



SPECIAL ARTICLE

More than 3 hours and less than 3 years: Safety of anaesthetic procedures in infants less than 3 years old subjected to surgery for more the 3 hours[☆]



Julián Álvarez Escudero^a, Rosa María Paredes Esteban^b,
Francisco José Cambra Lasasa^c, Máximo Vento^{d,*}, Maite López Gil^e,
Juan Carlos de Agustín Asencio^f, María Teresa Moral Pumarega^g

^a Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor (SEDAR), Servicio de Anestesiología y Reanimación, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain

^b Sociedad Española de Cirugía Pediátrica (SECP), Sociedad Andaluza de Cirugía Pediátrica (ACPA), Unidad de Gestión Clínica de Cirugía Pediátrica, Servicio de Cirugía Pediátrica, Hospital Universitario Reina Sofía, Córdoba, Spain

^c Sociedad Española de Cuidados Intensivos Pediátricos (SECIP), Unidad de Cuidados Intensivos Pediátricos, Hospital Universitario Sant Joan de Déu, Barcelona, Spain

^d Sociedad Española de Neonatología (SENeo), Retic Red de Salud Materno Infantil y del Desarrollo SAMID RD16/0022, Instituto Carlos III, Ministerio de Economía, Industria y Competitividad, Servicio de Neonatología, Hospital Universitario y Politécnico La Fe, Valencia, Spain

^e Sección Anestesia Pediátrica Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor (SEDAR), Hospital General Universitario Gregorio Marañón, Madrid, Spain

^f Sociedad Española de Cirugía Pediátrica (SECP), Servicio de Cirugía Pediátrica y Coordinador de Especialidades Quirúrgicas en Pediatría, Hospital General Universitario Gregorio Marañón, Madrid, Spain

^g Sociedad Española de Neonatología (SENeo), miembro de la Retic Red de Salud Materno Infantil y del Desarrollo SAMID RD16/0022 (Instituto Carlos III; Ministerio de Economía, Industria y Competitividad), Servicio de Neonatología, Hospital Universitario 12 de Octubre, Madrid, Spain

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Abstract An FDA alert in December 2016 on the safety of general anaesthesia and sedation in patients less than 3 years of age and pregnant women has raised doubts in relation to the attitude that professionals implicated in these procedures should adopt in relation to this specific group of patients.

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* Corresponding author.

E-mail address: maximo.vento@uv.es (M. Vento).

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Confronted with this situation, the following medical scientific societies: Sociedad Española de Anestesia y Reanimación (SEDAR), Sociedad Española de Cirugía Pediátrica (SECP), Sociedad Española de Cuidados Intensivos Pediátricos (SECIP) y Sociedad Española de Neonatología (SENeo), have established a working group to analyse and clarify the safety of these techniques. In the present article we conclude that at present both general anaesthesia and profound sedation are considered safe procedures because there is no evidence of the opposite in studies with human beings. However, this ascertained safety should not obviate the problem which still needs to be followed with attention, especially in patients less than 3 years of age undergoing anaesthetic procedures for more than 3 hours or prolonged sedation in the Neonatal or Pediatric Intensive Care Units.

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PALABRAS CLAVE

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Más de 3 horas y menos de 3 años: Seguridad de procedimientos anestésicos en menores de 3 años sometidos a cirugía de más de 3 horas

Resumen La alerta de la FDA de diciembre 2016, sobre la seguridad de la anestesia general y las sedaciones en pacientes menores de 3 años y en mujeres embarazadas, ha suscitado numerosas dudas sobre la actitud que deben tomar los profesionales implicados en el tratamiento de estos pacientes.

