



## Editorial

## Guidelines to the use of laboratory animals: what about neuromuscular blocking agents?

Stephan C.U. Marsch\*, Wolfgang Studer

*Department of Anaesthesia, University of Basel, 4031 Basel, Switzerland*

Received 29 January 1999; accepted 29 January 1999

*Cardiovascular Research* requires that investigations in animals conform with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health. These guidelines advocate that neuromuscular blocking drugs must not be used to provide “surgical restraint” in case of inadequate anaesthesia [1]. There is no doubt that performing painful or distressing procedures on an animal that is paralysed yet conscious is cruel and that animals have to be protected accordingly. The question arises, whether the above mentioned guidelines protect animals sufficiently against less overt dangers associated with the use of neuromuscular blocking drugs, e.g. awareness.

Awareness with explicit memory is defined as patient perception and recall of events during general anaesthesia. Patient perception with explicit memory requires conscious processing of information, i.e. the patient has to be awake during a period of time during general anaesthesia. By contrast, patient perception with implicit memory relates to subconscious processing of intraoperative information and may be tested using hypnosis or behavioural suggestions. The incidence of awareness with recall in a general surgical population is approximately 0.2% [2]. However, in patients undergoing caesarean section (0.4%) and cardiac surgery (1.1%), the incidence of awareness is significantly higher [3,4].

Awareness almost invariably results from the combination of inadequate anaesthesia and the use of neuromuscular blocking agents. Unfortunately, there is presently no monitor of the depth of anaesthesia available that can reliably indicate the presence or absence of risk of awareness. However, in the absence of muscle paralysis painful and/or distressing stimuli during too light an anaesthesia result in movements prior to the gain of consciousness. Thus, the avoidance of neuromuscular

blocking agents could completely eliminate the problem of awareness.

Why are neuromuscular blocking agents still in use if they are to blame for the occurrence of awareness? Neuromuscular blocking agents are routinely used to facilitate tracheal intubation. Loss of airway control is a major cause of perioperative death and most, if not all, practitioners would argue that in many cases the advantage of optimal intubation conditions, brought about by muscle paralysis, outweighs the increased risk of awareness. Moreover, in some types of surgery muscle paralysis is a prerequisite for a successful operation. In cardiac surgery, moving or coughing may even be life-threatening should the movement lead to a displacement of the cannulas of the extracorporeal circulation. Thus, in the clinical settings the indications for neuromuscular blocking are based on specific anaesthetic and surgical requirements.

For obvious reasons, the incidence of awareness in animals subjected to laboratory research under general anaesthesia is unknown. Is there any reason to believe that the incidence of awareness is lower in these animals than in patients undergoing general anaesthesia? We do not think so. Awareness may potentially occur in every single patient. Moreover, in many countries awareness will most likely result in litigation. Thus clinical anaesthetists are concerned by the possibility of awareness and try to prevent its occurrence using adequate technique. One might argue that researchers are under less time pressure than their clinical colleagues and, therefore, preparations for and execution of anaesthesia are performed more carefully. However, even the presence of the most careful anaesthesia provider is no guarantee against human error or equipment malfunction. Examples of equipment problems are malfunction of perfusion pumps and disconnection of perfusion lines. Examples of human error include drug errors (i.e. mixing up drugs, calculating the wrong dose, preparing syringes with wrong concentrations of the drug) and vigilance errors (e.g. failure to notice empty

\*Corresponding author. Tel.: +61-265-7254 fax: +61-265-7320.

E-mail address: [marsch@ubaclu.unibas.ch](mailto:marsch@ubaclu.unibas.ch) (S.C.U. Marsch)

syringe or vaporiser, failure to notice equipment malfunction). In the presence of neuromuscular blocking agents all these errors can lead to awareness.

Are there any valid indications for neuromuscular blocking drugs in animals undergoing laboratory investigation? In general, the answer has to be a firm no. Rare exemptions may include the investigation of the effects of neuromuscular blocking drugs or the suppression of residual electromyographic activity for neurophysiologic recordings [5]. As far as cardiovascular research in intact animals is concerned, there is generally no need to administer neuromuscular blocking drugs. Investigators may fear that anaesthesia interferes with their results and, therefore, chose to administer light anaesthesia in combination with neuromuscular blocking drugs to prevent movement. However, pain and distress associated with too light an anaesthesia may have a more profound effect on haemodynamic variables than anaesthetic agents. Due to inter-species differences, laboratory research in the intact animal is performed for qualitative (e.g. insight into physiologic mechanisms) rather than quantitative reasons. Although the response to experimental interventions may differ quantitatively in the anaesthetic state compared to the conscious state, anaesthetics do not affect the qualitative response of the cardiovascular system. Researchers that are concerned that their findings might be confounded by anaesthesia may repeat their experiments in the presence of different anaesthetic agents.

As the depth of anaesthesia can not be reliably assessed, the only protection against awareness is the unrestricted ability to move. By preventing movement, neuromuscular blocking agents may lead to unnecessary suffering of the animal. We therefore recommend that institutional animal committees adopt the policy of banning these drugs. Researchers claiming that muscle paralysis is a precondition for the success of their investigation should be forced to extensively justify the use of neuromuscular blocking agents and modify their anaesthetic technique in order to minimise the risk of awareness. This policy is already

implemented in *The United Kingdom Animals Act* that require a special project licence as well as a special personal licence to use any neuromuscular blocking agent [6]. The strongest impact on standards of animal care within the research community has undoubtedly been the editorial policy of scientific journals. Accordingly, we recommend that scientific journals announce that the use of neuromuscular blocking drugs will inevitably lead to the rejection of the manuscript unless the authors are able to convincingly justify the use of these drugs in the methods' section. *Anesthesiology*, one of the leading scientific journals in the anaesthetic field recently clarified its policy on the inappropriate use of neuromuscular blocking drugs arguing that *our treatment of animals must be beyond reproach for the sake of our animal subjects, for the sake of scientific validity and for the sake of preserving our privilege to perform scientifically important investigations* [5]. All we want to add to this sentence is the recommendation that researchers should no longer employ an anaesthetic management that has been judged to be inappropriate for ethical reasons by expert anaesthesiologists.

## References

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