Influence of central neuraxial blockade on anesthetic pharmacology and brain function

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Chapter 1

Introduction

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Central neuraxial blockade is the injection of local anesthetics (with or without an opioid) around the nerves that exit the spinal cord. In modern clinical practice, neuraxial blockade is an essential part of the armamentarium of the anesthesiologist in providing safe and effective anesthesia. There are several techniques for neuraxial blockade including spinal injection of local anesthetics into the intrathecal space, epidural injection into the (lumbar or thoracic) epidural space, combined spinal-epidural and caudal injections, and finally continuous or patient-controlled epidural administration of local anesthetics. All techniques are applicable in different clinical settings.

The principle of central neuraxial blockade was first described by James Leonard Corning (1855–1923). In 1884, he injected cocaine between the spinous processes of the lower lumbar vertebrae, in a dog and later in a healthy human volunteer.[1] The surgeon August Bier performed the first surgery under spinal anesthesia in 1899.[2] In 1921, Spanish military surgeon Fidel Pagés (1886–1923) developed the modern technique of lumbar epidural anesthesia.[3] No publicity was given to this revolutionary anesthetic technique at that time. Dogliotti first utilized the epidural technique in 1931.[4] He advocated its use and wrote a book, which was later translated into English. The first lumbar continuous anesthesia was performed by Manuel Martinez Curbelo in 1947. [5] Since these early years, techniques have been developed further and new anesthetics have been registered for use in neuraxial anesthesia and analgesia.

The discovery of local anesthetics goes back to the Middle Ages, Calatayud et al. did a thorough search of the first use of coca leaves and the first documentation of its anesthetic and adverse effects.[6] They discovered that the isolation of cocaine out of coca leaves was a joint venture of Austrian naturalist Carl von Scherzer (1821-1903) and German chemist Albert Niemann (1834-1861).[7,8] From here steps were taken to apply it as a local anesthetic. Niemann reported numbness of the tongue caused by this new alkaloid, cocaine.[7] In the mid and late 19th century, the first experimental studies on cocaine were published. They described injection of cocaine solutions causing insensitivity in rats, pigeons and frogs. Basil von Anrep, a Russian aristocrat, performed experiments on animals and experimented on himself. A solution of cocaine injected under the skin resulted in insensitivity of the area.[9] It was the Viennese ophthalmologist Carl Koller (1857-1944), who experimented with cocaine solutions for surgery first on animals and performed the first operation using this local anesthetic on a patient with glaucoma.[10] The news and use as an anesthetic for surgery spread quickly, the increase in usage coincided with its alarming side effects, one of them was abuse and addiction to cocaine. This and other side effects resulted in an ongoing search for new local anesthetic drugs. In 1905 novocaine, invented by Alfred Einhorn, was the first to replace cocaine as a local anesthetic.[11] The urge to search for better and safer local anesthetics maintained and led to the development and clinical introduction in 1948 of lidocaine by Nils Löfgren and Bengt Lundquist.[12] The first amide-type local anesthetics, mepivacaine and bupivacaine, were

developed by Ekenstam et al. [13] Bupivacaine, on the market since 1965, is still one of the most intensively used local anesthetics despite the presence of neurological and cardiovascular toxicity at high dose. Several experiments were carried out to determine the cause of toxicity and to improve our understanding of how local anesthetics work. As a result, two amide local anesthetics, ropivacaine and levobupivacaine were developed with less cardiotoxicity compared to bupivacaine. The clinical use and pharmacology of these long acting local anesthetics since their introduction in late 20th century is one of the topics in this thesis.