Ante esta situación, las siguientes sociedades científicas médicas: Sociedad Española de Anestesia y Reanimación (SEDAR), Sociedad Española de Cirugía Pediátrica (SECP), Sociedad Española de Cuidados Intensivos Pediátricos (SECIP) y Sociedad Española de Neonatología (SENeo), han constituido un grupo de trabajo para analizar y clarificar la seguridad de estas técnicas. En este artículo concluimos que en el momento actual tanto la anestesia general como la sedación profunda deben seguir siendo consideradas como técnicas seguras, porque no existen evidencias de lo contrario en estudios con seres humanos. Esta seguridad no nos permite ignorar el problema, que debe ser seguido con atención, fundamentalmente en pacientes de menos de 3 años, sometidos a procedimientos anestésicos de más de 3 horas o a sedaciones prolongadas en las Unidades de Cuidados Intensivos Neonatales o Pediátricos.

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Every year, sedation and general anaesthesia are used in millions of interventions in paediatric patients, and while it is well known that modern anaesthetic agents have excellent safety profiles during the perioperative period, some experimental and clinical data reported in recent years suggest that these drugs may interfere with mechanisms of brain maturation in humans.

On December 14, 2016, the Food and Drug Administration (FDA) of the United States issued a safety communication on the use of general anaesthesia and sedatives in young children and pregnant women (*FDA review results in new warnings about using general anaesthetics and sedation drugs in young children and pregnant women*).¹ The drugs affected by the warning detailed in this communication were desflurane, etomidate, halothane,

isoflurane, ketamine, lorazepam, methohexital, midazolam, pentobarbital, propofol and sevoflurane. The concern seems mainly centred on children aged less than 3 years that undergo surgeries lasting 3 or more hours, repeated sedation or general anaesthesia.

The communication does not cite solid clinical evidence because it does not exist, but has generated sufficient interest in the scientific community to inspire a recent editorial in the *New England Journal of Medicine* (NEJM)² that urges for careful consideration of this information, avoiding inappropriate interpretations that could lead to the unwarranted delay or with holding of necessary treatments in paediatric patients. On the other hand, the communication corroborates the safety of these agents in children aged more than 3 years and in procedures lasting less than 3 hours, but also calls for changes in the labelling of involved agents to warn of this potential risk, and for informing parents and guardians of patients of it.¹

This issue raises scientific, legal and ethical concerns for medical professionals involved in the care of these patients. The evidence that is currently available seems to suggest that the use of these agents could have neuroanatomical consequences and affect neurocognitive

outcomes in patients aged less than 3 years overall, and particularly in children born preterm, newborns and infants, who are especially vulnerable because they are at a critical stage in the development of the nervous system and neural networks. These changes are believed to result only from repeated and/or prolonged exposure, although the data are not conclusive yet.

The evidence that is currently available comes from animal studies or *in vitro* research, and while there is insufficient clinical data to extrapolate the results of these experiments to human beings, the issue cannot be ignored. The suspicion that sedative and/or general anaesthetic agents combined with pathophysiological changes caused by surgery (chiefly, inflammation in general, and neuroinflammation in particular) may affect neurocognitive outcomes in patients is not new. There is a clear consensus that only surgical interventions that are absolutely necessary should be performed in pregnant women and newborns.³ Similarly, the only surgical procedures that are performed in patients aged less than 3 years are those that are absolutely necessary and whose postponement carries a greater risk than their performance. Although every case needs to be assessed individually, it may be possible to systematically delay certain interventions without a foreseeable impact on patient outcome, which would require some modifications in the recommended timetable for paediatric surgeries. It is also quite possible that some repeated examinations that require multiple exposures to sedatives could be scheduled differently.^{1,2}

We have already remarked on the lack of clinical evidence, and do not know whether this warning will eventually also be applied to summaries of product characteristics (SmPCs) in Europe, which would require new definitions of specific clinical situations in paediatric patients aged less than 3 years.

