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Emergency Informed Consent

ANESTHESIOLOGISTS often provide care in emergency settings. In an ideal world, clinical decisions in these situations would be based on data collected in well-controlled randomized clinical studies performed for patients with the same acute disorders (*e.g.*, trauma, cardiac arrest, perioperative cardiovascular events, among others). Unfortunately, we are not in an ideal world, and clinical decisions are often based on data extrapolated from studies performed with patients without acute critical illness or injury. In this issue of ANESTHESIOLOGY, Balser *et al.*[1] start to close the knowledge gap in the treatment of one form of critical illness.

Balser *et al.*[1] conducted a randomized prospective comparison of esmolol to diltiazem in patients with acute supraventricular tachycardia in the postoperative period, patients for whom treatment with adenosine was ineffective. They showed the superiority of esmolol in controlling supraventricular tachycardia (SVT). However, this editorial will not focus on the clinical details of the study or its results, but rather on the process by which research is performed in emergency situations, particularly the process by which informed consent is handled.

Freely given, informed written consent before participation in any clinical study is ethically and legally necessary. The importance of informed consent is emphasized by the first principle of the Nuremberg Code, approved in 1946 states: "The voluntary consent of the research subject is absolutely essential."[2]

This demand for informed consent has carried into contemporary research ethics and into all US federal regulations that govern the conduct of research. This requirement for informed consent by either a potential research subject or a representative (usually the next of kin) ensures the protection of the research subject. Unfortunately, this protection makes some types of research effectively impossible to perform. How does one adequately inform a patient when treatments must be started within a few minutes of noting the disorder? How does one obtain consent from comatose or sedated patients, again when treatment must be started before there is any reasonable possibility of even contacting the family? The inability to obtain prospective consent after severe injury or during critical illness has made the type of study performed by Balser *et al.*[1] extremely difficult to perform. A unique approach to the consent process must be implemented to ensure patient protection balanced with the ability to answer the question of interest.

The authors proceeded with a randomized drug study at the time dysrhythmia was noted in the ICU. A formal consent for enrollment in the study was not obtained before administration of the study drugs. As the authors correctly pointed out, patients in the intensive care unit often are sedated, intubated, or otherwise unable to provide informed consent. The authors apparently did not obtain prospective consent from family members because of the desire to rapidly treat the dysrhythmia. Consent was obtained from the patient or relative for further data collection within 24 hours of the inception of the study. Thus, the authors obtained deferred consent.

It is important to remember that all clinical research must be reviewed and approved by the Institutional Review Board (IRB). This Board is necessary to guarantee that all protocols protect human subjects and also to ensure that federal regulatory requirements are met. Although I was not a party to any of the committee's deliberations regarding this study, it is possible to speculate how the local IRB allowed the study to go forward as presented. Perhaps the investigators pointed out to the committee that both diltiazem and esmolol are well-proven treatments for SVT and that the use of these drugs as treatment for SVT is not experimental *per se*; only randomization and the collection and analysis of data were experimental. The investigators could have then pointed out that the collection of anonymous data poses no risk to the patients involved, therefore, it would be appropriate to obtain consent after the dysrhythmia was treated initially.

The federal regulations governing informed consent do not specifically allow for the routine use of deferred

◆ This Editorial View accompanies the following article: Balser JR, Rosenfeld BA, Martinez EA, Winters BD, Perdue PW, Clarke AW, Huang W, Tomaselli GF, Dorman T, Campbell K, Lipsett P, Brewslow MJ: Beta-adrenergic blockage accelerates conversion of postoperative supraventricular tachyarrhythmias. ANESTHESIOLOGY 1998; 89:1052–9.

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consent from research subjects or family members, unless special circumstances exist. Because this study could have been presented as an observational study of drug effects, perhaps the IRB deemed previous consent to be unnecessary in this situation because of the minimal risk to the involved participants that is represented by data collection. Final approval of a study rests with the IRB and its application of regulations to a specific situation. Not all IRBs would give the same interpretation of the federal guidelines, and some IRBs might not allow this form of consent.

Federal guidelines recognize the fact that multiple levels of risk are possible when humans participate in research projects. These risks range from nil (such as retrospective chart review) to very real (as in a dose-ranging study of a toxic chemotherapy agent). In response to the risk levels, the IRB is allowed to classify research into exempt, expedited, or full-board review protocols. Exempt research is composed of such areas as educational surveys or the study of existing data. These studies do not necessitate specific informed consent from individual participants. Another category is that of expedited review. This type of research is well covered by federal regulations. The research is characterized by minimal risk to patients. The level of risk that is found in minimal-risk studies is defined as the risks that are encountered in daily life or during the performance of routine clinical examinations.[3]

In contrast, more than the minimal-risk studies necessitate full IRB review and approval. Studies of new drugs or anesthetic techniques generally are classified in this category of research.

