescue interventions will be stipulated in the study design, then these should be explained as well.

A third category of information concerns the potential benefits for subjects related to participation in the study. Because both propofol and standard sedative agents are widely used in the treatment of mechanically ventilated children, it must be explained that there is no unique treatment being offered that is available only in the context of the research study. As a result, there are no direct benefits to subjects associated with the treatment used in the safety study that are not available outside the research study. On the other hand, there may be indirect benefits associated with study participation that should be disclosed to the parents of prospective subjects. Available survey evidence suggests that there may be substantial variation in ordinary clinical practice with respect to the propofol dosages used and the duration of its administration. In particular, it appears that dosages and duration of exposure often exceed those limits that are thought to be safe according to available evidence. If the dosage and duration of propofol administration in the study are limited within parameters that are thought to be safe according to available evidence, then it can be stated that study participation may provide an extra margin of safety for those randomized to receive propofol. Similarly, if the monitoring procedures and the criteria for discontinuing the sedatives used in the study are more stringent than those employed in standard clinical practice, then it can be fairly stated that study participation might provide more rigorous protection of subjects from the harms associated with sedative use. However, if standard practice protocols for monitoring patients and discontinuing particular sedative agents are not significantly less rigorous than those specified in the study design, then any indirect benefits associated with trial monitoring and withdrawal procedures are likely to be rather limited.

A final category of information that reasonable parents would need to know involves

the alternatives to trial participation. Again, because both propofol and standard sedative agents might be available in particular PICUs outside the context of the safety trial, parents of prospective subjects must be told that various sedative agents might be selected in consultation with the attending physician, including those agents used in the trial. If the parents have specific concerns about propofol or other sedative agents used in the study, then a preferred treatment can be identified and the uncertainty of randomization avoided. It should also be explained what screening and monitoring procedures are being performed only for research purposes and would not be necessary if parents choose not to permit participation of their child in the safety study.

While disclosure of the information that a reasonable parent would need to know is a necessary condition for assuring proper respect for parental authority, it is also important to determine that parents comprehend the information provided and that the circumstances allow for careful consideration of the decision, free from any elements of coercion, duress or undue influence. These additional ethical requirements present a complex challenge under the circumstances in which children become eligible for the propofol safety study. Parents will be approached after learning that mechanical ventilation is required by deterioration in their child's condition or for post-operative management after major surgery. Given the complex emotional strains under which they will be laboring, special attention is necessary to assure that parents of prospective subjects understand essential information related to the purpose, risks, benefits and alternatives to trial participation. Assuring adequate comprehension requires an interactive consent interview in which investigators or their designees probe parents' understanding of the key elements of information provided. When shortcomings in comprehension are identified, then the relevant information must be further reviewed. Similarly, it is difficult to assure that the decision to participate will be free from elements of duress or undue influence. In particular, parents may feel highly dependent on the PICU physician to protect their child from harm, and they may be highly disinclined to risk alienating caregivers by refusing participation in the safety study. The impact of this sense of dependency on their decision about trial participation can only be mitigated by reassurance that their child will receive optimal care whether or not they participate in the study.

Thus, the two fundamental moral requirements for conducting a randomized clinical trial of the safety of propofol for sedation of mechanically ventilated children are that the risk-benefit ratio is reasonable and that adequate informed permission of the parents will be secured. Assuring a reasonable risk-benefit ratio requires that the objective of the study is valuable, that subjects not be significantly disadvantaged by receiving any of the randomized treatment assignments, and that the risks to subjects are minimized. Assuring adequate informed consent requires that the information disclosed be sufficient for the decision by reasonable parents, that the investigators assure that they comprehend the information, and that the circumstances of informed consent allow for a considered decision, free from any factors that may undermine the voluntary nature of the choice.

Although these conditions must be satisfied in order for a propofol safety trial to merit societal approval through the IRB process, individual practitioners of pediatric critical care medicine must decide whether to serve as local investigators and to offer participation to their patients. In making this assessment, pediatric intensivists must be guided by their fundamental obligation to recommend only those interventions that protect and promote the welfare of their patients. Because there are strong and conflicting opinions in the clinical community regarding the safety of propofol for sedation in mechanically ventilated children, the opportunity to participate in a randomized trial may pose a thorny dilemma for many practitioners. On what basis should they decide whether it is consistent with their therapeutic obligation to participate as local investigators?

There are two rather different answers to this question. According to one view, individual physicians must be genuinely uncertain about what treatment regimen is preferable, taking into account their clinical experience with alternative treatments and their understanding of evidence available in the literature, as well as the ways in which they weigh the

importance of particular risks and benefits of alternative regimens.[8,9] Moreover, on this view, if the individual physician believes that clinical experience and available information tip the scales in favor of a preferred treatment regimen, then he or she is morally committed to recommending that treatment to patients. Offering randomization under this circumstance violates the obligation to recommend only that course of treatment that the physician believes will best serve the patient's interests.

According to an alternative view, the obligation to protect and promote the welfare of the patient does not require that physicians recommend their preferred treatment regimen, but rather that they offer a treatment regimen that is consistent with the standard of care as defined by the relevant community of experts.[10] When the standard of care within the clinical community is not settled, because the relevant experts disagree regarding the evidential basis for alternative treatments, then individual physicians may satisfy their obligations to patients provided only that they recommend a treatment that is supported by a respectable minority of the relevant experts. If two or more of the treatments recommended by a respectable minority of the experts are utilized in a randomized trial, then practitioners/researchers can offer randomization to patients while simultaneously fulfilling their obligation to promote the patients' best interests. This recommendation is morally acceptable even if the individual physician prefers one of the treatments based on his or her own clinical experience and interpretation of available scientific evidence.

The latter view appears to be the more plausible interpretation of the obligation of physicians to protect their patients' interests. Developing standards of medical practice is an inherently social process, dependent on the evidentiary consensus developed through clinical research and experience within the relevant expert community. When different groups of experts within the relevant clinical community draw conflicting conclusions about optimal treatment based on a careful review of incomplete evidence, individual practitioners must grant the reasonableness of the competing views. Because insufficient evidence exists to define the optimal treatment approach, obligations to patients can be satisfied by recommending any of the leading alternatives. Moreover, practitioners should also recognize the reasonableness of randomizing patients among these leading alternatives in order to implement a controlled evaluation of their preferred treatments, provided that the trial is designed in a fashion that may resolve the current treatment controversy.

Recent history confirms that some clinical trials have been difficult to mount because individual practitioners are unwilling to submit their treatment preferences to definitive comparative assessment in RCTs. Accrual in the landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) trial of segmental mastectomy, with or without radiation, versus total mastectomy in the treatment of breast cancer was stymied, in part, by the strong treatment preferences of practitioners.[11] A similar problem stalked efforts to define in randomized fashion the parameters for the use of extracorporeal membrane oxygen therapy in the newborn intensive care unit.[12] It remains to be seen whether a safety trial of propofol for sedation of mechanically ventilated children in the PICU can surmount this difficulty. If the design of a safety study adequately addresses the moral parameters outlined above, it may provide a basis for widespread acceptance and participation.

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