The first—and simplest—situation would entail the anticipated use of anaesthesia a single time or for a brief period of time, in which the approach of the anaesthesiologist would not be affected by any changes in the SmPC or product label. The second possibility is the anticipation of a prolonged or repeated use of anaesthesia and/or sedation. In this situation, practitioners should assess whether it is possible to use techniques that do not involve the agents included in the warning (for instance, regional sedation or anaesthesia, anaesthesia based on high-dose opioid agents or nonpharmacological sedation) or to delay surgery, weigh risks against benefits, inform parents and document everything in the patient's health records. In cases in which it is not possible to delay the surgery or procedure, an alternative anaesthetic technique is not an option or the need for prolonged or repeated use of anaesthesia is anticipated in patients aged less than 3 years, practitioners could use conventional techniques with the agents included in the warning as an "exceptional use", a legal concept regulated by Royal Decree 1015/2009⁴ in Spain, while taking every possible action to minimise potential harmful effects.

The problem arises because the drugs included in the broad group of medicines known as general anaesthetics act on numerous receptors and ion channels in the central nervous system, which may have adverse effects on brain development.⁵ However, the results of experimental studies

in animals have been inconsistent, and it is very difficult, and frequently impossible, to translate these findings into a human clinical context.⁶

A different but very relevant situation in the subject under discussion is that of patients hospitalised in neonatal and paediatric intensive care units, where the administration of anaesthetic and sedative drugs over relatively long periods of time, usually at lower doses, may be required to maintain necessary treatments such as prolonged mechanical ventilation. In these situations, the drugs considered safest ought to be used at their minimal effective doses and for the shortest possible time.^{7,8} The extrapolation of animal data to human patients is very complex. The experimental designs employed in these studies included a variety of drugs and largely ignored noxious stimuli, which human patients undergoing surgery are subjected to. In animal models it is difficult to distinguish the harm caused by situations such as sepsis, changes in plasma glucose levels, hypotension, stress, inflammation or other critical states that could promote or trigger neuronal changes in humans under anaesthesia and/or sedation. There are studies in the paediatric age group that have not found an association between exposure to general anaesthesia and adverse outcomes, such as the Pediatric Anesthesia Neuro-Development Assessment (PANDA) study and the General Anesthesia Compared to Spinal Anesthesia (GAS) trial.^{9–14} The PANDA study is an observational study that has compared children with a history of brief exposure to siblings not exposed to anaesthesia, and concluded there were no significant differences between these two groups. The GAS trial is an international, randomised control multicentric study comparing neurocognitive outcomes following randomisation to general anaesthesia or spinal anaesthesia with sedation in children undergoing surgical repair of inguinal hernia. Participants are aged less than 60 weeks and were born at 26 weeks gestation or later. This trial has not found any significant differences between the two groups, either. On the other hand, there have been studies that found significant changes. These studies, most of which have a retrospective design, show that longer and/or repeated exposure to general anaesthesia may contribute to the development of cognitive and behavioural problems, including neurodevelopmental delay-related diagnoses, learning disabilities and attention deficit hyperactivity disorder.^{15–25} It is evident that preterm infants with birth weights of less than 1500 g are a particularly vulnerable group. The survival of these patients continues to increase, but many need to undergo urgent surgeries, sometimes even performed in neonatal units during a critical stage in neurodevelopment. Retrospective studies have found an increased risk of death or neurocognitive disorders at 18 to 22 months of corrected age in preterm children with a history of surgery in the neonatal period. General anaesthesia seems to play a role, but the evidence on it is not yet solid.²⁴ We ought to mention that the methodology of many of these studies is questionable, to which we must add that their results are not conclusive. Furthermore, we are not sure whether this hypothetical neurocognitive impairment results from the use of general anaesthesia or from the underlying disease that prompted the surgery or prolonged sedation due to the vulnerability of these patients. Multivariate analyses capable of

differentiating the causative role played by each associated factor would require a sample size that has not been reached in these studies.

We are thus confronted with a dilemma: we do not have sufficient evidence to confirm the neurotoxicity of these drugs, but we also have insufficient evidence to be certain of their harmlessness.^{26–33} The MASK study (Mayo Safety in Kids) is currently underway; it is a cohort study comparing possible sequelae of anaesthesia exposure in preschool children at the time of evaluation in elementary school or high school. The final results of this study have yet to be published, but initial analyses have not found significant differences.

