

The CABMM's **Dr Peter Kronen** writes on the importance of anaesthesia and analgesia expertise and the related refinement as an ethical, scientific and legal principle

Requirements of anaesthesia and analgesia

The Center for Applied Biotechnology and Molecular Medicine (CABMM) at the University of Zürich integrates existing research groups within its network and provides a platform for collaborative research. There are four major areas of activity, namely experimental medicine and surgery, molecular medicine, regenerative medicine, and applied biotechnology.

After extensive laboratory testings, projects from inside and outside the CABMM may reach a point of development at which experiments in a living organism become unavoidable in order to safely apply techniques and devices to patients – both human and veterinary. This is done in the Experimental Medicine and Surgery Section of the CABMM.

This section works to a particularly high standard of scientific and ethical principles in order to provide results to biomedical questions of only the utmost importance and exclusively under strict adherence to the reduction and refinement principles of the 3Rs (Russell and Burch, 1959). The structure of this part of the CABMM is further based on well-designed equipment infrastructure and particularly transparent and gap-free documentation. In fact, the Experimental Medicine and Surgery Section based at the University of Zürich's veterinary faculty is one of the very few institutions in Europe that hosts multiple-field expertise in veterinary specialties (surgery, anaesthesia and analgesia, radiology etc.) applied to experimentation and that is GLP-(good laboratory practice) certified.

Ethical guidance

Each project undergoes an intensive scrutinising process and is uniquely designed from its inception by a collaborative approach employing multiple veterinary experts together with human medical experts, engineers, histologists, and statisticians before its submission to an ethical review committee. Only with this committee's approval is the project carried out.

Biomedical testing situations frequently require one or even many anaesthetics to be performed. The influence on both the wellbeing of the animals involved as well as on the tests themselves are multiple. The cardiovascular system and the respiratory system are particularly affected, but the nervous system, the detoxifying organs, e.g. the liver and kidneys, and the musculoskeletal system are also affected. The impact that application of anaesthesia has on an animal, as well as on the outcome of the project, needs to be evaluated constantly and consistently. Even slight changes in the function of these body systems during an anaesthetic can make a huge difference in the organism's response to an implant or drug.

Furthermore, the impact that anaesthesia itself, alongside the implant or drug, has on the wellbeing of the animal and its proper body function is also part of the necessary evaluation. Such evaluation, though, can be performed on the basis of expert anaesthesia training only. This is particularly true for short term projects, but has been shown to strongly

A veterinary anaesthesiologist and a surgeon implanting a port into the carotid artery for invasive monitoring during anaesthesia



affect long term outcome as well. The impacts caused may be aggravated if a project directly involves the nervous, respiratory and cardiovascular systems or detoxifying or musculoskeletal organs.

For example, alterations of cerebral blood flow may be required in certain models in order to resemble a disease state in humans. Cardiac or intravascular implantations clearly alter blood flow, but may also affect rheological and coagulation patterns. Implantation of bone implants may require a very invasive surgical approach. In many situations these alterations are a threat to life, and complication, morbidity or even mortality rates are unacceptably high. The animals involved are put at risk, and scientific outcome becomes questionable if generated on a variation of complications and morbidities.

Therefore, it seems a clearly stateable requirement to involve veterinary anaesthesiologists in such a research setting in order to help evaluate the impact that anaesthesia itself has on a specific research question, but also to enhance the animals' wellbeing and alleviate any possible suffering involved. The application of less stressful and inflictive

anaesthetic techniques in research projects has to be at the forefront of specialty knowledge in veterinary anaesthesia.

Pain and analgesia

During invasive procedures, such as the ones involving surgery, nociceptive activation and resulting pain are of particular concern. Pain is a particular stressor on all body systems and alters their function profoundly. Again, from the animal wellbeing point of view, the nociception and pain may result in significant suffering. This, however, has to be minimised or ideally annulled for ethical, scientific and legal reasons. Veterinary anaesthesiologists have expert training to prevent and treat pain in animals. They may choose between an array of prevention and treatment options.

The pain situation is further complicated by the many different types of pain that may be involved in a single procedure. With every surgical intervention, there are acute and inflammatory pain types inflicted, but, depending on the specifics of a project, chronic pain, neuropathic pain or any other types may also be present. Each may require a different analgesic intervention. Anaesthesiologists, in fact, are trained in the application of such techniques, and often the simple, systemic administration of analgesic drugs does not suffice.

Instead, loco-regional anaesthetic techniques, such as specific nerve blocks or neuraxial anaesthesia and analgesia, may be required. The application of such specific analgesic techniques not only alleviates pain effectively and reduces suffering (definition of refinement), but also allows for a more stable plane of anaesthesia, aiding the stability of research data generated. As a surplus, if a disease state is to model a human disease, the application of techniques that alleviate pain increases the validity of the model, as human patients with the real disease may receive similar treatments.

Reduction

The application of safe anaesthetic techniques allows for a reduction in complication, morbidity and mortality rates. This leads to a possible reduction in animal numbers involved and constitutes a direct fulfilment of the 3R-principles. Safer anaesthetics and better analgesic techniques may lead to fewer animals used also through the creation of more intervention possibilities. In a drill hole model (used to test dental implants, for example) developed at the CABMM's Experimental Medicine and Surgery Section, it was possible

to realise nine implants per side in one animal, while a normal dental implantation model allows for two to three implants per side only. With this model, a threefold reduction in animal numbers became possible. Due to its invasiveness, however, the creation of this model required the introduction of a specific anaesthesia technique.

Publication

Publication either to scientific journals or to governmental authorities (such as the Food and Drug Administration in the United States) in one form or another is an end goal of experimental research. There are clear guidelines published and adherence is required by many already. Prominent guidelines are the ARRIVE (NC3Rs) guidelines and the CONSORT statement. The reporting of animal wellbeing, specifically including pain, is required, as are the anaesthetic and analgesic techniques involved. Professional veterinary and animal protectionist organisations are rightly screening published literature for adherence to these guidelines.

Involving a veterinary anaesthesiologist in the reporting and paper writing constitutes a major help, therefore, when trying to publish or submit research work. Furthermore, experimentation requests prior to starting a project require similar information, and to help consolidate an application from an animal wellbeing and scientific point of view, the input of a specialised veterinary anaesthesiologist circumvents any problems otherwise arising.

Highest possible standards

In most countries, animal experimentation legislation foresees the highest possible standard of care to be applied to animals used in biomedical research. As in all other fields, this requires specialist support in anaesthesia and analgesia.

In summary, from ethical and scientific standpoints, a veterinary specialist in anaesthesia and analgesia should be involved in any invasive (i.e. requiring anaesthesia) research using animals.

The presence of an anaesthesiologist in a project from the design stage, throughout the carrying out and up to the reporting allows for significant refinement and reduction of experimental research.

Reporting and scientific paper writing of animal experimentation should involve a veterinary anaesthesiologist.

Intra-project evaluation of the impact of anaesthesia and surgery on the animals' wellbeing and the data generated can best be performed by a veterinary anaesthesiologist.

At the CABMM, we involve anaesthesiologists in all projects. Veterinary Anaesthesia Services - International offers services in all of the mentioned fields worldwide.

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