Since the publication of federal regulations regarding human research subjects in 1991, it has become apparent that it was impossible to investigate many important clinically problems because of the restrictive nature of existing regulations.[3] Many situations, such as acute head injury research or cardiac arrest research, could not be studied because of the lack of availability of a competent individual to provide informed consent: the patient would be too sick to provide consent and the next of kin might not be present in time to consent to the proposed procedure.

To lift the existing barriers to emergency research the Food and Drug Administration allowed exemption from informed consent requirements for emergency research in November 1996. Multiple provisions for this exemption were designed to ensure study-subject protection. First, human subjects must be in a life-threatening position in which available treatments are unsatisfactory or less than optimal. Second, it must not be feasible to obtain informed consent. Third, participation in the research holds out the prospect of direct benefit to the participant. Fourth, the investigation could not be performed without the waiver. Fifth, the investigators must define a therapeutic window based on scientific evidence, must commit to attempting to contact legally authorized representatives to provide consent within that time window, and may not proceed further without such consent. Sixth, the IRB must have reviewed and approved the informed consent procedures.[4]

In addition to these procedures, the federal regulations necessitate that consultation with representatives of the communities in which the research will occur must take place. Additionally, there must be public disclosure of the study and the results.

The existence of such stringent rules will ensure that research-subject protection remains in place, but some studies with potential immediate benefit may proceed. It is unlikely that many such studies will be performed, again because of the rigid standards that must be met. In fact, only two studies have been approved since the rule was put into place: one involving a new device to treat cardiac arrest and another evaluating a blood substitute.[5] Clearly, more trials are necessary to answer relevant questions, but it is unlikely that a large number of trials will ever operate at any one time. Governmental consent regulations in place before 1991 allowed for the limited use of deferred consent. In certain studies of life-threatening disease, researchers were allowed to enroll patients in studies without consent, then inform the patient or surrogate of their participation in the study at a later time using deferred consent. This type of consent subsequently was banned by the Federal Government in 1992 after revelation of the finding that unsuspecting patients received nontherapeutic radiation in federally sponsored studies during the 1950s.[6] This elimination of deferred consent occurred despite the finding that no abuses of the deferred consent process were noted.

Despite the multitude of protections built into the law, there is considerable concern regarding the true protection given to study participants. It has been claimed that the need for informed consent is absolute, and that no exception to this rule should exist.[4] It has also been asserted that the Food and Drug Administration paid too much attention to the concerns of companies developing new treatments and not enough concern to the rights of those who may be affected by these new treatments.[6] Finally, because most of the research will be performed in inter-city hospitals serving a minority population, concerns about racism also were raised.[7]

Is the current system ideal? Certainly not. Recent reports have claimed that IRB are seriously overworked and subject to many undesirable outside influences that could weaken research reviews.[8,9] Is the current system a suitable first step toward expanding the availability of life-saving therapy? Perhaps. Only in time will this question be answered. Until any further refinements to the system are instituted, anesthesiologists must be aware of the current regulations and work within them to design ethically appropriate emergency trials. Only then will there be sufficient progress toward the future in answering the important questions about emergency research.

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AMPA/Kainate Receptor Antagonists as Novel Analgesic Agents

THE pharmacology of amino acid neurotransmission has brought new understanding for the mechanisms of action of drugs used in anesthesia. A number of agents used by anesthesiologists facilitate γ-aminobutyric acid–mediated inhibitory neurotransmission[1]; molecular research techniques continue to define these mechanisms.[2] Potentially equally important, but less accessible, to anesthesiologists are drugs inhibiting excitatory amino acid (EAA) neurotransmission by glutamate and aspartate. In this issue of ANESTHESIOLOGY, the study by Sang *et al.*[3] presents evidence agreeing with mediation of experimentally induced human hyperalgesia by action at one class of EAA receptors not previously evaluated in humans.

The EAA receptors in the central nervous system convey information through ionotropic, cation-selective, ligand-gated ion channels (ionotropic glutamate receptors) and G protein–coupled metabotropic receptors. Ionotropic EAA receptors can be divided into N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors. Basic research suggests that new drugs acting at either ionotropic or metabotropic glutamate receptors may have clinical usefulness for various pathophysiologic conditions.

The NMDA receptors are largely permeable to calcium, use glycine as a coagonist, are enhanced by polyamines, have a voltage-dependent magnesium block, and demon-

◆ This Editorial View accompanies the following article: Sang CN, Hostetter MP, Gracely RH, Chappell AS, Schoepp DD, Lee G, Whitcup S, Caruso R, Max MB: AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not pain in normal skin in humans. ANESTHESIOLOGY 1998; 89:1060–7.

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