Today, central neuraxial blockade is one of the most used stand-alone anesthesia techniques or is combined with general anesthesia to reduce opioid consumption during surgery and can provide effective postoperative pain relief. Additionally, the epidural analgesia has been widely accepted as an effective method of pain relief during labor and childbirth. Although the use of local anesthetics and central neuraxial blockade is widely studied, several issues remain still unknown, such as:

(1) What is the effect of the (transient) state of deafferentation induced by the neuraxial blockade on pain perception of the non-deafferented part of the body? Deafferentation is the disruption of afferent and efferent signals between the central and peripheral nervous system and occurs albeit transiently during neuraxial blockade. When peripheral input to supra-spinal areas of the central nervous system (CNS) is lost, various changes occur within the brain including behavioral changes. For example, patients experience illusionary changes of the affected limbs during spinal and epidural anesthesia. Another observation is an improvement of function of contralateral or adherent limbs during temporary deafferentation. Also pain perception may change.[14,15] How this relates to changes within brain networks remains unknown but may be studied using functional magnetic resonance imaging (*f*MRI). Generally, there are two approaches, task-based *f*MRI and resting state *f*MRI (RS-*f*MRI). Task-based *f*MRI is frequently utilized to identify brain regions that are functionally involved in a given task performance. RS-*f*MRI is used to investigate the fundamentally functional segregation or specialization of brain areas and brain networks. Different resting state networks have been discovered by studying functional brain connectivity in the state of rest, each of which depicts unique functions and spatia. This relative new technique is noninvasive and easy to perform and needs no cooperation of patient or subject.

(2) Epidural (and spinal) anesthesia is often combined with general anesthesia. How these two anesthetic states interact on various endpoints is poorly studied. We know, for example, that the state of deafferentation from neuro-axial blockade affects the level of hypnosis induced by general anesthetics. Importantly, these two states negatively affect hemodynamics either through pharmacokinetic or pharmacodynamic interactions, or both. Such issues are best addressed by performing pharmacokinetic-pharmacodynamic modeling studies.

(3) Finally, although various local anesthetics are available, we remain uninformed on their efficacy in terms of anesthesia, analgesia and adverse effects. Three long acting local anesthetics are currently available for use in epidural anesthesia. Long acting local anesthetics, bupivacaine, ropivacaine and levobupivacaine differ in potency, efficacy and central nervous system (CNS) and cardiovascular (CV) toxicity. The difference in toxicity of these long acting local anesthetics implies a possible preferred application in anesthetic practice. Comparisons, particularly when these local anesthetics are combined with an opioid in general practice are needed.

The aim of this thesis was to address these issues by gaining more insight in the pharmacodynamics and pharmacokinetics of central neuraxial blockade and to explore the effect of spinal anesthesia on brain networks and pain perception using *f*MRI.

In **Chapter 2**, the efficacy of epidural postoperative analgesia using levobupivacaine and ropivacaine was evaluated in postoperative patients in a randomized and double-blind study. The anesthetics were evaluated at two concentrations in combination with the opioid sufentanil.

In **Chapter 3**, the effect of epidural analgesia with ropivacaine on the pharmacokinetics of propofol was studied in a double-blind, placebo-controlled study. The data were analyzed using a population pharmacokinetic modeling approach in NONMEM.

In **Chapter 4**, we examined the effect of epidural analgesia with ropivacaine during propofol sedation on cardiac output, mean arterial pressure and bispectral index. The data were analyzed using a population pharmacodynamic modeling approach in NONMEM. The goal of both chapters was to identify whether possible interaction between neuraxial blockade and general anesthesia are pharmacokinetic or pharmacodynamic in nature or have components from both.

In **Chapter 5**, we examined whether spinal anesthesia changes pain perception in non-deafferented skin areas. Pain sensitivity and offset analgesia (a form of endogenous pain modulation) were tested in healthy volunteers at dermatomes above the level of deafferentation during spinal versus sham anesthesia.

In **Chapter 6**, the influence of spinal anesthesia on resting state fMRI brain networks was tested in healthy volunteers using 10 predefined networks, generally accepted and pain sensitivity on non-deafferented body parts were evaluated. In Chapter 7, to further identify the effect of deafferentation on pain areas in the brain, we explored the effect of spinal anesthesia on brain functionality using (pain) task-related functional magnetic resonance imaging.

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