This situation brings up two questions. The first is whether we need to change our current clinical practice.^{34–36} The second concerns the information that we need to provide to parents and/or legal guardians.^{37,38} It would be reasonable to base this information on ethical considerations, but also taking into account legal aspects.

The approach of physicians involved in the care of these patients should adhere to the principles of health care ethics. The principle of *beneficence* calls for preventing pain and stress related to surgical or diagnostic procedures in all patients. Untreated pain may be harmful to the nervous system of the developing child, and can result in persistent hyperalgesia due to its neuroplasticity.³⁴ The prolonged or repeated use of a drug as required by the medical condition of the patient, when there is no alternative treatment, adheres to the *lex artis*, that is, constitutes good clinical practice. Several scientific societies, including the American Academy of Pediatrics, American Surgical Pediatric Association, American Society of Anesthesiologists, International Anesthesia Research Society, Society for Pediatric Anesthesia and Society for Pediatric Pain Medicine, among others, advise against irresponsible delays in necessary therapeutic or diagnostic procedures.

To avoid doing harm in adherence to the principle of *nonmaleficence*, and given that suspicions on potential neurotoxicity are well-founded, we have the duty to continue investigating the long-term effects of anaesthetic practises, analysing aspects such as risk by age, duration of exposure, underlying diseases of paediatric patients, critical doses etc. It would be poor practice to be unaware of the potential adverse effects of these drugs and to use them without taking the necessary precautions. It seems highly advisable that physicians be warned in some way, so it is very likely that the European Medicines Agency (EMA) and the Agencia Española del Medicamento y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices [AEMPS]) will take a similar stance to that of the FDA with the purpose of improving patient safety.

The principle of *distributive justice* guarantees equal opportunity in health care for all patients. In this regard, we must advocate to ensure that in hospitals, every child requiring anaesthesia or sedation is managed by a paediatric anaesthesiologist with experience and skill in techniques based on regional or opioid-based anaesthesia and who are comfortable using options that minimise or avoid the use of drugs included in the warning.

Lastly, we must adhere to the principle of respect for the *autonomy* of patients and their families. It is our duty to provide detailed and comprehensive information to parents or legal guardians regarding the options that are available

given the circumstances of the patient, and to carefully weigh the risks and benefits of any possible intervention. The process of informing patients and families should be documented in the medical record, and informed consent obtained.

We present this document in the hope that it will be helpful to Spanish physicians in facing a scientific and technical challenge of the first order, given the responsibility we hold in the current and future health of our young patients.

From a legal standpoint, we ought to keep in mind that regulatory agencies are responsible for authorising medicines and monitoring their safety and efficacy while they remain on the market. The FDA in the United States, the European Medicines Agency in Europe and the Medicines Agency of the Ministry of Health, Labour and Welfare in Japan are responsible for updating the information on the medicines that they authorise and/or review periodically.

We must not forget that no medicine is free of risk, small as it may be (there is no such thing as zero risk). This gives rise to the legal obligation to warn of these risks in SmPCs and package leaflets, including information on the incidence or frequency of these potential adverse events. Nevertheless, medical practitioners are obliged to prescribe drugs assuming these risks, which does not constitute malpractice.

The warnings that will be included from now on in the labelling (prescribing information and package insert) of specific sedative and anaesthetic agents in the United States is based on interim data from preclinical studies. The use of the word “may” suggests possibility or probability, and thus does not imply that a given effect will certainly occur in every patient. For the time being, the FDA has not chosen a different wording—such as “causes”, “induces” or “provokes”—because there is no evidence from clinical trials to support such a statement.

In Spain, we await the recommendations to be issued by the AEMPS—through information sheets, circulars, etc.—to which we will adhere under the auspices of Royal Decree 1015/2009,⁴ which also regulates the use of medicines under conditions that differ from those authorised (that is, outside the indications approved in the SmPC). As an aside, Spain is the only country in the European Union that regulates this issue, known as *off-label* use, with provisions similar to those established in the United States. The text stipulates that the use of medicines outside the conditions detailed in the summary of product characteristics is allowed if the use is exceptional or occurs in situations when there is no alternative authorised treatment. Furthermore, said use must take place in the context of everyday clinical practice, that is, not as part of a clinical trial or any other type of research.

Royal Decree 1015/2009⁴ places the burden of responsibility on the prescribing physician, who must justify the need for the off-label use of the pharmacological agent, inform the patient—or the patient’s parents or legal guardians physicians, in the context that currently concerns us—of the label warnings, and obtain the appropriate informed consent, although the law does not specify whether the consent may be verbal or must be formalised in writing, and it currently suffices to document in the medical record that parents were informed and gave their consent. Similarly, prescribing physicians are not required to request individual authorisations by the AEMPS or to obtain the approval of the ethics committee of the health care facility, contrary to

what applies to the *compassionate use* of pharmaceuticals, which is also regulated in this decree.

Nevertheless, in the hypothetical case of a medical lawsuit linking the development of a presumed and manifest adverse effect on the cognitive development of a patient with a past repeated or prolonged exposure to the aforementioned hypnotic anaesthetics, the law would need to differentiate between 2 possible situations based on timing. If the suit referred to a time before the Spanish authorities added the warning to the SmPC of the anaesthetic agent, the practitioner would have conformed to the information provided in the label, that is, to current scientific knowledge, and said warnings could not be used as an argument to support the suit, as the law does not allow sentencing on the basis of facts or data that became known at a later date applied retroactively. This legal reasoning also applies to the scientific evidence that is used to try cases. If the suit was filed after the warning was approved, it should still not be cause for concern to physicians as the *lex artis*—acting according to the principles of good medical practice—allows the physician to select various technical solutions, as there is usually more than one single option.

In addition, it is highly probable that in response to the inclusion of such a warning, hospital and clinical departments would develop protocols to approach every possible situation, thus protecting physicians that act in adherence to them.

At any rate, medical practitioners will not be made responsible if their intervention conforms to the *lex artis ad hoc*, as the use of these agents is exceptional and motivated by a lack of alternative treatments, based on scientific evidence and, in this context, covered by protocols. In other words, clinicians will only be legally liable in case of malpractice, which would be the case even if their intervention conformed to the summary of product characteristics.

To address these concerns and others that may arise in the future, the Sociedad de Anestesiología, Reanimación y Terapéutica del Dolor (Spanish Society of Anaesthesiology, Resuscitation and Pain Management, SEDAR), the Sociedad Española de Cirugía Pediátrica (Spanish Society of Paediatric Surgery, SECP), the Sociedad Española de Cuidados Intensivos Pediátricos (Spanish Society of Paediatric Intensive Care, SECIP) and the Sociedad Española de Neonatología (Spanish Society of Neonatology, SENEo) have created a working group with the purpose of analysing the situation and develop a consensus document with the key recommendations that we believe could currently minimise potential adverse effects. This document will have two clear objectives: to inform and guide health care professionals to the extent possible, and to reassure the parents and guardians of these paediatric patients, who are experiencing the deep anxiety of having their child put under prolonged general anaesthesia or sedation, that the intervention is the best option among those available and for their child's current state of health.

We also want to communicate to every specialist involved in this type of procedures our firm intent to establish stable and enduring pathways for communication and collaboration with the purpose of working together to improve the integration of care, striving to always offer excellent medical care to our patients while optimising the use of the available health care resources.

Conflicts of interest

Julián Álvarez has received fees for conferences from Orion Pharma. He has received funding for clinical and experimental research from Orion Pharma and Cardiva. The rest of the authors have no conflicts of interest to declare.

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